Glycative Stress Research

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Review article

Cognitive impairment and glycative stress

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Abstract

The relationship between dementia and advanced glycation end products (AGEs), one of the glycative stress markers, has been gaining attention in recent years. The increased production of AGEs is related to many conditions, such as increased inflammation and oxidant stress associated with diabetes. Aging is one of the conditions, and dementia, like Alzheimer's disease, is more accelerated than normal aging. It is known that in the case of diabetes, the increase of AGEs causes dementia or mild cognitive impairment (MCI). However, there are almost no data regarding the relationship between AGEs and cognitive function under non-diabetic states. We examined the relationship between the accumulated amount of skin auto fluorescence (SAF) and MCI of anti-aging medical checkup examinees who were not presenting clear symptoms of diabetes. The number of subjects was 226 (84 males with an average age of 69 ± 11 and 142 females with an average age of 67 ± 10). Kidney function, brain natriuretic peptide (BNP), brachial ankle pulse wave velocity (baPWV), brain atrophy (temporal horn area) and SAF value were significantly higher in the group of the subjects who were evaluated as showing MCI (n = 18) than those of the group showing no MCI. Even after the adjustment of various confounding factors using logistic regression analysis, the fact that the SAF value was high (≧ 2.27) was significantly related to the existence of MCI. The measurement of the SAF level is considered to be useful from the perspective of prevention of dementia.

***KEY WORDS*:** advanced glycation end products (AGEs), mild cognitive impairment (MCI), Anti-Aging Medical Checkup, MCI screen, skin auto fluorescence (SAF)

Introduction

Cognitive impairment (dementia) is one of the most important diseases in an aging society. There are approximately 4.62 million dementia patients in Japan, and furthermore, there are approximately four million elderly presenting mild cognitive impairment (MCI) who are considered to be future dementia patents. MCI was described as a general disorder of aging increasing the risk of dementia including Alzheimer disease (AD) for the first time in 1999, and it is known that if MCI is diagnosed, the patient progresses toward dementia at the rate of 10-15% a year.

It is estimated that dementia patients will increase to seven million by 2025. However, no method leading to the radical cure of dementia has been established. Because there is no fundamental treatment method for dementia at present, it is important to detect the onset of dementia and MCI and appropriately intervene in the lives of patients as soon as possible.

Meanwhile, advanced glycation end products (AGEs) are drawing attention as glycative stress marker in association with dementia recently. AGEs are protein and lipid nonenzymatic glycative products. The AGEs produced are not only caused by diabetes as being imagined from its naming, but also caused by aging, oxidative stress, inflammatory conditions and kidney failure and at present, it is considered to be one of main causes of the progression of arterial sclerosis. Most of the AGEs have not been covered by health insurance. However, pentosidine is a fluorescent and cross-linking AGE effectively produced from ribose, arginine and lysine and this AGE only is covered by health insurance as an early marker of kidney diseases.

This research focused on AGEs and outlined the relationship of AD, a typical dementia, and MCI with AGEs also using the data of our laboratory.

Background
– Relationship of AD and MCI with AGEs –

AD patients are considered to have an accumulation of AGEs [1]. The accumulation of AGEs in cells and tissues is a

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normal characteristic of aging: however it is accelerated in the case of AD, suggesting its definite contribution to the cause of AD. According to recent research, in the case of diabetic patients, the level of AGEs rises in relation to the enhancement of inflammation and oxidative stress, which leads to the onset of dementia and MCI [2]. On the other hand, the data similar to the above can be rarely observed in the case of non-diabetic patients. Therefore, in order to better understand the relationship between MCI and AGEs in the case of healthy people without clear diabetic symptoms, we examined the accumulation status of AGEs in the tissues of community members who received thorough medical checkups.

