Asian Journal of Urology (2021) 8, 189–196

Available online at www.sciencedirect.com

ScienceDirect

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

Original Article

Association of advanced glycation end-product accumulation with overactive bladder in community-dwelling elderly: A cross-sectional Sukagawa study

Kenji Omae [a,b,c,d], Noriaki Kurita [b,c,e,*], Sei Takahashi [a,b], Shingo Fukuma [b,f], Yosuke Yamamoto [a], Shunichi Fukuhara [a,b], The Sukagawa Study Group*

[a] *Kyoto University, School of Public Health in the Graduate School of Medicine, Department of Healthcare Epidemiology, Yoshida Konoe-cho, Sakyo-ku, Kyoto, Japan*
[b] *Fukushima Medical University, Center for Innovative Research for Communities and Clinical Excellence, 1 Hikarigaoka, Fukushima City, Fukushima, Japan*
[c] *Fukushima Medical University Hospital, Department of Innovative Research and Education for Clinicians and Trainees, 1 Hikarigaoka, Fukushima City, Fukushima, Japan*
[d] *Tokyo Women's Medical University, Department of Urology, 8-1 Kawada-cho, Shinjuku-ku, Tokyo, Japan*
[e] *Fukushima Medical University, Graduate School of Medicine, Department of Clinical Epidemiology, 1 Hikarigaoka, Fukushima City, Fukushima, Japan*
[f] *Kyoto University, Graduate School of Medicine, Human Health Sciences, Yoshida Konoe-cho, Sakyo-ku, Kyoto, Japan*

Received 1 April 2019; received in revised form 16 December 2019; accepted 31 December 2019
Available online 27 March 2020

KEYWORDS
Advanced glycation end-products;
Elderly;
Overactive bladder;
Skin autofluorescence;

Abstract *Objective:* This study aimed to evaluate the influence of advanced glycation end-product (AGE) accumulation on the prevalence and severity of overactive bladder (OAB) in community-dwelling elderly adults.
Methods: We conducted a cross-sectional study involving 269 Japanese community dwellers aged ≥75 years in 2015. AGE accumulation was non-invasively measured via skin autofluorescence (SAF) values using AGE Reader. The primary and secondary outcomes were the presence and severity of OAB evaluated using the Overactive Bladder Symptom Score (OABSS). Individuals with an urgency score of ≥2 and sum score of ≥3 were considered to have OAB. The

* Corresponding author. Fukushima Medical University, Center for Innovative Research for Communities and Clinical Excellence, 1 Hikarigaoka, Fukushima City, Fukushima, Japan.
E-mail address: kuritanoriaki@gmail.com (N. Kurita).
Peer review under responsibility of Second Military Medical University.
* Other members of the Sukagawa Study Group are listed in the supplementary text.

https://doi.org/10.1016/j.ajur.2020.03.004

Urinary incontinence

associations of SAF with the prevalence and severity of OAB were assessed using logistic and linear regression models, respectively, adjusted for clinically important confounders.
Results: The median age of participants was 78 years. Of 269 participants, 110 (40.9%) were men and 75 (27.9%) had OAB. The median SAF was 2.2 arbitrary units (AUs). Increasing median SAF was observed with increasing age. Multivariable analysis revealed that SAF was not associated with either the likelihood of having OAB (odds ratio per AU = 0.77, 95% confidence interval: 0.37–1.62) or the natural log-transformed OABSS (β per AU = −0.07, 95% confidence interval: −0.26–0.12).
Conclusions: In this study, AGE accumulation, as assessed by SAF, was not associated with the prevalence and severity of OAB in Japanese community-dwelling elderly people aged ≥75 years.

1. Introduction

Aging and age-related diseases such as cardiovascular disease, cancer, and neurodegenerative disorders are prevalent, relevant, and challenging issues in medicine worldwide. A great number of studies have attempted to elucidate the mechanisms of aging and age-related diseases by characterizing their pathophysiology. Although numerous theories of aging have been proposed, the mechanism remains poorly understood [1–3]. In recent years, the roles of advanced glycation end-products (AGEs) have been increasingly discussed in this context.

