Clinical Characteristics of Geriatric Patients With Non-Specific Chronic Low Back Pain

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Abstract

Although the prevalence and the associated burden of LBP increase with age, research on LBP has primarily focused on young people and adults, and little attention has been given to the elderly population. Chronic inflammation is well-known as senescence associated secretory phenotype (SASP), which produces numerous proinflammatory cytokines leading to age-related inflammation. We enrolled 203 patients with an average age of 79.0 years, with non-specific CLBP; the patients were compared with age- and sex-matched controls without CLBP using a propensity score-matched analysis. We performed laboratory analysis, radiographic evaluations for global spinal parameter and lumbar degeneration assessment, and body composition analysis using whole-body dual-energy X-ray absorptiometry. We observed a higher red blood cell distribution width (RDW), as well as a lower skeletal muscle mass index and a higher fat mass in patients with CLBP. Moreover, patients with geriatric CLBP had significantly lower lumbar lordosis, and higher sagittal vertical axis was correlated with lower muscle mass in the extremities and trunk, independent of lumbar degeneration. Geriatric CLBP is associated with senescence. RDW, which is an index of aging, was high among elderly patients with CLBP. Furthermore, geriatric patients with CLBP often have age-related skeletal muscle mass reduction and spinal sagittal malalignment.

Introduction

Low back pain (LBP) is one of the most frequently encountered complaints in clinical setting, and is the most common type of chronic musculoskeletal pain in Japan ¹. The prevalence and associated burden of LBP increase with age ²; however, research on LBP has primarily focused on youths and adults, and little attention is given to the elderly population ³. LBP is classified as idiopathic in approximately 85% of patients with LBP ^{4,5}, nonetheless, a recent study revealed that 78% of LBPs could be diagnosed by orthopedists using trigger point injection, facet joint block, discography, and sacroiliac joint block ⁶. The National Institute for Health and Care Excellence defines non-specific LBP as tension, soreness, and/or stiffness of unknown etiology in the low back region with joint, disc, and connective tissue involvement potentially contributing to symptoms ⁷. However, these lumbar spine degenerative changes are highly prevalent with age, and the mechanism whereby they cause LBP remains poorly understood. Recent systematic reviews regarding the association between chronic inflammation and non-specific LBP have been published, suggesting that inflammatory cytokines such as TNF- α and IL-6 may be biomarkers of inflammation in the pathogenesis of non-specific LBP ^{8,9}. Chronic inflammation is well known as a senescence-associated secretory phenotype (SASP), which produces numerous proinflammatory cytokines leading to age-related inflammation (“inflammaging”) ¹⁰. Age-related low muscle mass (sarcopenia) and/or intramuscular fat deposition (sarcopenic obesity), which are associated with geriatric LBP ^{11,12}, are considered part of systemic inflammation ^{13,14}. Biobank-based approaches are necessary to elucidate the senescent mechanisms of geriatric LBP; thus, Japanese Cohort Study and Biobank for Non-specific Chronic Pain (J-BINC) has been developed at the National Center for Geriatrics and Gerontology since 2018. This project was established based on clinical data systematically collected

by orthopedic specialist (spine and joint surgeon) and biobanking regarding non-specific chronic pain, including LBP, neck pain, and knee pain in the elderly. We conducted a comprehensive analysis of clinical information in patients with chronic LBP to clarify the clinical characteristics of geriatric chronic LBP (CLBP) from a senescent perspective.

Materials And Methods

The study protocol was approved by the institutional review board at the National Center for Geriatrics and Gerontology (Approval number 1229), and carries out in accordance with relevant guidelines and regulations. Written informed consent was obtained from all patients.