Method
– Including MCI Screening of Anti-Aging Medical Checkup –

The subjects were the participants in Anti-Aging Medical Checkups of a health examination in the Anti-Aging Center (AAC) in Ehime University Hospital specifically designed to evaluate age-related diseases including arterial sclerosis and problems of physical functions [3-5] for the period from April 2013 to April 2015. All clinical data were obtained through the Anti-Aging Medical Checkup inspection process. The requirements for participation in this research were "the subject should not have received periodic drug treatment for hypertension or diabetes for at least 6 months and be 40 years or older." In order to exclude the influence of cerebral-and-cardio-vascular disease treatment as an exclusion requirement, in addition to the items described above, the data of the participants with a history of stroke and cardiovascular diseases including ischemic heart disease were excluded. Items for inspection were, general blood tests, brachial ankle pulse wave velocity (baPWV) test and the measurements of clinical parameters relating to arterial sclerosis, including brain MRI examination, in addition to the measurement of the accumulation volume of AGEs in skin tissue and MCI screening test, which will be discussed later. For general blood examination, blood samples were collected from the cubital vein from 9 am to 10 am after a fasting period of longer than 12 hours and the following biochemical parameters were measured: fasting blood sugar (FBS), HbA1c, serum creatinine (sCr), high-density-lipoprotein-cholesterol (HDL-C), triglyceride (TG), high-sensitivity-C-reactive protein (hsCRP), brain natriuretic peptide (BNP), low-density-lipoprotein-cholesterol (LDL-C) and estimated glomerular filtration rate (eGFR). LDL-C level was calculated using Friedewald's formula[6]. eGFR was calculated using Cockcroft-Gault [7]. baPWV was measured using the device (FORM/ABI ; Omron Colin Co. Ltd., Komaki, Ehime, Japan) [8] after five-minute rest and the average value of right and left was used as a data. After a brain MRI examination was conducted, as was already reported, right and left sides of temporal horn area (THA) were measured at the level of pentagon using a T2 flair-weighted image and the average value was used as data. It is reported that THA evaluated by MRI is an independent predictive factor for the progress of dementia [9].

This clinical research was conducted by strictly observing the ethical principles based upon the Helsinki Declaration and it was also approved by the Ethical Committee of Ehime University Graduate School of Medicine. Informed consent forms were received from all subjects before the research.

Measurement of Accumulation Amount of AGEs in Skin Tissue

SAF (skin auto fluorescence) is used to measure the AGEs in tissue using AGE-reader (DiagnoOptics Technologies VB, Groningen, The Nederland) by the methods based on several fluorescence properties. An AGE-reader is a desktop-type device and it can presume the level of AGE accumulation in the skin by noninvasive measurement [10]. Specifically, it is to measure AGEs utilizing the characteristic of AGEs that when an ultraviolet ray irradiates the skin, fluorescent AGEs accumulated in the skin tissue are excited and radiate a unique auto-fluorescence. All measurements are conducted on the palmar side of forearm in the range from 10 cm to 15 cm under the elbow. The measurement value is calculated in a way that the average value of emitted light intensity per nm in the range from 420 nm to 600 nm is divided by the average value of excitation light intensity per nm in the range from 300 nm and 420 nm, and it is shown by arbitrary unit (AU).

In a precedent research, it was verified that the SAF value is determined by the accumulation of multiple AGEs and that there are strong correlations between SAF value and the amounts of AGEs (pentosidine, carboxymethyl-lysine [CML], carboxycthyl-lysine [CEL] in particular) contained in skin tissue [10]. Furthermore, it is reported in the same research that the error rate of SAF value per day is 5.0%, and that due to seasonal change, it is 5.9%.

Screening Test of MCI

Although various methods for diagnosis of MCI are internationally approved, only a few Japanese versions have been studied for validation. We have been using the Japanese version of the MCI screening inspection "MCI screen" developed by Shankle *et al*. [11,12] since the start of our "Anti-Aging Medical Checkup" in 2006. This is for a staff management test that can be conducted in 10 minutes. Its cross-validation was confirmed by referring to clinical dementia rating scale (CDRS) and its overall accuracy of identifying the subjects presenting MCI is 97% [13]. It is one of the methods verified as the most highly sensitive in the medical institutions in the community and has been employed by an internet healthy subjects registration system, IROOP™ (Integrated Registry of Orange Plan: Iroop, Kodaira, Tokyo, Japan) aiming at the prevention of the onset of dementia in Japan since last year.

Results
– SAF value as Independent Risk Factor of the Existence of MCI –

The number of the subjects who were evaluated as exhibiting MCI was 18 (7.9%) out of 226 subjects (84 males with an average age of 69 ± 11 and 142 females with an average age of 67 ± 10). The clinical characteristics of subjects showing MCI and showing no MCI were summarized in ***Table 1***. The group showing MCI was significantly older than the group showing no MCI. There were no significant differences in other known dementia risk factors including systolic blood pressure between the two groups. However, the values of sCr, eGFR, BNP, baPWV, THA and SAF of the group showing MCI were significantly higher than those of the group showing no MCI. By univariate analysis, there were significant correlations of

SAF value with the values of age, sCr, eGFR, UACR, BNP, baPWV, and THA (***Table 2***). No significant difference was recognized in education level between the two groups.

