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Relationship between locomotive syndrome and advanced glycation end products measured by skin autofluorescence in community-dwelling patients: the Yakumo Study

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ABSTRACT

Advanced glycation end products (AGEs) have been reported to be associated with osteoporosis, aging, sarcopenia, and frailty. This study aimed to investigate the association AGEs with locomotive syndrome (LS). Participants were Japanese individuals aged 39 years or older who participated in the Yakumo Study (n=230). AGEs were measured by skin autofluorescence (SAF) using an AGE reader. We investigated SAF values for each locomotive stage. Multivariate logistic regression models were used to calculate the odds ratios of LS-associated factors. The relationships between SAF and physical performance and bone mineral density (BMD) were investigated. A receiver operating characteristic (ROC) curves were generated to determine the optimal cut-off value of SAF for predicting LS. SAF values tended to increase correspondingly with LS severity. SAF was an independently explanatory factor for LS (odds ratio 2.70; 95% confidence interval [CI] 1.040–6.990). SAF was positively correlated with the 10-m walking speed, The Timed Up and Go test results, and was negatively correlated with BMD. ROC curve represented by SAF for the presence or absence of LS risk had an area under the curve of 0.648 (95% CI: 0.571–0.726). High SAF values were identified as an independent risk factor for LS. AGEs could be a potential screening tool for people for LS.

Keywords: locomotive syndrome, advanced glycation end products, skin autofluorescence, the Yakumo Study, bone mineral density

Abbreviations:
LS: locomotive syndrome
AGEs: advanced glycation end products
SAF: skin autofluorescence
GLFS-25: the 25-question Geriatric Locomotive Function Scale
ROC: receiver operating characteristic

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INTRODUCTION

Locomotive syndrome (LS) was proposed by the Japanese Orthopaedic Association in 2007. LS is defined as the risk of needing nursing care because of reduced mobility due to musculoskeletal disorders.[1] Worsening LS affects the quality of life and activities of daily living.[2] LS is diagnosed using the two-step test, stand-up test, and the 25-question Geriatric Locomotive Function Scale (GLFS-25).[3] However, LS diagnosis can be challenging in general medical practice owing to time and space constraints when conducting the three tests. Several biomarkers are being investigated to facilitate the diagnosis of LS such as insulin-like growth factor 1,[4] ratio of HbA1c value to albumin,[5] ratio of human nonmercaptalbumin to human mercaptalbumin,[6] and miRNA-199.[7] However, the measurement requires special blood sampling and specific calculations.[4-7] A simpler screening test is necessary to diagnose LS.

Advanced glycation end products (AGEs) are irreversible molecular adducts formed by the nongenetic reaction of reducing sugars, such as fructose and glucose, with proteins and lipids in a series of complex reactions accelerated by heat, as first described by Louis Camille Maillard in 1912.[8,9] AGEs can form crosslinks between collagen fibres in intramuscular connective tissues, causing muscle rigidity and loss of elasticity. Skin autofluorescence (SAF) is a reliable method for reproducible estimation of tissue AGEs and can be measured using an AGE reader. This device can noninvasively measure SAF in just 30 s, making it both convenient and portable (Fig. 1). AGEs have been reported to be associated with sarcopenia and frailty.[10-13] Furthermore, it's worth noting that SAF is also associated with conditions such as diabetic retinopathy, depression, and carotid artery stenosis.[14-16] There are few reports on the relationship between AGEs and LS.

We hypothesised that AGEs would be associated with LS. Therefore, the aim of this study in community-dwelling Japanese were 1) to determine the association between SAF and LS, 2) to investigate the association between SAF and physical performance, and 3) to investigate whether SAF can be used as a diagnosis tool for LS.

MATERIALS AND METHODS

This cross-sectional study used data from the Yakumo Study, which was conducted in 2022

Fig. 1 Measurement of SAF by AGE reader
The measurement can be done quickly in 30 seconds by placing the forearm on it.
SAF: skin autofluorescence
AGE: advanced glycation end product

in Yakumo Town (with a population of 15,132 in 2021). The Yakumo Study has been conducted annually since 1982 and includes subjective orthopaedic and physical function assessments, medical examinations, and psychological evaluations. The participants were Japanese individuals aged 39 years or older who participated in the Yakumo Study. The study protocol was approved by the Nagoya University's Human Research Ethics Committee and Clinical Trials Review Committee, and all procedures were performed in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all the participants in the study.

Study participants

In August 2022, 407 participants participated in the Yakumo Study. Among them, those who declined to participate in this study had a severe disability in walking, did not undergo the orthopedic examinations, and did not answer the GLFS-25. A total of 230 patients (97 males and 133 females) were included in the study.

