Insulin Resistance as a Risk Factor for Flavum Hypertrophy in Lumbar Spinal Stenosis

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Abstract:

Introduction: Ligamentum flavum (LF) hypertrophy is the main etiological factor in the development of lumbar spinal stenosis (LSS); however, its molecular pathology remains unclear. Histologically, LF hypertrophy is characterized by a reduction in elastic fibers and an increase in collagen fibers. We previously performed miRNA transcriptomic analysis on excised LF from elderly patients with LSS and identified the insulin receptor signaling along with TGFβ-mediated signaling as pathways involved in ligament hypertrophy. Therefore, this study aimed to investigate the involvement of endogenous insulin as a risk factor for LF hypertrophy in patients with LSS.

Methods: A total of 1,119 patients aged ≥65 years (average: 76.1±5.9 years) treated for LSS including surgery and conservative treatment were analyzed. The flavum canal ratio (FCR) was calculated in the MRI cross-sectional image, and an FCR of 0.4275 or greater was defined as ligamentous stenosis according to Sakai's criteria. Homeostatic model assessment for insulin resistance (HOMA-IR) was calculated and values ≥2.5 were indicative of insulin resistance in Japanese people.

Results: Fifty-one percent of patients with LSS exhibited LF hypertrophy, correlating with higher age, proportion of males and diabetic patients, BMI, HOMA-IR, and creatinine. Among LSS patients, 43.0% had insulin resistance, with 47.1% exhibiting LF hypertrophy and 38.6% without LF hypertrophy, with a significant difference ($p<0.01$). LSS patients with high insulin resistance also demonstrated significantly higher FCR ($p<0.05$) and a higher percentage of LF hypertrophy ($p<0.01$). Conditional logistic regression analysis, adjusting for age, identified HOMA-IR as a significant factor.

Conclusions: The study establishes an association between LF hypertrophy and insulin resistance. Considering LF hypertrophy as an inflammation-triggered degeneration of elastic fibers, age-related changes in LF may underlie the basis of inflammatory aging.

Keywords:

Lumbar spinal stenosis, Ligamentum flavum, Insulin resistance, Pathology

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Introduction

Lumbar spinal stenosis (LSS) is as a degenerative condition of the lumbar spine. It is typically observed in older adults. Its primary manifestation includes pain and/or numbness stemming from neuropathic lesions in the lower limbs, often leading to decreased activity of daily living (ADL) and gait disturbance due to intermittent claudication. LSS pathology involves degenerative changes in the hypertrophy at the facet joint and ligamentum flavum (LF), wherein the spinal canal becomes narrow, and this irreversible change often requires surgical intervention. The thickness of the LF stands as the principal etiological factor in the development of LSS, first reported by Elsberg in 1913[1)]. Despite numerous research endeavors on the pathophysiology of LF hypertrophy, its molecular pathology remains unclear, although histologically it is considered to be a decrease in elastic fibers and an increase in collagen fibers[2,3)]. From the preventive medicine perspective, elucidation of the clinical pathology related to LF thickness would be a major achievement in the prevention of mobility loss and nursing care for older adults due to age-related degeneration of the locomotion system in a hyper-aging society.