The formation of AGEs occurs through a non-enzymatic multistep process called the Maillard reaction, in which reducing sugars such as glucose modify nucleotides, lipids, and peptides/proteins to form irreversible chemical modification products [4]. Production of AGEs is increased in hyperglycemic states in diabetic patients, and AGEs accumulate in various organs with age, particularly in long-lived proteins such as lens crystallins and tissue collagen [5]. This can induce cellular and tissue damage, as AGEs can modify proteins directly and generate oxidative stress through interaction with the receptor for AGE (RAGE) [6,7]. Seftel et al. [8] identified AGE accumulation in penis tissues, and suggested a pathophysiologic mechanism for AGE-mediated erectile dysfunction via the upregulation of inducible nitric oxide synthase (NOS) and downregulation of endothelial NOS. Immunohistochemical studies have indicated the presence of AGEs in the bladders of patients who underwent radical cystectomy [5], and Gali et al. [9] demonstrated a positive correlation of serum AGEs with overactive bladder (OAB) in patients with type 2 diabetes mellitus.

The chronic syndrome of OAB is characterized by urgency—with or without urge—urinary incontinence, increased frequency, and nocturia, and is estimated to affect over 400 million people worldwide [10]. Furthermore, OAB is an age-related condition, which therefore poses an increasing health concern in aging societies because it affects many aspects of patients' lives including their sexual, physical, psychological, and social health [11,12]. However, evidence for the association between AGEs and OAB is sparse, especially in non-diabetic people. Hence, we conducted a cross-sectional study to evaluate the association of AGE accumulation with the prevalence and severity of OAB in community-dwelling elderly adults.

2. Patients and methods

2.1. Setting

The Sukagawa Study cohort has been described in detail previously [13]. Briefly, in this cross-sectional study, we recruited residents aged ≥75 years from the central area of Sukagawa City, which is located in the central part of Fukushima Prefecture, Japan. Relatively independent individuals in terms of activities of daily living aged ≥75 years were invited by the local government of Sukagawa City to participate in the health check-up and survey used in this study. We obtained written informed consents from all participants. The Internal Ethics Review Board of Fukushima Medical University School of Medicine approved this study and its protocols, which were performed in accordance with the tenets of the Declaration of Helsinki (registered approval number: 2975).

2.2. Participants

Eligible participants were those aged ≥75 years who were invited to participate in the health check-up. Participants with dementia or with mini-mental state exam (MMSE) scores of ≤23 were excluded from the analysis because of potential underreporting of self-reported outcomes.

2.3. Measurement of advanced glycation end-product accumulation

Skin autofluorescence (SAF), which reflects the amount of AGEs in the body, was measured as the exposure variable using the AGE Reader SU (DiagnOptics Technologies BV, Groningen, Netherlands). Calculation of SAF was performed by taking the average light intensity in the 420–600 nm range, dividing by the average light intensity in the

300–420 nm range, and multiplying by 100, and it was expressed in arbitrary units (AU). Measurement of SAF was carried out on the surface of the lower arm by trained nurses, with the participant in a seated position. The intensity of SAF strongly correlates with individual AGE compounds, such as collagen-linked fluorescence, pentosidine, ε-carboxymethyllysine and ε-carboxyethyllysine, and skin biopsy is the gold standard measurement of tissue accumulation of AGEs [14,15]. The coefficient of variation for individual SAF measurements taken over a few days has been reported to be 5.82% in the Japanese population [16]. Use of the AGE Reader for SAF measurement has been extensively validated, and predictability of various diseases—such as type 2 diabetes and cardiovascular diseases, and death—using SAF has also been established via a number of large observational studies [17–21].

2.4. Outcomes

The primary and secondary outcomes were the presence and severity of OAB, which were evaluated using the Overactive Bladder Symptom Score (OABSS) validated by Homma et al. [22]. The OABSS is a four-item questionnaire on daytime frequency, nighttime frequency, urgency, and urgency incontinence. The total score is the simple sum of the four symptom scores (range, 0–15). Individuals with an urgency score of ≥2 and sum score of ≥3 are considered to have OAB, and a higher score indicates increased severity of OAB. In this study, individuals with a score of ≥1 for each item were considered to have each symptom.