Definition of LS

LS was diagnosed using the three tests introduced by the Japanese Orthopaedic Association: the stand-up test, two-step test, and GLFS-25 (Supplemental Table 1 and Table 2).[3] Based on the clinical criteria proposed by the Japanese Orthopaedic Association, the participants were classified into LS stages 0, 1, 2, and 3.

In the stand-up test, a physical therapist measured the patient's ability to stand up on one or both feet from stools at heights of 40, 30, 20, and 10 cm. Difficulty was defined as 40 < 30 < 20 < 10 cm using both feet, and < 40 < 30 < 20 < 10 cm using one foot (Fig. 2). As indicated in Supplemental Table 2, performance was allocated a score of 0 to 8. Scores of 4 or 3 were classified as LS1, 2 as LS2, and 0 or 1 as LS3.

Fig. 2 Stand-up test for LS

LS: locomotive syndrome

In the two-step test, the physical therapist measured the length of the two steps from the starting line to toe position. The scores were calculated by normalizing the maximum length of the two steps by the height. Scores <1.3, <1.1, and <0.9 were defined as LS stages 1, 2, and 3, respectively.[17]

The GLFS-25 is a self-reported questionnaire with a total score ranging from 0 (no symptoms) to 100 (most severe symptoms). The scale consists of four questions on pain, 16 questions on Activities of Daily Living, three questions on social functioning, and two questions on mental health. Each item is graded from no disability (0 points) to severe disability (4 points). Total scores between 7 and less than 16 points are defined as LS Stage 1, scores between 16 and less than 24 points are defined as LS Stage 2, and scores equal to or greater than 24 points are defined as LS Stage 3.

Skin autofluorescence

SAF was measured using an AGE reader (Diagnoptics Technologies B.V., Groningen, Netherlands). This noninvasive method takes advantage of the characteristic fluorescent properties of AGEs and has been validated with specific AGE measurements in skin biopsies.[18] The AGE reader irradiates ultraviolet A with an excitation peak of 370 nm onto a skin surface of approximately 4 cm^2 protected from external light. The emitted light (λem: 420–600 nm) from the skin and the reflected excitation light (wavelength: 300–420 nm) are measured. SAF is calculated as the ratio of emitted light to reflected excitation light, multiplied by 100 and expressed in arbitrary units. Measurements are made in approximately 30 seconds by placing the inner forearm on a table (Fig. 1).

Physical performance

We conducted the 10-m walking, Timed Up and Go (TUG) and back muscle test as a physical performance test. The 10-m walking speed was measured for each participant as the time taken to walk at the fastest possible pace. Each participant performed the test twice at the maximum pace, and the average value was used in the analysis.[19] The TUG test measures the time taken by a participant to get up from a standard chair (46 cm seat height) and walk 3 m. The average of the two tests was used for the analysis.[20] Back muscle strength was measured from the maximum isometric strength of the trunk muscles in a standing posture with 30° lumbar flexion, using a back muscle strength meter (T.K.K.5002; Takei Co, Japan).[20]

Measurement of bone status parameters

We used the quantitative ultrasound methods to assess the monitoring of osteoporosis. The quantitative ultrasound system (model A-1000 Plus II; Lunar, Madison, WI, USA) can measure bone status parameters in the calcaneus of the independent foot.[21] Stiffness (automatically calculated from broadband ultrasound attenuation and sound speed), T-score, percentage young adult mean, Z-score, and percentage age-matched values were recorded using a standard protocol provided by the manufacturer. The accuracy of the T-scores had a coefficient variation of ± 2%.

Statistical analyses

The Jonckheere-Terpstra test was used to test the trend of SAF in LS stages. LS stage 1 or higher was defined as the locomotive group (LG) and LS stage 0 was defined as the non-locomotive group (NLG). Comparisons were made for age, gender, height, weight, body mass index, skeletal mass index, SAF, and percentage of lifestyle-related diseases in both groups. Comparisons between LG and NLG were made using the chi-square test and Student's t-test. Factors associated with LS were evaluated using a multivariate logistic regression analysis for

items with a p-value less than 0.1. A receiver operating characteristic (ROC) curve was created to determine the optimal SAF cut-off value for predicting LS. All values were expressed as means ± standard deviations. The correlation between the SAF and physical performance for normally distributed data was assessed using Pearson's correlation test. For all analyses, statistical significance was set at $P < 0.05$. All statistical analyses were performed using EZR software (Saitama Medical Center, Jichi Medical University, Japan).[22]