The ratio of subjects showing MCI was analyzed using the tertile method by each of six factors. The mobility of MCI was different among the tertile method groups of age, eGFR, BNP, baPWV, THA and SAF (***Fig. 1-a～f***). Furthermore, in order to obtain an SAF cut-off value, a curve analysis of receiver operating characteristic (ROC) regarding the existence of MCI was conducted, and as a result, the highest sensitivity was obtained at SAF value 2.27 and it was employed as a cut-off value. Finally a logistic regression analysis was conducted. As shown in ***Table 3***, even after the adjustments of confounding factors considered to include age, eGFR, BNP, baPWV and THA, SAF value ≧2.27 was significantly related to the existence of MCI (odds ratio 6.402; 95% CI, 1.590 – 25.773, p = 0.009).

Although, there have been multiple reports concerning the significant relationships between SAF value with brain atrophy and cognitive decline in diabetic patients [14, 15], these relationships in the non-diabetic patient group are reported for the first time in our research. However, recent research by Waateringe *et al*. verifies that SAF value is related to some clinical and life-style factors including age, BMI and kidney function in non-diabetic patients [16]. Furthermore, it is clarified that AGEs are formed not only under diabetic conditions, but also under disease conditions including chronic kidney disease associated with high level oxidant stress. Therefore, a higher level of circulation AGEs may possibly cause neurotoxicity through oxidant stress [17]. Putting all of this together, the existence of an important relationship between MCI and SAF in non-diabetic patients that we demonstrated in this research should be further verified.

Conclusion

The recent development of research concerning anti-aging is remarkable. As introduced in this research, it was clarified that SAF value reflecting the accumulation of AGEs in skin tissue can be an independent screening marker of MCI. Although this research is relatively small scaled and further research is required, it is considered that when an abnormal value is recognized in the measurement of SAF during an anti-aging medical checkup, it is necessary to keep following-up with outpatients with risk of onset of dementia in the future being taken into account even if the patient is in a non-diabetic state, and needless to say if the patient is in diabetic state.

Conflict of interest

The authors declare no conflict of interest in this study.

Table 1. Profile of participants.

Index	Unit	MCI	Normal	p value
Number		18	208	-
Age	year	76.5 ± 6.7	67.2 ± 9.9	<0.001
Men	number (%)	9 (50)	75 (37)	0.190
Presently smoking	number (%)	2 (12)	8 (4)	0.189
BMI	kg/m^2	22.9 ± 2.1	22.8 ± 3.0	0.826
SBP	mmHg	124.4 ± 13.3	123.7 ± 14.9	0.843
HbA1c [NGSP]	%	5.9 ± 0.8	5.8 ± 0.6	0.256
sCr	mg/dL	0.84 ± 0.18	0.74 ± 0.16	0.012
eGFR	mL/min/1.73 m^2	59.1 ± 9.5	68.4 ± 11.1	0.002
UACR	mg/gCr	39.2 ± 66.5	24.0 ± 48.7	0.242
LDL-C	mg/dL	119.2 ± 32.6	117.1 ± 29.7	0.779
HDL-C	mg/dL	61.6 ± 11.7	61.9 ± 14.6	0.952
TG	mg/dL	90.2 ± 38.1	97.9 ± 48.5	0.528
hsCRP	mg/L	0.10 ± 0.09	0.08 ± 0.12	0.610
BNP	pg/dL	47.5 ± 27.9	28.8 ± 35.7	0.039
baPWV	cm/s	1770 ± 319	1577 ± 277	0.006
THA	$x10^{-2}cm^2$	24.5 ± 12.2	13.0 ± 7.6	<0.001
SAF		2.56 ± 0.55	2.10 ± 0.41	<0.001

MCI, mild cognitive impairment; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c [NGSP], HbA1c equivalent to the internationally used HbA1c defined by the National Glycohemoglobin Standardization Program; sCr, serum creatinine; eGFR, creatinine-based estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, serum triglyceride; hs-CRP, high sensitivity C-reactive protein; BNP, brain natriuretic peptide; baPWV, brachial ankle pulse wave velocity; SAF, skin autofluorescence; THA, temporal horn area

