Relationship Between Locomotive Syndrome And Advanced Glycation End Products: The Yakumo Study

Yuto Ozawa, Yasuhiko Takegami, Shiro Imagama
Department of Orthopedic Surgery, Nagoya University Graduate School of Medicine, Nagoya, Aichi, Japan
Email of Presenting Author: ozawayuuto2000@yahoo.co.jp

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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. Worsening LS affects the quality of life and activities of daily living. LS is diagnosed using the two-step test, stand-up test, and the 25-question Geriatric Locomotive Function Scale (GLFS-25). 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, ratio of HbA1c value to albumin, ratio of human nonmercaptalbumin to human mercaptalbumin, and miRNA-199. However, the measurement requires special blood sampling and specific calculations. 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. 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. AGEs have been reported to be associated with sarcopenia and frailty. 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.

METHODS: 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.

RESULTS: SAF increased significantly with LS stage progression. SAF was significantly higher in the significant LSG (2.19 ± 0.39) than in the NLSG (2.01 ± 0.34). (Table1) SAF was an independently explanatory factor for LS after adjustment [Odds ratio, 2.70;95% CI 1.040-6.990]. (Table2) 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. 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). (Table3)

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). 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. Increased SAF levels have been associated with an increased prevalence of osteoarthritis. 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. 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. 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, 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. The cross-linking of AGEs within collagen fibres is generally believed to lead to the deterioration of the biological and mechanical functions of bones. AGE formation occurred in the bone of patients with postmenopausal osteoporosis. AGE may contribute to bone loss due to the remodelling imbalances seen in osteoporosis. 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. Ratio of human nonmercaptalbumin to human mercaptalbumin and microRNAs are also difficult to test in general hospitals and unsuitable for screening. Unlike conventional biomarkers, 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. In screening for LS, SAF is very useful because it can be measured quickly, easily, and anywhere by anyone. 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.

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

Table

Table1 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/m2	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/m2	6.82 ± 1.01	6.63 ± 1.08	0.204
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

Table2 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

Table3 ROC analysis of SAF to determine the optimal cut-off values for identifying locomotive syndrom

Cut-off of SAF, AU	Sensitivity, %	Specificity, %	AUC (95% CI)
1.8	25.0	88.6	
1.9	36.1	82.3	
2.0	50.0	77.2	0.648 (0.571-0.
2.1	58.3	63.3	
2.2	70.1	49.4	
2.3	76.4	39.2	