2.5. Statistical analysis

Baseline characteristics are presented using standard descriptive statistics, means and medians (25th and 75th percentiles) for continuous variables, and numbers and percentages for categorical variables. A scatter plot was used to visualize the distribution of age, SAF, and total OABSS. Odds ratios (ORs) and 95% confidence intervals (CIs) for the likelihood of having OAB and the four symptoms were estimated using logistic regression models. In multiple logistic regression models, we adjusted for the following clinically important confounding factors related to both the accumulation of AGEs and OAB: Age, sex, presence of diabetes mellitus (prescription of an antidiabetic drug or HbA1c ≥6.5%, based on National Glycohemoglobin Standardization Program values), hypertension (prescription of an antihypertensive drug or systolic/diastolic blood pressure ≥140/90 mmHg [1 mmHg=0.133 kPa]), and being overweight (body mass index ≥25 kg/m^2), and history of smoking (identified using a self-administered questionnaire). To evaluate the association between SAF and OAB severity using the OABSS as a continuous variable, we employed uni- and multivariable linear regression models. The total OABSS was transformed using the following formula: $yT=\log_e(y+1)$, where y represents an individual's total OABSS and yT is the transformed total OABSS. This transformation assures a linear assumption of our models by making the distribution of the fitted model residuals symmetric and the variation of the residuals constant. To account for individuals with a score of 0, "1" was added. In the multivariable linear regression model, we adjusted for the same covariates as previously mentioned. Subgroup analyses by sex were also carried out because the cause and underlying mechanism of OAB could be different between men and women.

Participants with complete data on both exposure and outcome variables (*i.e.*, SAF and the OABSS) were included in the primary analyses. Markov chain Monte Carlo multiple imputation, with 20 imputations, was used for missing data. A *p*-value of <0.05 was considered statistically significant. Statistical analyses were conducted using STATA version 14 (Stata Corp LP, College Station, TX, USA).

3. Results

3.1. Baseline characteristics

A total of 291 residents participated in the health check-up. After excluding 20 participants with dementia and two with missing SAF or OABSS, 269 participants were included in the primary analyses (Fig. 1).

Baseline characteristics of participants are summarized in Table 1. The median (interquartile range [IQR]) age of the participants was 78 (76, 82) years. Of the 269 participants, 110 (40.9%) were male and 75 (27.9%) had OAB. The median (IQR) SAF was 2.2 (2.0, 2.5) AU. The information on diabetes was missing in 86 (32.0%) participants, and their baseline characteristics are presented in Supplementary Table S1. They were older, more frequently male, with a higher likelihood of being overweight and having a smoking history and higher SAF and total OABSSs.

3.2. Observed results

Scatter plots for age and SAF, and SAF and total OABSS are shown in Fig. 2. As the diagram shows, SAF was positively associated with age (β per year =0.012 AU; 95% CI: 0.0005–0.024). No significant association between SAF and the log-transformed total OABSS was observed (β per AU =0.019; 95% CI:−0.16–0.19) (Table 2).

3.3. Primary outcomes

In the crude analyses, SAF was not associated with either OAB (OR per AU =0.77; 95% CI: 0.37–1.62) or with any of

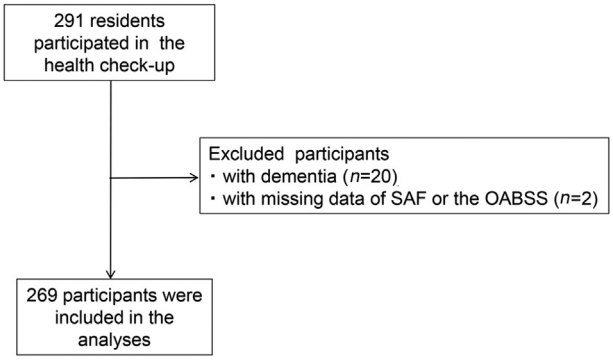

Figure 1 Flowchart of the study participants. OABSS, Overactive Bladder Symptom Score; SAF, skin autofluorescence.

Table 1 Baseline characteristics of the participants.