A previous study, we defined LF hypertrophy in LSS on

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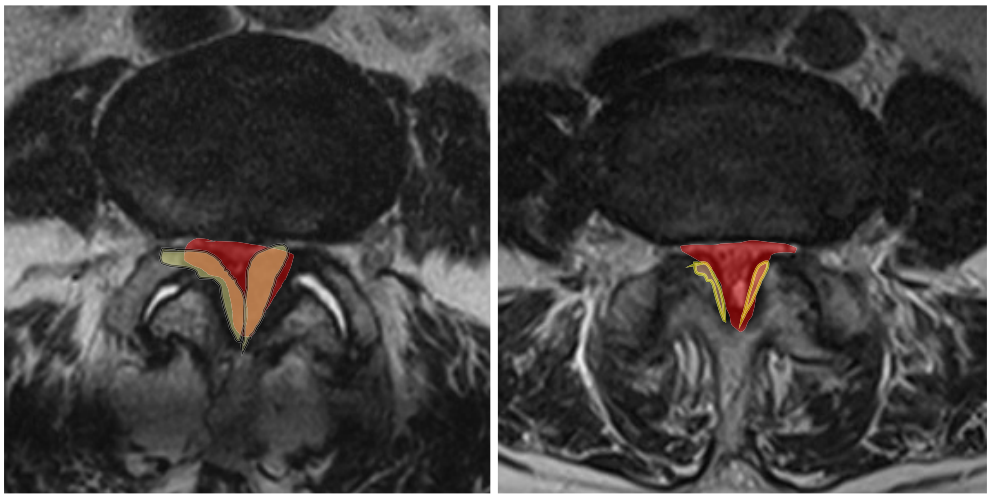

Figure 1. Classification of flavum hypertrophy according to MRI T2-weighted images.
Flavum hypertrophy was evaluated by the area ratio of the flavum to that of the spinal canal at the most severely stenosed level on MRI cross sectional images (flavum canal ratio; FCR). Ligamentous stenosis was defined as 0.4275 or greater in FCR.

MRI cross-sectional images and demonstrated favorable outcome with conservative treatment for stenosis with LF hypertrophy compared to stenosis without hypertrophy[4]. During the clinical diagnosis of LF hypertrophy, transcriptomic analysis of LF specimens removed during spinal surgery showed the involvement of aryl hydrocarbon receptor (AhR), Wnt/β-catenin, and insulin receptor signaling[5]. The results of this study suggest that changes in insulin resistance signaling contribute to ligament thickening, in addition to the involvement of TGFβ, a major regulator of tissue fibrosis, while AhR and Wnt/β-catenin signaling have been implicated in LF hypertrophy in the previous study[6]. While hyperinsulinemia has been linked to ossification of the anterior longitudinal ligament through insulin receptor activation[7], there are no clinical reports on the involvement of insulin resistance in LF, and its clinical significance remains completely unknown. This study aimed to clinically investigate the involvement of endogenous insulin as a risk factor for LF hypertrophy by evaluating LF in over a thousand patients with LSS.

Materials and Methods

The institutional review board approved this cross-sectional study, and written consent was obtained from patients.

A total of 1,119 patients aged ≥65 years (mean age 76.1± 5.9 years, 65-96 years, 584 males and 535 females) presenting our hospital treated for lumbar spinal stenosis, including surgery and conservative treatment, from 2015 to 2021 were included. Three spine surgeons established lumbar spinal canal stenosis diagnosis based on neurogenic claudication with or without back pain, MRI findings, and neurological findings. Th inclusion criteria for participation in the study were as follows: (1) no previous lumbar spine surgery, (2) ability to walk, (3) no previous vertebral fracture, and (4) no systemic disease such as rheumatoid arthritis, infection, or malignancy.

Ligamentum flavum evaluation on MRI

The Flavum canal ratio (FCR) was calculated by dividing the sum of the area of the left and right yellow ligaments by the area of the spinal canal at the height of the most severely highest stenosed part of the spine in the MRI T2-weighted cross-sectional image, and an FCR of 0.4275 or greater was defined as ligamentous stenosis according to Sakai's criteria[1] (Fig. 1). The LF and spinal canal areas were measured using image analysis software (SYNAPSE®, FUJIFILM MEDICAL).