Patients Enrollment and Eligibility

This observational study was carried out from January 2018 to April 2020 in our institute from a prospectively collected database in the J-BINC. This cohort was a patient-based study that openly recruited individuals aged ≥ 65 years with non-specific chronic pain lasting for more than 6 months, including LBP, neck pain and knee pain. Non-specific CLBP (NCLBP) in this study was defined as follows: (1) LBP with visual analogue scale (VAS) score for LBP ≥ 3 ; (2) persistent pain localized below the costal margin and above the inferior gluteal folds for more than 6 months; (3) the absence of specific spinal pathology such as infection, tumors, and vertebral fractures on both plain radiographs and lumbar magnetic resonance imaging (MRI); (4) the absence of dominant leg pain caused by radicular and cauda equina disorders; (5) the absence of prominent instability such as spondylolysis, isthmic spondylolisthesis, and degenerative spondylolisthesis more than grade II; (6) no previous lumbar and/or thoracolumbar spine surgery. Degenerative lumbar structures such as the vertebral disc, facet joint, and sacroiliac joint were omitted from the inclusion criteria because available diagnostic procedures for these conditions are inaccurate¹⁵.

Age/sex-matched Control

The retrospective collection was conducted with data from a prospectively maintained database of Sarcopenia Study for Elderly Patient for patients who underwent whole-body dual-energy X-ray absorptiometry (DXA) and evaluated skeletal muscle mass. Registration in this database requires that whole spine radiograph, lumbar MRI, and blood data be performed within 1 year of DXA. Of 2,390 patients (65-100 year, averaged 78.7 years, male 1014 patients, female 1376 patients), 1195 patients excluding lumbar degenerative disease, 683 without complaint of LBP were recruited as control participants.

Laboratory Measurements

Upon enrollment, we collected fasting venous blood samples from patients in the NCLBP and control groups. We recorded complete blood count parameters such as hemoglobin, mean corpuscular volume, white blood cell (WBC) count, lymphocyte count, and red blood cell distribution width (RDW). The RDW is an automated measure of the heterogeneity of red blood cell sizes due to inflammation and senescence of erythropoietic cells in the bone marrow ¹⁶.

Radiographic Evaluation

All patients underwent conventional radiography in the standing position. For lateral films, the patients stood with their knees locked, with feet shoulder-width apart, and looking straight ahead. Measured parameters of interest included coronal Cobb angle between the superior edge of L1 and S1, lumbar lordosis (LL), thoracic kyphosis (TK), S1 slope (SS), sagittal vertical axis (SVA), pelvic tilt (PT), pelvic incidence (PI), the presence of spondylolisthesis (anterior slip > 3 mm), and the lumbar range of motion (ROM) defined as the difference in lumbar lordosis angle between flexion and extension. Spinopelvic mismatch was determined when PI-LL is more than 10 ° ¹⁷.

Body Composition Analysis

Body composition was assessed using DXA (Lunar iDXA, GE-Healthcare, Tokyo, Japan). Osteoporosis was evaluated using the young adult mean on the lumbar spine (L2-4). Sarcopenia was evaluated using the appendicular lean mass derived from the sum of lean mass in the upper and lower extremities with bone mineral content removed, and skeletal muscle mass index (SMI) was calculated using height squared (kg/m²) ¹⁸.

MRI Evaluation

Axial T2-weighted slices at L1/2 and L4/5 were obtained to measure the cross-sectional area (CSA) of the lumbar multifidus and erector spinae muscles for the levels of L1/2 and L4/5. Paraspinal muscle CSAs for both the right and left side were added together for each participant. The CSAs were measured using an area calculation software (SYNAPSER, FUJIFILM MEDICAL, Tokyo, Japan). Vertebral endplate and intervertebral disc degeneration were evaluated based on Modic changes ¹⁹ and Pfirrmann classification ²⁰). End plate and disc degeneration were defined as Modic type I, II, and III (except for type 0), and Pfirrmann grade IV and V, respectively.

Statistical Analysis

We determined that a minimum sample of 394 (197 per group) would be required for a power of 90% to detect a clinically importance between-group difference of 0.35 points in the SMI value. Assumptions for the SMI included a two-sided alpha level of 0.05 and a mean standard deviation of 1.07 points ¹¹.