RESULTS

There were 72 patients with LS stage0, 129 with LS stage 1, 21 with LS stage 2, and 8 with LS stage 3. SAF increased significantly with LS stage progression (Fig. 3). There were 158 patients in the LG group and 72 in the NLSG group. The LG group was significantly older than the NLSG group ($p<0.001$) and had greater weight and BMI ($p=0.009$). No significant differences were found in age, BMI, or percentage of lifestyle-related diseases. SAF was significantly higher in the significant LSG (2.19 ± 0.39) than in the NLSG (2.01 ± 0.34; Table 1). The results of logistic regression analysis adjusted for age, sex, and skeletal mass index (SMI) showed that SAF was an independently explanatory factor for LS after adjustment (odds ratio, 2.70; 95% CI 1.040-6.990; Table 2).

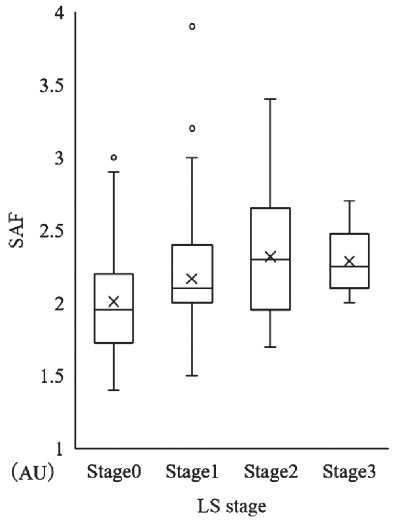

Fig. 3 LS stage and SAF trends (the Jonckheere-Terpstra test)
SAF increased significantly with LS stage progression ($p<0.001$).
LS: locomotive syndrome
SAF: skin autofluorescence
AU: arbitrary units

Table 1 Patient demographics

	LG (n=158)	NLSG (n=72)	p
Male/Female no. (%)	64 (41)/94 (59)	33 (46)/39 (54)	0.474
Age, mean index ± SD years (range)	66.8 ± 10.6	61.3 ± 11.5	<0.001
Height, mean index ± SD cm	159.8 ± 12.7	159.6 ± 8.3	0.818
Weight, mean index ± SD kg	60.8 ± 12.0	57.4 ± 11.6	0.035
Body mass index, mean index ± SD kg/m^2	23.8 ± 4.0	22.4 ± 3.4	0.009
SAF, mean index ± SD AU	2.19 ± 0.39	2.01 ± 0.34	0.009
Skeletal mass index ± SD kg/m^2	6.82 ± 1.01	6.63 ± 1.08	0.204
Skeletal mass index (Male) ± SD kg/m^2	7.65 ± 0.78	7.47 ± 0.79	0.288
Skeletal mass index (Female) ± SD kg/m^2	6.26 ± 0.73	5.92 ± 0.73	0.018
Hypertension (present/absent) no. (%)	96 (61)/62 (39)	19 (26)/53 (74)	0.074
Diabetes mellitus (present/absent) no. (%)	9 (6)/149 (94)	2 (3)/70 (97)	0.510
Hyperlipidemia (present/absent) no. (%)	24 (15)/134 (85)	9 (12)/63 (88)	0.687

LG: locomotive group (locomotive stage (LS) 1, 2 or 3)
NLSG: non-locomotive group (LS 0)
SAF: skin autofluorescence
SD: standard deviation
AU: arbitrary units

Table 2 The multivariate logistic regression model for predicting locomotive syndrome

	Odds ratio	95% CI	p value
Age (years)	1.03	1.000–1.070	0.044
Sex (female)	1.81	0.971–3.360	0.567
Body mass index	1.10	1.011–1.190	0.027
SAF	2.70	1.040–6.990	0.041
Hypertension	1.17	0.579–1.170	0.665

95%CI: 95% confidence intervals
SAF: skin autofluorescence

SAF was positively correlated with the 10-m walking speed, TUG test, and negatively correlated with bone status parameters. In contrast, SAF was not correlated with back muscle strength (Fig. 4).

The ROC curve represented by SAF for the presence or absence of LS had an area under the curve value of 0.648 (95% CI: 0.571-0.726). SAF threshold was 2.000 (sensitivity, 0.772 and specificity 0.500; Fig. 5). Table 3 shows the sensitivity and specificity for LS for SAF value.