Characteristics	All participants ($n=269$)	Participants with OAB ($n=75$)	Participants without OAB ($n=194$)	Number of participants with missing data
Age (year)	79.4, 78 (76, 82)	80.1, 79 (77, 83)	79.1, 78 (76, 81)	0
Male sex, %	40.9	46.7	38.7	0
BMI, kg/m^2	22.8, 22.7 (20.3, 25.1)	22.9, 23 (21, 25.6)	22.7, 22.7 (20.2, 24.6)	0
Smoking, %	31.2	41.3	27.3	19
Hypertension, %	36.8	33.3	38.1	0
Diabetes, %	8.6	9.3	8.3	86
Overweight, %	26	33.3	23.2	0
SAF (AU)	2.3, 2.2 (2.0, 2.5)	2.3, 2.3 (1.9, 2.6)	2.3, 2.2 (2.0, 2.5)	0
OABSS				
Total	3.6, 3 (2, 5)	6.9, 7 (5, 8)	2.3, 2 (1, 3)	0
Daytime frequency	0.5, 1 (0, 1)	0.7, 1 (0, 1)	0.5, 0 (0, 1)	0
Nighttime frequency	1.5, 1 (1, 2)	2.0, 2 (1, 3)	1.3, 1 (1, 2)	0
Urgency	1.0, 0 (0, 2)	2.9, 3 (2, 3)	0.2, 0 (0, 0)	0
Urgency incontinence	0.6, 0 (0, 1)	1.4, 1 (0, 3)	0.2, 0 (0, 0)	0

AU, arbitrary unit; BMI, body mass index; OAB, overactive bladder; OABSS, Overactive Bladder Symptom Score; SAF, skin autofluorescence. Continuous variables are presented as mean, median (interquartile range).

the four symptoms in the OABSS: Daytime frequency (OR per AU =0.85; 95% CI: 0.47–1.54), nighttime frequency (OR per AU =1.23; 95% CI: 0.47–3.22), urgency (OR per AU =1.20; 95% CI: 0.66–2.18), or urgency incontinence (OR per AU =0.98; 95% CI: 0.51–1.87) (Table 3).

After adjustment for age, sex, presence of diabetes mellitus, hypertension, overweight, and history of smoking, no significant associations were found between SAF and either OAB (OR per AU =0.77; 95% CI: 0.37–1.62) or any of the four symptoms: Daytime frequency (OR per AU =1.11; 95% CI: 0.57–2.18), nighttime frequency (OR per AU =0.65; 95% CI: 0.21–2.01), urgency (OR per AU =0.86; 95% CI: 0.44–1.68), or urgency incontinence (OR per AU =0.92; 95% CI: 0.44–1.89). Moreover, the analyses showed that participants with diabetes had a lower likelihood of high daytime frequency (OR=0.33; 95% CI: 0.14–0.80); female participants had a lower likelihood of high nighttime frequency (OR=0.08; 95% CI: 0.01–0.43); overweight participants had a higher likelihood of urgency (OR=2.15; 95% CI: 1.20–3.86); and participants with hypertension had a lower likelihood of urgency incontinence (OR=0.49; 95% CI: 0.27–0.90), whereas higher age was associated with higher likelihood of urgency incontinence (OR per year =1.07; 95% CI: 1.00–1.15).

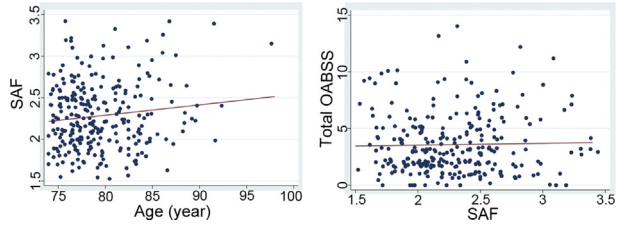

Figure 2 Scatter plots of age and SAF, and SAF and OABSS. OABSS, Overactive Bladder Symptom Score; SAF, skin autofluorescence.

3.4. Secondary outcomes

After adjustment for the covariates described above, no significant association was observed between SAF and the log-transformed total OABSS (β per AU =−0.07; 95% CI:−0.26–0.12), whereas age was positively associated with the log-transformed total OABSS (β per year =0.02; 95% CI: 0.005–0.039). Presence of hypertension was negatively associated with the log-transformed total OABSS (β=−0.18; 95% CI:−0.33–0.036).

The results of the multivariable analysis for participants with complete data ($n=174$) are shown in Tables S2 and S3.

3.5. Subgroup analyses

Figure S1 and Table S4 show scatter plots for SAF and total OABSS and the results of the multivariable analyses evaluating the association between SAF and OAB by sex, respectively. We confirmed no association of SAF with OAB in either men or women.

4. Discussion

4.1. Summary of findings

This cross-sectional study was conducted to evaluate the association between AGE accumulation, assessed by SAF measured using the AGE Reader, and the prevalence and severity of OAB defined using the OABSS in community-dwelling elderly adults. We found no significant association of SAF with either the likelihood of OAB or the total OABSS, irrespective of sex. Furthermore, SAF was not associated with the likelihood of having any of the four main symptoms

of OAB: Daytime frequency, nighttime frequency, urgency, and urgency incontinence.