Proportions and means with standard deviations (SD) for normally distributed data and median with minimum and maximum values for not normally distributed data were calculated for covariates and

demographic information, moreover, categorical variables were expressed as frequencies or percentages. The chi-square or Fisher exact test was used to assess differences in categorical variables, and means were compared using independent t-test and Mann-Whitney U test for normally and non-normally distributed data, respectively. Normality was checked using the Kolmogorov-Smirnov test. To minimize the effects of potential confounding influences of measured covariates in the 2 study groups (NCLBP vs. control), a propensity score-matched analysis for age and sex was applied. Finally, patients were matched 1:1 without replacement using a nearest-neighbor approach with caliper restrictions set at 0.2. A propensity score was calculated for each patient using the results of this model, regardless of the statistical significance of the independent variables in the model. The correlation between skeletal muscle mass and spinal sagittal alignment parameters were analyzed using simple linear regression analysis (Pearson correlation coefficient). Statistical analyses were performed using the EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan). A *P* value less than 0.05 was considered statistically significant.

Results

We enrolled 203 patients with CLBP with average age of 79.0 ± 6.04 years, comprising 126 (62.1%) women and 77 (37.9%) men. Among patients with CLBP, 203 patients were matched (1:1) for age and sex to control subjects. (Fig. 1) Demographic and laboratory data are shown in Table 1. There were no significant differences in anthropometry, cytometry, renal function, and nutritional condition. The RDW and the prevalence of elevated RDW were significantly higher in patients in the NCLBP group than in those in the control group; however, there were no significant differences in CRP level. A comparison of body composition is shown in Table 2. Extremity muscle mass, SMI, and trunk muscle CSAs were significantly lower in patients with NCLBP than in those with the control. Lower extremity fat mass and body fat ratio were significantly higher in patients with the NCLBP than in those with the control. In reference to lumbar degeneration in patients with the NCLBP, the frequency of lumbar spondylolisthesis was equal to that in patients with the control, and the prevalence of end plate and disc degeneration was lower in patients with the NCLBP than in those with the control. (Table 3)

Table 1
Demographic and laboratory data

	CLBP	nCLBP	p-value
N	203	203	
Age (year)	79.00 ± 6.04	78.96 ± 5.98	0.934
Sex (M :F)	77:126	77:126	1.000
VAS for LBP	6.61 ± 2.01	1.69 ± 0.55	< 0.001
Height (cm)	153.22 ± 9.41	151.67 ± 9.66	0.103
Weight (kg)	56.42 ± 11.71	55.68 ± 11.53	0.525
BMI	23.92 ± 3.77	24.07 ± 3.63	0.695
Hb (g/dl)	12.96 ± 3.00	12.63 ± 1.51	0.172
Alb(g/dl)	4.07 ± 0.46	4.16 ± 2.14	0.552
T-cho (mg/dl)	192.99 ± 31.60	193.00 ± 35.81	0.998
eGFR (mL/min/1.73m ²)	64.29 ± 17.59	65.36 ± 16.82	0.532
Cre (mg/dl)	0.79 ± 0.25	0.78 ± 0.26	0.772
WBC (/μL)	5967.98 ± 1632.32	5932.51 ± 1857.80	0.986
Lymphocyte (%)	29.42 ± 9.87	29.97 ± 9.27	0.565
CRP (mg/dl)	0.30 ± 0.68	0.33 ± 1.47	0.805
RDW (%)	Mean 14.01 ± 1.55 Median 14.00 (12.0–23.0)	Mean 13.43 ± 1.02 Median 13.00 (12.0–16.0)	< 0.001
Elevated RDW Pts. (%)	32.0	6.90	< 0.001
25OHD (ng/ml)	14.95 ± 7.09	16.89 ± 7.85	0.002
VD deficiency Pts. (%)	80.2	77.7	0.167
CLBP: chronic low back pain, nCLBP: no chronic low back pain			
VAS: visual analogue scale, BMI: body mass index, Hb: hemoglobin, Alb: albumin, T-cho: total cholesterol, eGFR: estimated glomerular filtration rate, Cre: creatinine, WBC: white blood cell, CRP: C-reactive protein, RDW: Red cell Distribution Width (cut off ≥ 15.0%), 25-OHD: 25-dihydroxyvitamin D, VD: vitamin D (< 20ng/ml = deficiency, < 30ng/ml insufficiency).			