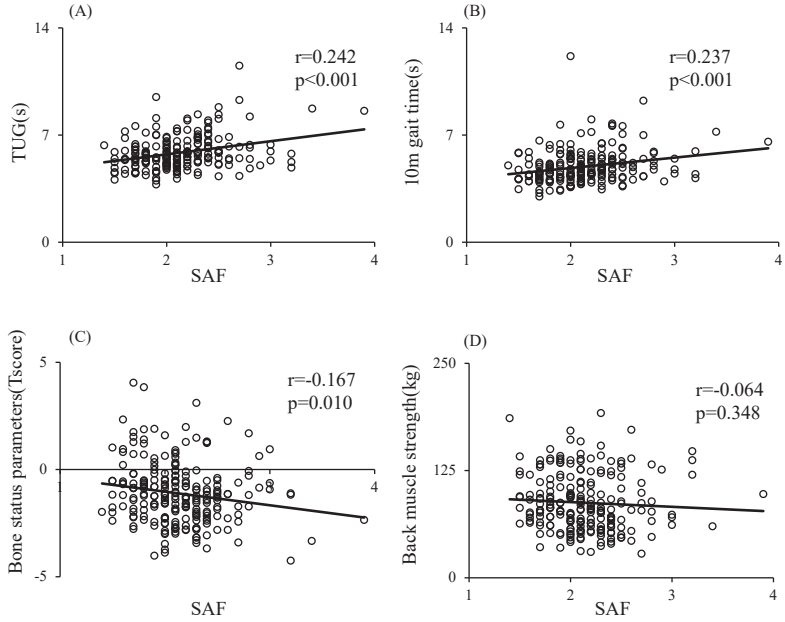

Fig. 4 Pearson's correlation test

Fig. 4A: Correlation between SAF and TUG.
Fig. 4B: Ten-meter gait time.
Fig. 4C: Bone status parameters.
Fig. 4D: Back muscle strength.
SAF: skin autofluorescence
TUG: Timed Up and Go

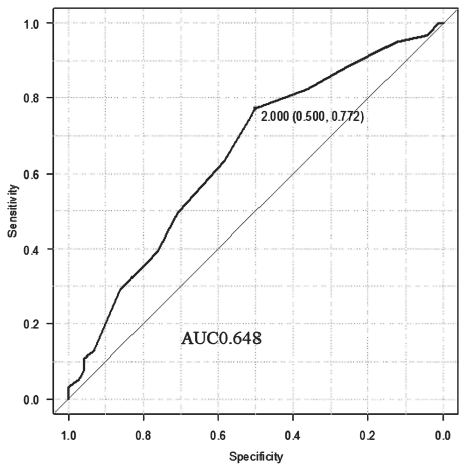

Fig. 5 ROC curve of SAF values to indicate the risk of locomotive syndrome
The area under the ROC curve was 0.648. The cut-off value is 2.0 with a sensitivity of 0.772 and specificity of 0.500.
ROC: receiver operating characteristic
SAF: skin autofluorescence
AUC: area under the curve

Table 3 ROC analysis of SAF to determine the optimal cut-off values for identifying locomotive syndrome

Cut-off of SAF, AU	Sensitivity, %	Specificity, %	AUC (95% CI)
1.8	25.0	88.6	0.648 (0.571-0.726)
1.9	36.1	82.3	
2.0	50.0	77.2	
2.1	58.3	63.3	
2.2	70.1	49.4	
2.3	76.4	39.2	

ROC: receiver operatorating characteristic
SAF: skin autofluorescence,
95%CI: 95% confidence intervals
AU: arbitrary units
AUC: area under the curve

DISCUSSION

We demonstrated that 1) SAF was an independent factor associated with LS and SAF tended to increase correspondingly with LS stage. 2) SAF showed a positive correlation with the 10-m walking speed and TUG test, while not correlated with back muscle strength. SAF was weakly negatively correlated with bone mineral density. 3) The area under the ROC curve was 0.648 (95% CI: 0.571-0.726).

In previous reports, the prevalence of LS in patients ranged 33.4-86.4%.[23,24] Meanwhile, our study, which included patients aged 39 years and older, found a similar prevalence 68.9% of LS.

LS is characterised by age-related loss of motor function, which is closely related to age-related changes such as bone loss, muscle atrophy, and osteoarthritis.[25] Increased SAF levels have been associated with an increased prevalence of osteoarthritis.[26] In chondrocytes, AGEs have been found to enhance the expression and enzymatic activity of matrix metalloproteinases and a disintegrin and metalloproteinase with thrombospondin motifs, resulting in decreased type II collagen production.[27] Because AGEs are closely related to these changes, it is reasonable to assume that there is a strong association between AGEs and LS.