4.2. Comparison with previous studies and interpretation of results

To the best of our knowledge, there has been only one observational study evaluating the association of AGEs and OAB, in which serum and urinary AGEs were measured and OAB was assessed using both the OAB-q score [23] and urodynamic examination, and this study involved 40 diabetic patients with moderate/severe lower urinary tract symptoms (LUTS) [9]. The authors reported that serum AGEs exhibited a positive correlation with OAB-q score, whereas a negative correlation was found between the score and urinary AGEs. Moreover, increased serum AGEs level was found to be associated with detrusor overactivity in the urodynamic examination. The discrepancies in results between the previous study and ours could be explained by differences not only in the methods for measuring AGEs and OAB, but also in the characteristics of the study participants. Only 8.6% of the participants in our study had diabetes, and the average value of SAF was lower than that among Japanese patients with diabetes [16,24], but similar to that reported in a study involving healthy elderly Japanese individuals (Table 1) [25]. It has been shown that health-conscious people are generally more likely to attend health check-ups [26]. Given this, we speculate that the development of OAB requires a threshold of AGE accumulation, and therefore, we could not determine the effect of AGE accumulation on OAB in a relatively healthy population. On the other hand, positive associations of AGE accumulation with certain age-related conditions have been observed even in the healthy population. For example, in our previous study—conducted in the same setting as the present study—we found that SAF was significantly associated with hearing impairment as measured by the pure-tone average, and that the association of 1 AU of SAF with hearing impairment was equivalent to that of 6 years of actual aging in elderly community-dwellers [13]. These findings suggest that the effect of AGEs on functional decline could differ between organs, and hearing function might deteriorate linearly with AGE accumulation over time, unlike OAB.

4.3. Clinical implications and suggestions for further studies

To the best of our knowledge, this is the first study to assess the association between SAF and OAB in the general elderly population. Therefore, the data presented could provide a helpful reference for future studies. Measurement of SAF using the AGE Reader is non-invasive, simple, and takes only a few minutes. Hence, it is a preferable approach for use with elderly patients. Moreover, it is an objective investigation that can avoid the weaknesses and limitations of other subjective screening tools using questionnaires for OAB. However, our findings suggest that measuring SAF using the AGE Reader might not be a useful screening test for detecting populations at high risk of developing OAB, at least among healthy people. Further studies including a wider range of participants, such as diabetic and non-diabetic patients as well as healthy subjects are required. To confirm our findings and elucidate the molecular biological or neurophysiological mechanisms, future studies should also evaluate the association between the amount of AGE accumulation in bladder tissues measured by assays rather than the AGE Reader and objective LUTS findings in addition to a symptom score [27].

4.4. Strengths and limitations

This study had several limitations. First, given that the definition of OAB used in this study was based on the criteria defined by the Japanese Urological Association, the presence of other urological disorders such as urinary tract infections (UTI) or cancer could not be ruled out. UTIs are common in patients with OAB symptoms [28], particularly females, so symptoms of urgency and frequency may have

Table 2 Association between SAF and the log-transformed total OABSS.

Variables	Log-transformed OABSS	
	Coefficient, median (95% CI)	*p*-Value
Model 2[a]		
SAF, per AU	0.019 (−0.16–0.19)	0.83
Model 4[b]		
SAF, per AU	−0.07 (−0.26–0.12)	0.45
Age, per year	**0.02 (0.005–0.039)**	**0.013**
Female sex (*vs.* male)	−0.13 (−0.34–0.078)	0.22
Overweight, yes (*vs.* no)	0.15 (−0.011–0.31)	0.067
Diabetes, yes (*vs.* no)	0.12 (−0.14–0.39)	0.35
Hypertension, yes (*vs.* no)	**−0.18 (−0.33–−0.036)**	**0.015**
Smoking, yes (*vs.* no)	−0.0005 (−0.22–0.22)	1

AU, arbitrary unit; CI, confidence interval; OABSS, Overactive Bladder Symptom Score; SAF, skin autofluorescence. *p*-Values <0.05 are highlighted with boldface.

[a] Model 3 is used for the crude analysis of SAF via a linear regression model.