Table 2
Body composition data

	CLBP	nCLBP	p-value
N	203	203	
BMD: L2-4YAM (%)	101.49 ± 26.55	99.68 ± 22.69	0.462
Muscle mass (upper) (g)	3837.64 ± 1170.98	4053.13 ± 1138.93	0.071
Muscle mass (lower) (g)	11108.69 ± 2608.75	11734.62 ± 2789.33	0.007
SMI (kg/m ²)	6.23 ± 0.92	6.43 ± 1.02	0.045
Trunk muscle CSA (L1/2) (mm ²)	2267.42 ± 804.56	2683.55 ± 836.45	< 0.001
Trunk muscle CSA (L4/5) (mm ²)	1819.12 ± 770.98	2433.14 ± 715.87	< 0.001
Fat mass (upper) (g)	2086.59 ± 763.62	2089.59 ± 887.54	0.971
Fat mass (lower) (g)	5292.28 ± 1867.88	5142.19 ± 1757.62	0.042
Body Fat (%)	32.17 ± 7.07	29.28 ± 7.48	< 0.001
NCLBP: non-specific chronic low back pain, LSS: lumbar spinal stenosis			
BMD: bone mineral density, YAM: young mean adult, SMI: skeletal muscle mass index, CSA: cross-sectional area			

Table 3
Comparison of lumbar degeneration

	CLBP	nCLBP	p-value
N	203	203	
Degenerative spondylolisthes (%)	36.0	42.9	0.187
Modic type (0:I:II:III)	101:7:44:51	117:14:36:36	0.050
Modic change (+) (%)	50.7	41.8	0.089
Modic type I (%)	3.7	7.0	0.182
Pfirrmann (II:III:IV:V)	0:38:142:18	0:22:163:13	0.002
Disc degeneration (%)	81.6	90.1	0.015
NCLBP: non-specific chronic low back pain, LSS: lumbar spinal stenosis			
Modic change (+) and disc degeneration (+) were defined as Modic type I, II, and III except for type 0, and Pfirrmann grade IV and V, respectively.			

A comparison of spinal sagittal alignment is shown in Table 4. LL was significantly lower in patients with the NCLBP than in those with the control, whereas SVA, PT, and PI-LL were significantly higher in patients with the NCLBP than in those with the control. Spinopelvic mismatch was significantly higher in patients with the NCLBP group than in those in the control group.

Table 4
Comparison of spinal sagittal alignment data

	CLBP	nCLBP	p-value
N	203	203	
LL (degree)	26.76 ± 13.06	30.12 ± 13.54	0.024
SS (degree)	23.42 ± 9.03	24.30 ± 10.38	0.364
ROM (degree)	25.03 ± 11.35	26.16 ± 10.52	0.301
TK (degree)	36.38 ± 11.53	36.45 ± 11.60	0.954
SVA (mm)	77.87 ± 54.82	61.86 ± 45.49	0.006
PT (degree)	27.65 ± 11.01	22.16 ± 10.52	< 0.001
PI (degree)	51.12 ± 11.78	48.13 ± 12.65	0.019
PI minus LL (degree)	24.20 ± 15.09	19.72 ± 14.80	0.004
Spinopelvic mismatch cases (%)	164 (83.2)	127 (73.0)	0.022
NCLBP: non-specific chronic low back pain, LSS: lumbar spinal stenosis			
LL: lumbar lordosis, SS: sacral slope, ROM: range of motion in lumbar spine, TK: thoracic kyphosis, SVA: sagittal vertical axis, PT: pelvic tilt, PI: pelvic incidence			
Spinopelvic mismatch was determined as PI-LL $\geq$ 10 °.			