SAF demonstrated a positive correlation with both 10-m walking speed and TUG test. Negative correlations between SAF and grip strength, quadriceps muscle strength, and hip abductor muscle strength have been previously reported.[28] However, in the present study, we did not observe a correlation between SAF and back muscle strength. Trunk muscles have a low correlation with age-related changes and are less affected by LS,[29] potentially explaining their resistance to muscle weakness caused by AGE accumulation. Notably, the AGE reader used in this study measured AGEs in the forearm skin, which may account for its correlation with grip strength but not back muscle strength.

SAF was very weakly negatively correlated with bone mineral density. In osteogenesis, AGEs inhibit osteogenic differentiation of mesenchymal stem cells and promote bone resorption by osteoclasts.[30,31] The cross-linking of AGEs within collagen fibres is generally believed to lead to the deterioration of the biological and mechanical functions of bones.[32] AGE formation occurred in the bone of patients with postmenopausal osteoporosis.[33] AGE may contribute to bone loss due to the remodelling imbalances seen in osteoporosis.[34]

The area under the ROC curve was 0.648 (95% CI: 0.571-0.726) in our study. Current

biomarkers of LS comprising insulin-like growth factor 1, ratio of human nonmercaptalbumin to human mercaptalbumin, and microRNA require blood sampling. Insulin-like growth factor 1 fluctuates diurnally and requires fasting.[35] Ratio of human nonmercaptalbumin to human mercaptalbumin and microRNAs are also difficult to test in general hospitals and unsuitable for screening.[6,7] Unlike conventional biomarkers,[4-7] SAF can be measured noninvasively and quickly, making it a useful biomarker for LS. The ROC curve represented by the SAF for the presence or absence of LS risk is that the area under the curve was not so high, with a value of 0.648. SAF values are not a definitive diagnosis of LS, but are considered only as a convenient screening. Due to the ease and simplicity of SAF measurement, it can be readily incorporated into routine screenings at general healthcare facilities and wellness center. Much like blood pressure checks, conducting SAF measurements as part of regular health assessments can make it more accessible to older adults and those involved in their care. This approach has the potential to enhance the early detection and prevention of LS, benefiting individual health management.

Our study had several limitations that should be considered when interpreting the results. First, the cross-sectional design of the study did not allow for conclusions about causality between SAF and LS. Second, the sample size was relatively small. We plan to investigate whether LS progresses longitudinally in participants with a high or low SAF.

Finally, a notable strength of this study lies in its potential to reduce the cumbersome tests currently used for evaluating locomotive syndrome. When compared to the stand-up test, the two-step test, or the GLFS-25, SAF can be easily measured, making it a more suitable option for screening purposes.

CONCLUSIONS

High SAF values were identified as an independent risk factor for LS. AGEs could be a potential screening tool for people with LS.

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CONFLICT OF INTEREST

There are no conflicts of interest among the authors.

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Not applicable.

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SUPPLEMENTARY INFORMATION

Supplemental Table 1

The 25-question Geriatric Locomotive Function Scale (GLFS-25)
Pain
1. Did you have any pain (including numbness) in your neck or upper limbs?
2. Did you have any pain in your back, lower back or buttocks?
3. Did you have any pain (including numbness) in your lower limbs?
4. To what extent has it been painful to move your body in daily life?
ADL
5. To what extent has it been difficult to get up from a bed or lie down?
6. To what extent has it been difficult to stand up from a chair?
7. To what extent has it been difficult to walk inside the house?
8. To what extent has it been difficult to put on and take off shirts?
9. To what extent has it been difficult to put on and take off trousers and pants?
10. To what extent has it been difficult to use the toilet?
11. To what extent has it been difficult to wash your body in the bath?
12. To what extent has it been difficult to go up and down stairs?
13. To what extent has it been difficult to walk briskly?
14. To what extent has it been difficult to keep yourself neat?
15. How far can you keep walking without rest? 0 = 2–3 km; 1 = 1 km; 2 = 300 m; 3 = 100 m; 4 = 10 m
16. To what extent has it been difficult to go out to visit neighbors?
17. To what extent has it been difficult to carry objects weighing 2 kg?
18. To what extent has it been difficult to go out using public transportation?
19. To what extent have simple tasks and housework been difficult?
20. To what extent have load-bearing tasks and housework been difficult?
21. To what extent has it been difficult to perform sports activities?
22. Have you been restricted from meeting your friends?
23. Have you been restricted from joining social activities?
24. Have you ever felt anxious about falls in your house?
25. Have you ever felt anxious about being unable to walk in the future?

Supplemental Table 2 Scoring system of stand-up test

Height	Two-leg stand					One-leg stand			
	Fail at 40 cm	40cm	30cm	20cm	10cm	40cm	30cm	20cm	10cm
Score	0	1	2	3	4	5	6	7	8