[b] Model 4 is used for the multivariate analyses of SAF via linear regression models adjusted for age, sex, presence of diabetes mellitus, hypertension, overweight, and history of smoking.

Table 3 Association between SAF and Overactive Bladder Symptom Score.

Variable	OAB		Daytime frequency		Nighttime frequency		Urgency		Urgency incontinence	
	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Model 1[a]										
SAF, per AU	1.05 (0.55–2.05)	0.86	0.85 (0.47–1.54)	0.59	1.23 (0.47–3.22)	0.67	1.20 (0.66–2.18)	0.56	0.98 (0.51–1.87)	0.95
Model 2[b]										
SAF, per AU	0.77 (0.37–1.62)	0.49	1.11 (0.57–2.18)	0.75	0.65 (0.21–2.01)	0.46	0.86 (0.44–1.68)	0.65	0.92 (0.44–1.89)	0.81
Age, per year	1.07 (1.00–1.14)	0.061	1.02 (0.95–1.08)	0.61	0.94 (0.86–1.04)	0.22	1.06 (1.00–1.13)	0.053	**1.07 (1.00–1.15)**	**0.039**
Female sex (*vs.* male)	1.26 (0.53–2.96)	0.6	1.49 (0.70–3.15)	0.3	**0.08 (0.01–0.43)**	**0.004**	0.62 (0.29–1.32)	0.22	1.55 (0.67–3.57)	0.3
Overweight, yes (*vs.* no)	1.84 (0.99–3.44)	0.056	1.18 (0.66–2.11)	0.58	0.89 (0.35–2.27)	0.8	**2.15 (1.20–3.86)**	**0.01**	1.82 (0.97–3.39)	0.061
Diabetes, yes (*vs.* no)	1.44 (0.53–3.90)	0.47	**0.33 (0.14–0.80)**	**0.014**	3.18 (0.46–21.75)	0.24	1.69 (0.71–3.99)	2.64	2.02 (0.86–4.78)	0.11
Hypertension, yes (*vs.* no)	0.69 (0.38–1.25)	0.22	0.95 (0.56–1.61)	0.85	0.56 (0.24–1.28)	0.17	0.64 (0.37–1.10)	0.11	**0.49 (0.27–0.90)**	**0.02**
Smoking, yes (*vs.* no)	2.37 (1.00–5.60)	0.05	1.12 (0.52–2.44)	0.77	0.37 (0.08–1.72)	0.2	1.04 (0.48–2.25)	0.93	1.09 (0.46–2.59)	0.84

AU, arbitrary unit; CI, confidence interval; OAB, overactive bladder; OR, odds ratio; SAF, skin autofluorescence. *p*-Values <0.05 are highlighted using boldface.

[a] Model 1 was used for the crude analyses of SAF via logistic regression models.

[b] Model 2 was used for the multivariate analyses of skin autofluorescence via logistic regression models adjusted for age, sex, presence of diabetes mellitus, hypertension, and overweight, and history of smoking.

been related to an UTI, and not OAB. If these misclassifications in OAB occur disproportionately by degree of AGE accumulation, there could be a bias in our findings; its direction (namely, overestimation or underestimation) and magnitude are, however, unknown. Moreover, OAB symptoms could be affected by benign prostatic hyperplasia in men, as well as lifestyle and medical treatments, which were not measured in this study. Second, our analysis may have been statistically underpowered to detect significant differences or relationships.

Our study, however, had several strengths. First, the study involved community-dwellers because it is well-demonstrated that most individuals with OAB symptoms are likely to avoid seeking medical treatment [29]. Thus, targeting only those who are treated for OAB in the hospital is insufficient when evaluating the association between clinical factors and OAB symptoms. The prevalence of OAB in this study was similar to that reported in other population-based studies [12,30]. Second, we excluded people with an MMSE score of $\leq$23. Although the OABSS has been psychometrically validated and has demonstrated reliability, discriminant validity, and responsiveness among patients with OAB, including the elderly [22], the score is calculated based on self-reports, and, therefore, could be significantly affected by cognitive function.

5. Conclusion

This study demonstrates that AGE accumulation indicated by SAF measured using the AGE Reader was not associated with the prevalence and severity of OAB, as defined by the OABSS, among Japanese community-dwelling elderly individuals. Our findings suggest that measuring SAF might not be a useful screening test for detecting populations at high risk of developing OAB, at least among healthy people. External validation studies which include well-defined subjects other than healthy people, such as patients with metabolic syndrome and/or diabetes, and exclude those who have UTI are warranted.