Radiographic evaluation

Body composition was measured by dual-energy X-ray absorptiometry (DXA) (Lunar iDXA, GE-Healthcare, Tokyo, Japan). Bone mineral density was evaluated by T-score of lumbar vertebrae L2-4; skeletal muscle mass was evaluated by the skeletal muscle mass index (SMI; kg/m^2), which is the amount of upper and lower limb muscle divided by the square of height; and fat mass was evaluated by the total body fat divided by the weight in percent. Trunk muscle mass was evaluated as the sum of bilateral lumbar multifidus and erector spinae muscles at the L1/2 and L4/5 elevations on MRI T2-weighted transverse images. Sagittal alignment on the standing lateral spine radiographs was assessed using lumbar lordosis (LL), sacral slope (SS), thoracic kyphosis (TK), sagittal vertical axis (SVA), and pelvic tilt (PT), and the difference between pelvic incidence and LL (PI-LL) and lumbar range of motion (L-ROM) was evaluated on an anteroposterior flexion lateral view of the lumbar

Table 1. Demographic Data.

	Hypertrophy (+)	Hypertrophy (−)	P value
N	571	548	
FCR	0.63±0.15	0.30±0.10	<0.001
Age (years)	76.90±5.80	75.32±5.99	<0.001
Sex (male %)	56.9	47.3	0.0015
BMI	24.71±3.49	24.06±3.64	0.0024
Blood pressure (mmHg)	133.42±18.57	135.30±18.39	0.0986
Smoking index	242.53±404.61	242.24±430.79	0.9974
Hb (g/dl)	13.10±1.58	13.08±1.67	0.8173
HbA1C (%)	6.11±0.78	6.04±0.68	0.0773
GLU (mg/dl)	105.93±28.16	102.93±28.03	0.0595
Insulin (μU/mL)	14.98±16.69	11.88±12.21	<0.001
HOMA-IR	4.31±5.60	3.24±4.04	0.0004
Diabetes (%)	22.1	16.1	0.0120
Alb (g/dl)	4.12±0.39	4.09±0.39	0.1817
eGFR (ml/min/1.73m^2)	64.72±17.39	66.60±16.40	0.0719
Cre (ml/min)	0.84±0.29	0.78±0.25	0.0011
T-cho (mg/dl)	194.29±37.74	196.57±37.22	0.3103
CRP (mg/dl)	0.29±1.02	0.24±0.79	0.3560

Mean±S.D.

FCR, flavum canal ratio; BMI, body mass index; Hb, hemoglobin; GLU, glucose; HOMA-IR, homeostatic model assessment for insulin resistance; Alb, albumin; eGFR, estimated glomerular filtration rate; Cre, creatinine; T-cho, total cholesterol; CRP, C-reactive protein

spine. Modic changes[8] were evaluated by MRI T1- and T2-weighted images for endplate degeneration, and lumbar slip was defined as I° or greater.

Insulin resistance

Blood biochemical findings such as fasting insulin (IRI; μU/mL) and fasting plasma glucose levels, as well as glucose tolerance, are assessed as potential risk factors for LF hypertrophy. Blood insulin levels were measured using the chemiluminescent enzyme immunoassay (CLEIA) method, and insulin resistance was calculated using the following formula, which is the homeostatic model assessment for insulin resistance (HOMA-IR)[9].

HOMA-IR=fasting insulin (μU/mL)×fasting glucose (mmol/L)/22.5

Hereon, the denominator of 22.5 is a product of assumed normal fasting insulin (5 μU/mL) and glucose (4.5 mmol/L) concentrations for a typically healthy person[10]. A HOMA-IR value of ≥2.5 indicates insulin resistance in Japanese people[11].