Muscle mass in both legs and trunk was negatively correlated with PT, whereas only trunk muscle mass was negatively correlated with SVA. Muscle mass in both legs and trunk was negatively correlated with PI-LL; however, trunk muscle mass was more correlated with PI-LL compared with lower extremity muscle mass. (Fig. 2)

Discussion

In the present study, high RDW related to senescence such as chronic inflammation, oxidative stress, which present in the elderly, were observed in patients with CLBP. Moreover, low extremity and trunk muscle mass with high body fat, which previously reported, were demonstrated in the geriatric patients with CLBP. Previous studies have also reported an association with skeletal muscle mass reduction and LBP in the elderly ^{11, 12}; thus, sarcopenia is one of the risk factors for geriatric LBP development. However, it has been unclear how lower extremity muscle mass reduction, which occurs before trunk muscle mass

reduction with age, causes LBP in the elderly. Although the relationship between trunk muscle atrophy and LBP has been previously highlighted ^{21, 22, 23}, it has not been concluded whether trunk muscle atrophy is the cause or result of LBP. There is a view that trunk muscle atrophy is caused by disuse, denervation, reflex suppression ^{24, 25}, and there is conflicting evidence for a relationship between the morphological changes in the lumbar muscles and LBP. Age-related skeletal muscle mass reduction originates from type II fibers ²⁶; therefore, it is known that trunk muscles containing more type I fibers develop sarcopenic changes later than those in the lower extremities ²⁷. Currently, international guidelines for sarcopenia evaluation, define skeletal muscle mass as the skeletal muscle mass index (SMI), which is dependent on the muscle volume of the extremities ²⁸. The key to investigating the cause of non-specific LBP in the elderly from the perspective of aging musculature is to proceed with the analysis of geriatric LBP focusing on lower limb skeletal muscle.

Considering the pathophysiological condition of age-related skeletal muscle loss from the molecular biological mechanism of aging, senescence is associated with advanced aging in humans. Senescent cells involving irreversibly proliferative arrest can develop the SASP, consisting of proinflammatory cytokines and extracellular matrix-degrading proteins, which function as deleterious paracrine and systemic mild inflammation ²⁹. Thus, “inflammaging” is considered as a pervasive feature of aging tissue in age-related diseases ¹⁰. One of the most important organs of locomotor senescence is the skeletal muscle, and sarcopenia, which is an age-related loss of muscle mass, is also considered to be a pathology associated with chronic inflammation mediated by immunosenescence ³⁰. RDW, which was significantly higher in elderly patients with CLBP in the present study, has been attracting attention as a prognostic factor for various acute and chronic diseases in recent years. This is because it represents the red blood cell size variation and reflects changes in circulatory half-life due to chronic inflammation ^{31, 32, 33, 34}. Elevated RDW is associated with an increased risk of age-related diseases and mortality; moreover, RDW reflects overall inflammation because it is associated with overall and disease-specific mortality risk ^{33, 34}. Veeranna ³⁵ and Wei ³⁶ performed comparative analyses of RDW and CRP for mortality prediction in patients with coronary heart disease and infectious endocarditis, respectively. They concluded that RDW, and not CRP, was associated with mortality, independent of traditional risk factors. They also suggested that RDW may be a stronger biomarker for morbidity and mortality. In our study, RDW, and not CRP, was associated with CLBP occurrence in the elderly. This suggests that CLBP may develop in the elderly based on chronic inflammation and RDW may be useful as a biomarker of chronic pain that does not reflect acute inflammation. In addition to chronic inflammation, oxidative stress is another significant mechanism that may explain the elevated RDW. Oxidative damage is an inducer of irreversible cellular senescence mediated by DNA damage, thereby leading to cell survival reduction ³⁷. Cellular senescence is an irreversible process. Unlike traditional biomarkers of acute inflammation, RDW is a valid indicator of senescence because it is not affected by cases of acute inflammation, such as infectious diseases; more so, it increases over time without large fluctuation, and it has a low reversibility. The study results indicate that age-related physical changes in body composition, such as skeletal muscle loss and fat

accumulation, are mechanisms of senescence that occur based on chronic inflammation, and is a possible shows a possible role of senescence in CLBP development in the elderly.