Author contributions

Study concept and design: Kenji Omae, Noriaki Kurita, Sei Takahashi.
Acquisition of the data: Kenji Omae, Sei Takahashi, the Sukagawa Study Group.
Analysis and interpretation: Kenji Omae, Noriaki Kurita, Sei Takahashi, Yosuke Yamamoto, Shunichi Fukuhara, the Sukagawa Study Group.
Drafting the manuscript: Kenji Omae, Noriaki Kurita.
Critical revision of the manuscript for important intellectual content: Noriaki Kurita, Shingo Fukuma, Yosuke Yamamoto, Shunichi Fukuhara.
Final approval of the manuscript: Kenji Omae, Noriaki Kurita, Sei Takahashi, Shingo Fukuma, Yosuke Yamamoto, Shunichi Fukuhara, the Sukagawa Study Group.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgements

We thank the participants of the Sukagawa study, the government officers in the Department of Healthcare and Welfare, Sukagawa City who conducted the health checkups. Full details of these members are provided in the Supplemental Text S1. We also thank Naoaki Yamaga for technical support, and Editage for English language editing. Preliminary results of the present study were presented at the 47th Annual Meeting of International Continence Society, Florence, Italy, September, 2017.This work was supported by a Japan Society for the Promotion of Science Grant-in-Aid for Scientific Research (KAKENHI) [Grant No. JP18K09975].