Statistical analyses

Statistical analysis was performed using EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan), and normality was confirmed using the Kolmogorov-Smirnov test for comparison between the two groups in the presence of ligament hypertrophy. Continuous variables were expressed as mean±standard deviation (SD), and t-test was used for comparison of means, while χ^2 test was used for comparison of categorical variables, with $p<0.05$ as the significance level. For multivariate analysis, logistic regression analysis was used with $p<0.05$ as the explanatory variable for the comparison between the two groups in the presence or absence of ligament hypertrophy. The required number of cases was calculated by sample size calculation using data from a pilot study conducted in 2018 in 191 patients with lumbar spinal canal stenosis (mean age 75.0±9.1 years, 65-88 years). The sample size was 543 cases in each group, calculated with an alpha error of 0.01, a power of 0.8, and a ratio of 1:1, based on a mean difference of 1.27 and a SD of 6.12 in the HOMA-IR between the two groups according to the presence of ligamentous stenosis. The correlation between FCR and HOMA-IR was determined using the Pearson correlation coefficient and the area under curve (AUC) using the receiver operator characteristic (ROC) curve to calculate the optimal cutoff value for risk of ligamentous stenosis. Outliers were determined and excluded using the Smirnov-Grubbs test.

Results

The most severely stenosed levels were L4/5, L3/4, L2/3, L5/s1, and L1/2 in 799 (71.4%), 241 (21.5%), 45 (4.0%), 22 (2.0%), and 12 patients (1.1%), respectively. Of the 1,119 patients, 571 (51.0%) had LF hypertrophy with FCR ≥0.4275. The LF hypertrophy group showed significantly higher age, a higher proportion of males and diabetic patients, higher BMI, higher HOMA-IR, and higher creatinine (Table 1). Body composition and imaging findings showed significantly higher values for limb and trunk muscle mass,

Table 2. Body Composition and Radiographic Data Comparison.

	Hypertrophy (+)	Hypertrophy (−)	P value
N	571	548	
SMI (kg/m^2)	6.62±1.05	6.49±0.97	0.0327
BMD (L2-4 T-score)	0.50±2.34	0.09±2.09	0.0023
Body fat ratio (%)	32.97±7.59	32.26±9.19	0.1597
L1/2 trunk muscle CSA (mm^2)	2992.44±857.60	2761.99±796.51	<0.0001
L4/5 trunk muscle CSA (mm^2)	2662.28±788.08	2459.00±708.39	<0.0001
Modic change (%) Type 0	59.1	58.2	0.9809
Type I	6.5	7	
Type II	19.9	19.8	
Type III	14.5	14.9	
Spondylolisthesis (%)	35.38	39.42	0.1740
LL (°)	31.18±13.34	29.39±13.60	0.0263
SS (°)	26.28±14.22	24.50±10.59	0.0175
L-ROM (°)	27.80±10.83	26.59±11.67	0.0531
TK (°)	36.28±10.83	35.18±11.67	0.1582
SVA (mm)	69.07±66.71	67.12±45.29	0.6063
PT (°)	21.90±9.18	24.04±9.94	0.0007
PI-LL (°)	17.16±18.75	19.32±16.30	0.0634

SMI, skeletal muscle mass index; BMD, bone mineral density; CSA, cross-sectional area; LL, lumbar lordosis; SS, sacral slope; L-ROM, lumbar range of motion; TK, thoracic kyphosis; SVA, sagittal vertical axis; PT, pelvic tilt; PI, pelvic incidence

LL, SS, and SVA (Table 2). Comparison by analysis of covariance (ANCOVA) adjusted for age and sex showed no significant differences in HbA1C levels, but significantly higher insulin levels and HOMA-IR in LF hypertrophy ($p<0.001$).

Among LSS patients, 43.0% had insulin resistance with HOMA-IR ≥2.5, 47.1% with LF hypertrophy, and 38.6% without LF hypertrophy, with significantly more high insulin resistance in the LF hypertrophy group ($p<0.01$). LSS with high insulin resistance also had significantly higher FCR ($p<0.05$) and a significantly higher percentage of LF hypertrophy ($p<0.01$) (Fig. 2). There was a significant correlation between FCR and HOMA-IR (Fig. 3).

Logistic regression analysis using the statistically significant difference in the presence or absence of LF hypertrophy as an explanatory variable showed that older age, high BMI, and HOMA-IR were significant factors (Table 3). Moreover, conditional logistic regression analysis adjusting for age also found that HOMA-IR was a significant factor (Table 4).