Spinal sagittal alignment is also one of the most important factors influencing mechanical LBP in elderly patients. Progressive sagittal imbalance is strongly associated with health-related quality of life ³⁸. Skeletal muscle is important for maintaining sagittal spinal balance; thus, it is conceivable that sagittal imbalance occurs in elderly patients due to age-related muscle mass reduction and/or atrophy other than vertebral fracture. Since patients with vertebral fractures were excluded from this study, the increase in SVA in patients with CLBP was attributed to a decrease in skeletal muscle mass. Although a significant association between skeletal muscle mass reduction and high PT was found in both limbs and trunk, an association between SVA increase and skeletal muscle mass reduction was found only in the trunk. Considering that the decrease in skeletal muscle mass with aging occurs from the lower extremities, it is assumed that the subsequent decrease in trunk muscles accelerates the increase in SVA following pelvic posterior tilt due to skeletal muscle reduction in the extremities. The effect of skeletal muscles on pelvic tilt in our study is consistent with the findings of Hiyama, which demonstrated that pelvic tilt is the sagittal parameter most closely related to skeletal muscle mass in patients with spinal degeneration disease ³⁹. Studies evaluating LBP and skeletal muscle mass ^{11, 12, 40, 41} have reported the effect of skeletal muscle on sagittal spinal balance ^{39, 42, 43}; however, our study is the first to analyze the relationship between skeletal muscle reduction and spinal sagittal balance in elderly patients with CLBP.

Our study has a limitation because we used data from heterogeneous patient database of Sarcopenia Study for Elderly Patient for patients who underwent DXA without CLBP as a control. It is unclear whether similar results can be obtained by comparing patients with CLBP and healthy elderly persons. In addition, the cross-sectional study design of our study prevents renders our findings inclusive regarding the role of skeletal muscle mass and spinal alignment in the development of CLBP. Longitudinal investigations on changes in skeletal muscle and spinal parameters in the elderly are needed to clarify the cause of geriatric CLBP.

In conclusion, RDW, which is an index of aging, was high in elderly patients with CLBP. Moreover, geriatric CLBP is often associated with vitamin D deficiency, which affects the pain threshold, and triggers CLBP due to the age-related loss of skeletal muscle mass and spinal sagittal malalignment.

Declarations

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Author contributions

Y. S., N. W., H. M., T. W., H. I., and K. W. made substantial contributions to the conception and design of the work. Y. S., N. W., H. M., T. W., and H. I. collected the patient data and reviewed the radiographs. H. M. and

T. W. performed the statistical analysis. Y. S., N. W., H. M., T. W., H. I., and K. W. contributed to the interpretation of data. Y. S. and K. W. supervised the work. All authors reviewed the submitted version of manuscript.

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Competing interests

The authors declare no competing interests.

The device(s)/drug(s) is /are FDA approved or approved by the corresponding national agency for this indication.

No benefits in any form have been or will be received from a commercial party related directly or indirectly to the subject of this manuscript.

Ethical approval was given by National Center for Geriatrics and Gerontology Ethics Committee.

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Figures

Figure 1

Schematic diagram for patient enrollment of the 2 cohorts. NCLBP: non-specific chronic low back pain, LSS: lumbar spinal stenosis, J-BINC: Japanese Cohort Study and Biobank for Non-specific Chronic Pain, Control: recruited from database of Sarcopenia Study for Elderly Patient

Figure 2

Correlation between skeletal muscle mass and spinal sagittal alignment Lower muscle mass in both legs and trunk was negatively correlated with PT, whereas only trunk muscle mass was negatively correlated with SVA. Muscle mass in both legs and trunk was negatively correlated with PI-LL; however, trunk muscle mass had stronger correlation with PI-LL compared with lower extremity muscle mass. The total number of plots was obtained by summing 203 cases in the CLBP group and 683 cases in the nCLBP group excluding 512 cases with LBP. PT: pelvic tilt, SVA: sagittal vertical axis, LL: lumbar lordosis, PI: pelvic incidence