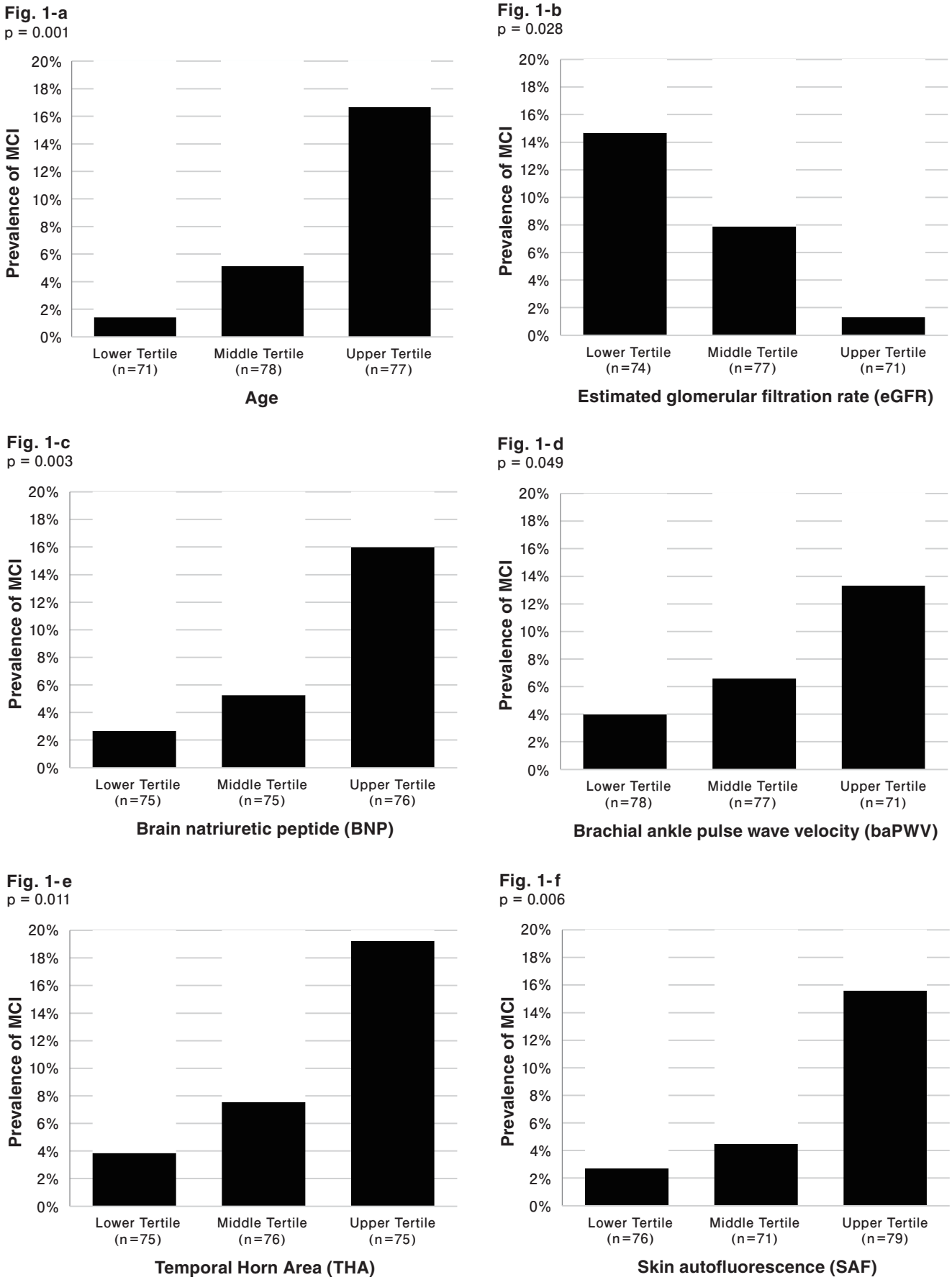

Fig. 1. **Analysis of MCI prevalence by participant's profile index**

a) Age, **b)** eGFR, **c)** BNP, **d)** baPWV, **e)** THA, **f)** SAF. MCI prevalence (%) in the participants is analyzed by each index. In these analyses, there are significantly differences in tertiles by one way analysis of variance (ANOVA). MCI, mild cognitive impairment; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; baPWV, brachial ankle pulse wave velocity; THA, temporal horn area; SAF, skin auto fluorescence.

Table 2. Simple correlation analysis between SAF and MCI-related parameter.

	r	p value
Age	0.423	<0.001
sCr	0.251	0.001
eGFR	−0.255	0.001
BNP	0.290	<0.001
baPWV	0.182	0.017
THA	0.419	<0.001

Pearson' s correlation analysis, n = 226. SAF, skin auto fluorescence; MCI, mild cognitive impairment; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; PR, pulse rate; FBS, fasting blood sugar; IRI, immunoreactive insulin; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, serum triglyceride; sCr, serum creatinine; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio; hs-CRP, high sensitivity C-reactive protein; BNP, brain natriuretic peptide; baPWV, brachial ankle pulse wave velocity

Table 3. Odds ratio of predictor variables regarding to the objective variable "Presence of MCI".

	OR	95% CI	p value
SAF ≥ 2.27	6.402	1.590 – 25.773	0.009
Age	1.116	1.013 – 1.231	0.027
THA	1.059	1.002 – 1.119	0.044

Multivariate logistic regression analysis, n = 226. OR, odds ratio; CI, confident interval; SAF, skin autofluorescence; THA, temporal horn area

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