Fig. 4 shows ROC curves for FCR and HOMA-IR, with an AUC of 0.709 (95% CI=0.676-0.742) and a threshold for insulin resistance resulting in LF hypertrophy of 2.169.

Discussion

The etiology of LF hypertrophy, a major pathology in LSS, has long been considered as a mechanical stress in the lumbar spine, particularly extension stress[12,13]. Clinical studies have established that mobility stress in lumbar spine segments is associated with LF hypertrophy[14], and mechanical stress is reportedly the cause of microdamage in ligamentous tissues. This stress in turn leads to chronic inflammation and fibrosis of elastic fibers, resulting in ligament thickening[15]. Inflammation-induced TGFβ plays a vital role in this inflammation-induced fibrosis process[13,16,17], and macrophage infiltration is considered the primary origin of TGFβ[18]. Regarding TGFβ, which plays an important role in inflammation during ligament fibrosis, by proteome analysis, we have identified the proteins associated with LF hypertrophy for the first time, through a comprehensive search for proteins in degenerating LF[19]. Among these proteins, we have identified the upregulation of high-temperature requirement A serine protease 1 (HTRA1)[20], a serine protease that suppresses the signaling by TGFβ family members, and fibronectin[21], a major target for TGFβ. The upregulation of HTRA1 in the ligamentum flavum, a major target for TGFβ[21], even downstream of TGFβ signaling, and tenascin[22], which are regulated by TGFβ signaling, was found to be expressed in the thickened LF of LSS patients, indicating the involvement of inflammation in ligament hypertrophy at the protein level. However, Saito et al.[23] found thickened ligaments, increased collagen fibers, and the expression of inflammatory cytokine genes in LF specimens obtained by continuously applying mechanical stress to the lumbar spine of mice, with no increased expression of macrophages or TGFβ. In their experiment, the ligament thickening was not higher as severe as in the so-called clinical setting. The ligament hypertrophy was mild rather than severe, suggesting the presence of factors other than mechanical stress.

To explain molecular pathways in LF hypertrophy, we performed miRNA transcriptomic analysis on excised LF from elderly LSS patients and extracted insulin receptor signaling as a pathway involved in ligament hypertrophy, in ad-

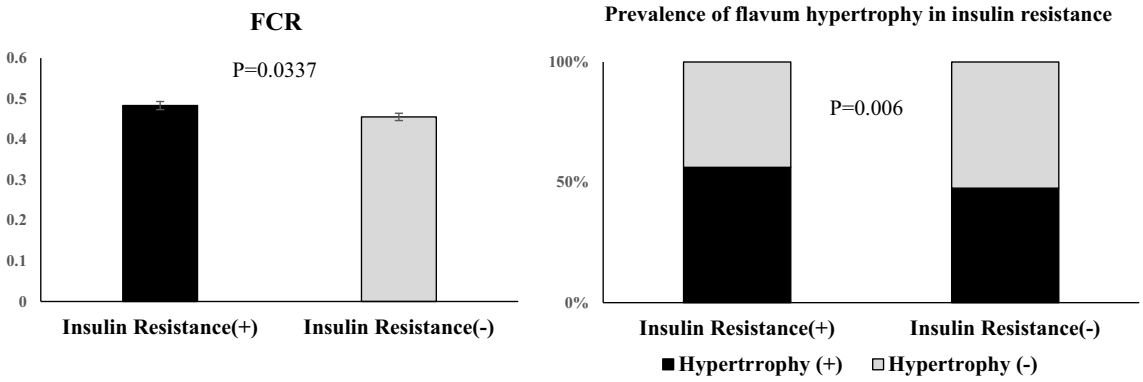

Figure 2. Insulin resistance and flavum hypertrophy.
Among 1,119 patients with lumbar spinal canal stenosis, 481 (43.0%) had insulin resistance with HOMA-IR≥2.5, with a significantly higher FCR ($p<0.05$) and a significantly higher percentage of flavum hypertrophy.
FCR, flavum canal ratio