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajur.2020.03.004

References

[1] Viña J, Borrás C, Miquel J. Theories of ageing. IUBMB Life 2007;59:249—54.
[2] Harman D. The free radical theory of aging. Antioxidants Redox Signal 2003;5:557—61.
[3] Medvedev ZA. An attempt at a rational classification of theories of ageing. Biol Rev Camb Phil Soc 1990;65:375—98.
[4] Ahmed N. Advanced glycation endproducts-role in pathology of diabetic complications. Diabetes Res Clin Pract 2005;67:3—21.
[5] Matsumoto K, Fujiwara Y, Nagai R, Yoshida M. Immunohistochemical detection of advanced glycation end products in human bladder with specific monoclonal antibody. Int J Urol 2009;16:402—5.
[6] Chaudhuri J, Bains Y, Guha S, Kahn A, Hall D, Bose N, et al. The role of advanced glycation end products in aging and metabolic diseases: bridging association and causality. Cell Metabol 2008;4:337—52.
[7] Nedić O, Rattan SI, Grune T, Trougakos IP. Molecular effects of advanced glycation end products on cell signalling pathways, ageing and pathophysiology. Free Radic Res 2013;47:28—38.
[8] Seftel AD, Vaziri D, Ni Z, Razmjouei K, Fogarty J, Hampel N, et al. Advanced glycation end products in human penis: elevation in diabetic tissue, site of deposition, and possible effect through iNOS or eNOS. Urology 1997;50:1016—26.
[9] Galì A, Mucciardi G, Butticè S, Subba E, D'Amico C, Lembo F, et al. Correlation between advanced glycation end-products, lower urinary tract symptoms and bladder dysfunctions in patients with type 2 diabetes mellitus. LUTS 2017;9:15—20.
[10] Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al. The standardisation of terminology in lower urinary tract function: report from the standardization sub-committee of the international continence society. Urology 2003;61:37—49.
[11] Irwin DE, Kopp ZS, Agatep B, Milsom I, Abrams P. Worldwide prevalence estimates of lower urinary tract symptoms, overactive bladder, urinary incontinence and bladder outlet obstruction. BJU Int 2011;108:1132—8.
[12] Coyne KS, Sexton CC, Irwin DE, Kopp ZS, Kelleher CJ, Milsom I. The impact of overactive bladder, incontinence and other lower urinary tract symptoms on quality of life, work productivity, sexuality and emotional well-being in men and women: results from the EPIC study. BJU Int 2008;101:1388—95.
[13] Niihata K, Takahashi S, Kurita N, Yajima N, Omae K, Fukuma S, et al. Association between accumulation of advanced glycation end-products and hearing impairment in community-dwelling older people: a cross-sectional Sukagawa study. J Am Med Dir Assoc 2007;19:235—9.
[14] den Dekker MA, Zwiers M, van den Heuvel ER, de Vos LC, Smit AJ, Zeebregts CJ, et al. Skin autofluorescence, a non-invasive marker for AGE accumulation, is associated with the degree of atherosclerosis. PloS One 2013;8:e83084. https://doi.org/10.1371/journal.pone.0083084.
[15] Genuth S, Sun W, Cleary P, Gao X, Sell DR, Lachin J, et al. Skin advanced glycation end products glucosepane and methylglyoxal hydroimidazolone are independently associated with long-term microvascular complication progression of type 1 diabetes. Diabetes 2015;64:266—78.
[16] Hangai M, Takebe N, Honma H, Sasaki A, Chida A, Nakano R, et al. Association of advanced glycation end products with coronary artery calcification in Japanese subjects with type 2 diabetes as assessed by skin autofluorescence. J Atherosclerosis Thromb 2016;23:1178—87.
[17] Lutgers HL, Graaff R, Links TP, Ubink-Veltmaat LJ, Bilo HJ, Gans RO, et al. Skin autofluorescence as a noninvasive marker of vascular damage in patients with type 2 diabetes. Diabetes Care 2006;29:2654—9.
[18] Ueno H, Koyama H, Tanaka S, Fukumoto S, Shinohara K, Shoji T, et al. Skin autofluorescence, a marker for advanced glycation end product accumulation, is associated with arterial stiffness in patients with end-stage renal disease. Metabolism 2008;57:1452—7.
[19] Meerwaldt R, Hartog JW, Graaff R, Huisman RJ, Links TP, den Hollander NC, et al. Skin autofluorescence, a measure of cumulative metabolic stress and advanced glycation end products, predicts mortality in hemodialysis patients. J Am Soc Nephrol 2005;16:3687—93.
[20] Yamagishi S, Fukami K, Matsui T. Evaluation of tissue accumulation levels of advanced glycation end products by skin autofluorescence: a novel marker of vascular complications in high-risk patients for cardiovascular disease. Int J Cardiol 2015;185:263—8.
[21] van Waateringe RP, Fokkens BT, Slagter SN, van der Klauw MM, van Vliet-Ostaptchouk JV, Graaff R, et al. Skin autofluorescence predicts incident type 2 diabetes, cardiovascular disease and mortality in the general population. Diabetologia 2019;62:269—80.
[22] Homma Y, Yoshida M, Seki N, Yokoyama O, Kakizaki H, Gotoh M, et al. Symptom assessment tool for overactive bladder syndrome—overactive bladder symptom score. Urology 2006;68:318—23.
[23] Coyne K, Revicki D, Hunt T, Corey R, Stewart W, Bentkover J, et al. Psychometric validation of an overactive bladder symptom and health-related quality of life questionnaire: the OAB-q. Qual Life Res 2002;11:563—74.
[24] Mori H, Kuroda A, Araki M, Suzuki R, Taniguchi S, Tamaki M, et al. Advanced glycation end-products are a risk for muscle weakness in Japanese patients with type 1 diabetes. J Diabetes Investig 2017;8:377—82.
[25] Isami F, West BJ, Nakajima S, Yamagishi SI. Association of advanced glycation end products, evaluated by skin autofluorescence, with lifestyle habits in a general Japanese population. J Int Med Res 2018;46:1043—51.
[26] Ikeda Y, Nakagawa H, Ohmori-Matsuda K, Hozawa A, Masamune Y, Nishino Y, et al. Risk factors for overactive bladder in the elderly population: a community-based

study with face-to-face interview. Int J Urol 2011;18:212—8.
[27] Digesu GA, Khullar V, Cardozo L, Salvatore S. Overactive bladder symptoms: do we need urodynamics? Neurol Urodyna 2003;22:105—8.
[28] Hessdoerfer E, Jundt K, Peschers U. Is a dipstick test sufficient to exclude urinary tract infection in women with overactive bladder? Int Urogynecol J 2011;2:229—32.
[29] Honma Y, Yamaguchi O, Hayashi K, Members of the Neurogenic Bladder Society Committee. Epidemiologic survey of lower urinary tract symptoms in Japan. Urology 2006;68:560—4.
[30] Milsom I, Abrams P, Cardozo L, Roberts RG, Thuroff J, Wein AJ. How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. BJU Int 2001;87:760—6.