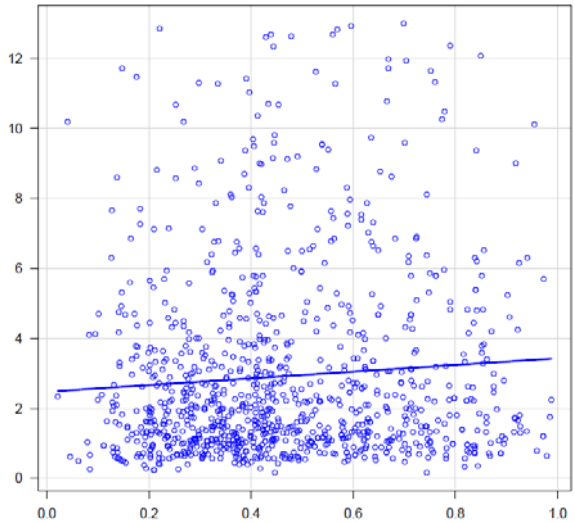

Figure 3. Correlation between FCR and HOMA-IR.
Flavum hypertrophy significantly correlated with insulin resistance.
FCR, flavum canal ratio; HOMA-IR, homeostatic model assessment for insulin resistance

dition to TGFβ-mediated signaling[5]. To explore the clinical significance of this result, we performed a multivariate analysis including insulin resistance as a risk factor for LF hypertrophy in LSS and found that LSS with LF hypertrophy had significantly higher blood insulin levels and higher levels of insulin resistance. Although there were significant differences in LF hypertrophy with respect to age, gender, BMI, diabetes mellitus incidence, and renal dysfunction, age and insulin resistance were the only significant factors in the multivariate analysis were age and insulin resistance, and insulin resistance was the significant variable in the multivariate model adjusted for age. This result supported the results of the comprehensive gene expression analysis[5,19].

In LF hypertrophy, which is histologically considered to be a decrease in elastic fibers and an increase in collagen fibers, research reports have found that age and disc degeneration are clinical factors related to thickening[3,24,25]. LF thickens with age, and in the 30s, hypertrophy already begins at L4/5[26]. Moreover, Takashima also reported a strong correlation with age in an analysis of a hundred cases[27]. However, age-related hypertrophy is no longer dependent on age at age 60 or older[28], and Yabe et al. reported a mild correlation between LF hypertrophy and age in their analysis of 56 LSS surgery cases[29]. Although age was a significant variable in the multivariate analysis of the crude model in this study, insulin resistance remained a significant variable in the multivariate model adjusted for age, suggesting that age-independent factors are associated with LF hypertrophy. Despite an observed positive correlation between LF hypertrophy and insulin resistance, the results of ROC analysis for the threshold of insulin resistance with respect to LF hypertrophy did not yield a high AUC, suggesting a multifactorial factor in ligament hypertrophy. While hypertrophy may have many confounding factors, such as age, sarcopenia, and spinal alignment, no studies use multivariate analysis with a small number of cases to explain the pathophysiology. Therefore, to the best of our knowledge, this is the first to report of an association between LF hypertrophy and insulin resistance.

Regarding the relationship between diabetes and LSS, the incidence of diabetes is higher in LSS than in the general population[30-32]. Although there are histological studies that report increased expression of matrix metalloproteinase 13 in the LF of diabetic LSS patients[33], more pronounced loss of elastic fibers[34], and accumulation of advanced glycation end products[35], there is no clear conclusion as to whether LF hypertrophy is caused by diabetes mellitus or impaired glucose tolerance. Insulin resistance, the basic pathophysiology of type 2 diabetes mellitus, is easily induced by obesity and is caused by inflammatory cytokines and free fatty acids (FFAs) released from adipose tissue[36]. Obesity causes DNA damage in adipocytes, which activates inflammatory senescence signals centered on p53[37]. Chronic inflammation caused by aging activates NF-κB, and adipokines such as resistin, leptin, and adiponectin secreted from adipocytes decrease systemic insulin sensitivity[38]. In addition, when FFAs

Table 3. Logistic Regression Analysis in Flavum Hypertrophy (Crude Model).

Crude model	Regression coefficient	Standard error	P value	OR	95% CI		VIF
					Lower	Upper	
Age	0.106	0.026	<0.001	1.110	1.060	1.170	1.181
Sex	0.041	0.245	0.8679	1.040	0.644	1.680	1.058
BMI	0.016	0.047	0.7343	1.020	0.927	1.110	1.652
Diabetes	0.248	0.322	0.4412	1.280	0.682	2.410	1.079
SMI	0.096	0.197	0.6246	1.100	0.749	1.620	2.578
BMD (T-score)	0.101	0.069	0.1450	1.110	0.966	1.270	1.450
Trunk muscle CSA (L1/2)	<0.0001	<0.0001	0.9468	1.000	1.000	1.000	3.031
Trunk muscle CSA (L4/5)	<0.0001	<0.0001	0.3592	1.000	1.000	1.000	2.183
HOMA-IR	0.068	0.027	0.0111	1.070	1.020	1.130	1.092
LL	–0.013	0.015	0.3921	0.987	0.959	1.020	2.501
SS	0.031	0.020	0.1291	1.030	0.991	1.070	2.406
PT	–0.018	0.014	0.1884	0.982	0.957	1.010	1.131
Cre	0.514	0.614	0.4031	1.670	0.501	5.570	1.286

BMI, body mass index; SMI, skeletal muscle index; BMD, bone mineral density; CSA, cross sectional area; HOMA-IR, homeostatic model assessment for insulin resistance; LL, lumbar lordosis; SS, sacral slope; PT, pelvic tilt; Cre, creatinine; OR, odds ratio; CI, confidence interval; VIF, variance inflation factor

Table 4. Conditional Logistic Regression Analysis in Flavum Hypertrophy (Age-matched Model).

Age-matched model	P value	OR	95% CI	
			Lower	Upper
Age	-	-	-	-
Sex	0.7460	1.080	0.662	1.780
BMI	0.8190	1.010	0.922	1.110
Diabetes	0.7180	1.130	0.584	2.180
SMI	0.5350	1.230	0.766	1.670
BMD (T-score)	0.2140	1.090	0.951	1.250
Trunk muscle CSA (L1/2)	0.9500	1.000	1.000	1.000
Trunk muscle CSA (L4/5)	0.3900	1.000	1.000	1.000
HOMA-IR	0.0174	1.070	1.010	1.120
LL	0.3340	0.986	0.957	1.010
SS	0.1070	1.030	0.993	1.080
PT	0.2640	0.985	0.959	1.010
Cre	0.4470	1.610	0.474	5.450

BMI, body mass index; SMI, skeletal muscle index; BMD, bone mineral density; CSA, cross sectional area; HOMA-IR, homeostatic model assessment for insulin resistance; LL, lumbar lordosis; SS, sacral slope; PT, pelvic tilt; Cre, creatinine; OR, odds ratio; CI, confidence interval

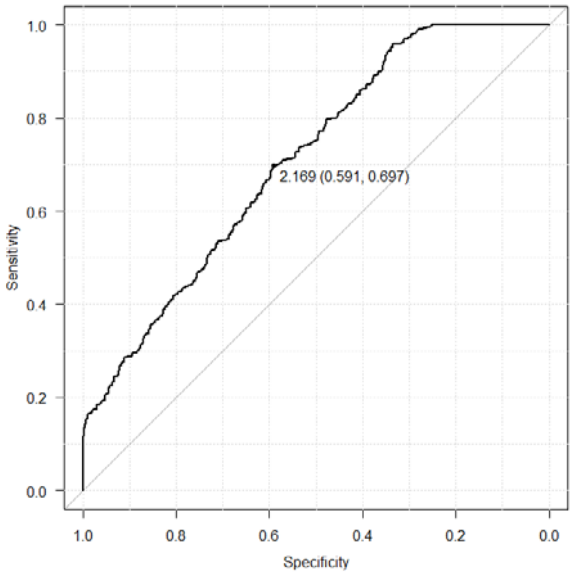

Figure 4. ROC curve of the flavum hypertrophy and insulin resistance.
According to the ROC analysis, the AUC was 0.709 and the 95% CI was 0.676–0.742. The cutoff value for the HOMA-IR threshold for risk of flavum hypertrophy was 2.169 (sensitivity: 0.697 and specificity: 0.591).
HOMA-IR, homeostatic model assessment for insulin resistance

are released from adipose tissues, they accumulate in the liver and skeletal muscle[39]. The presence of insulin resistance promotes hyperglycemia by stagnating glucose uptake in the liver, leading to accumulation of intracellular lipid (intramyocellular lipid) in the skeletal muscle, which is then converted to insulin by protein kinase C (PKC) and insulin receptor substrate-1, which in turn induces insulin resistance due to defective insulin signaling[39].

This study showed an association between LF hypertrophy and insulin resistance, but no association with diabetes incidence or HbA1C. Japanese populations are known to have lower insulin resistance than the populations of Western countries[40], and their percentage of insulin resistance with HOMA-IR ≥2.5 is about 6% in young healthy subjects and about 50% in obese subjects, with glucose intolerance[41,42]. Since Japanese people have low insulin resistance, they have low insulin secretory capacity and many have non-obese diabetes mellitus[40]. Therefore, insulin resistance and type 2 diabetes are not equivalent. Insulin resistance occurs in the liver and skeletal muscle. Insulin is a major regu-

lator of mitochondrial oxidative phosphorylation in the skeletal muscle and is also a factor in sarcopenia[43]. Considering that LF hypertrophy is an inflammation-triggered degeneration of elastic fibers, age-related changes in LF as a responsible lesion of LSS may be the basis of inflammatory aging. The LF hypertrophy may be caused by an increase in systemic insulin resistance, which is the basis of inflammatory senescence, considering that LF hypertrophy is an elastic fiber degeneration triggered by inflammation.

This study has some limitations; the difficulty in determining a causal relationship between LF hypertrophy and insulin resistance due to the cross-sectional nature of the study and the lack of information on diabetes treatment, including the use of insulin resistance-improving drugs.

In conclusion, a multivariate analysis of the association between LF hypertrophy and insulin resistance in 1,119 patients with LSS showed that insulin resistance was higher in LSS with LF hypertrophy, suggesting that factors other than mechanical stress may be influential.

Conflicts of Interest: The authors declare that there are no relevant conflicts of interest.

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Author Contributions: YS and KW conceived the idea for the work, designed the study, interpreted the data, and wrote the final version of the article. YS analyzed and managed the data. NW, HM, NO, and TW collected the data, prepared all tables and figures, and revised the manuscript. All authors provided input into the editing of the manuscript for publication. The corresponding author had full access to all data in the study and final responsibility for publication.

Ethical Approval: Ethical approval was given by National Center for Geriatrics and Gerontology Ethics Committee (approval number: 949-3). The device(s)/drug(s) is/are FDA approved or approved by the corresponding national agency for this indication.

Informed Consent: This cross-sectional study was conducted with the approval of the National Center for Geriatrics and Gerontology Ethics Committee and written patient consent was obtained (approval number: 949-3).

Data: The datasets generated and analyzed during this study are available from the corresponding authors on reasonable request.

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