Gerontology & Geriatric Medicine
Volume 9: 1–7

DOI: 10.1177/23337214231190146
journals.sagepub.com/home/ggm
Sage

Skeletal Muscle and Fat Mass Reflect Chronic Pain in Older Adult

Yoshihito Sakai, MD, PhD[1], Tsuyoshi Watanabe, MD, PhD[1], Norimitsu Wakao, MD, PhD[1], Hiroki Matsui, MD, PhD[1], Naoaki Osada, MD[1], Reina Kaneko, MD[1], and Ken Watanabe, PhD[1]

Abstract

Objectives: The prevalence of chronic pain increases with age. It has been reported that chronic pain is associated with sarcopenia and obesity. Age-related skeletal muscle loss and fat gain are known to occur due to chronic inflammation. The aim of this study was to analyze how skeletal muscle and fat, caused by chronic inflammation due to aging, regulate the development of geriatric chronic pain. **Methods:** The results of skeletal muscle and fat mass, 412 participants aged ≥65 years with non-specific chronic pain lasting ≥6 months, including low back, neck, and knee pain, was compared with the control without chronic pain. Body composition threshold regulating chronic pain was calculated. **Results:** A significantly lower skeletal muscle mass index and higher body fat percentage were observed in patients with chronic pain than that in the control. The muscle fat ratio (MFR) was significantly lower in the chronic pain group than in the control group. When the MFR threshold related to chronic pain was calculated by sex, it was 2.984 for men and 1.867 for women. **Conclusions:** Evaluation of the body composition of elderly patients with non-specific chronic pain revealed that the MFR was useful as an index related to chronic pain.

Keywords

orthopedics, pain and symptom management, obesity, chronic diseases

Manuscript received: June 7, 2023; **final revision received:** July 6, 2023; **accepted:** July 7, 2023.

Introduction

Chronic pain, conventionally defined as pain lasting longer than 3 months, is a global public health problem, imposes one of the most costly and prevalent sources of suffering. Chronic pain condition is often comorbid with psychiatric, depressive disorders and disorders of central nervous system (Linton & Bergbom, 2011; Pinho-Ribeiro et al.., 2017), and inflamed tissues which amplify and maintain pain due to decreased neural threshold as inflammatory pain (Kidd & Urban, 2001), however; the underlying mechanisms of pain are not fully understood. Inflammatory pain is characterized by the induction of cytokines, chemokines, and growth factors, which effect sensitized nociceptors and result in hypersensitivity both on local inflammatory site and systemic central sensitization (Woolf et al.., 1992). Recent systematic reviews regarding the association between chronic inflammation and non-specific low back pain (LBP) have been published, suggesting that inflammatory cytokines such as TNF-α and IL-6 may be biomarkers of inflammation in the pathogenesis of LBP (Lim et al.., 2020; Morris et al.., 2020). Considering the fact that pain is induced by inflammation and the epidemiological background that the prevalence of chronic pain increases with age (Nakamura et al.., 2011), it is logical to link pain generation and chronicity to the fact that human aging is based on a pathological chronic inflammation that called senescence-associated secretory phenotype (SASP) (Franceschi & Campisi, 2014). In clinical studies on chronic pain in the elderly, it has been reported that pain is associated with sarcopenia (Sakai et al.., 2017; Tanishima et al.., 2017), which is the age-related muscle mass reduction, and with increased fat (Brady et al.., 2019; Hussain et al.., 2017), and obesity (Eichwald & Talbot, 2020; Okifuji & Hare, 2015). Both age-related skeletal muscle loss and fat gain are known to occur on the basis of chronic inflammation

[1]National Center for Geriatrics and Gerontology, Obu City, Aichi Prefecture, Japan

Corresponding Author:
Yoshihito Sakai, National Center for Geriatrics and Gerontology, Department of Orthopaedic Surgery, 35 Gengo, Obu City, Aichi Prefecture 474-8511, Japan.
Email: jsakai@ncgg.go.jp

(Schrager et al.., 2007; Wilson et al.., 2017). Obesity and chronic pain are often comorbid, and sarcopenic obesity, which is a combination of both, seriously affects physical activity as locomotory aging. It is quite conceivable that if age-related pathology of skeletal muscle and fat tissue affects geriatric chronic pain, the addition of pain to locomotor dysfunction forms an even vicious cycle, afflicting the elderly. 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 older patients. The purpose of this study is to analyze whether age-related changes in body composition mainly composed of skeletal muscle and fat, caused by chronic inflammation as aging can regulate the development of geriatric chronic pain.

Materials and Methods

The study protocol was approved by the institutional review board at the National Center for Geriatrics and Gerontology (Approval Number 1229). All the participants were informed about the objectives of the study and written informed consent was obtained.

This observational study was carried out from January 2018 to December 2021 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 (CLBP), cervical pain (CCP) and knee pain (CKP). Non-specific chronic pain in the present study was determined as follows:

1. Chronic pain with visual analog scale (VAS) scale ≥ 3
2. Persistent pain in low back, neck pain, or knee pain for more than 6 months
3. Pain cannot relieve by using non-steroidal anti-inflammatory drugs (NSAIDs) for more than 1 month
4. None of the following radiographic abnormalities are observed in each pain, and can be judged as non-specific pain by an orthopedic specialist (Y.S, N. W, T.W.).

For all patients who gave informed consent, body composition evaluation was performed using dual-energy X-ray absorptiometry (DXA) (Lunar iDXA, GE-Healthcare, Tokyo, Japan). Lumbar spine (L2–4) bone mineral density (young adult mean; YAM), upper and lower extremity skeletal muscle mass (g), fat mass (g), and limb muscle mass divided by the square of height (skeletal muscle mass index; SMI) (kg/m^2), and body fat percentage (%) were calculated.

The following were excluded from non-specific LBP, neck pain, and knee pain.

1. History of vertebral fracture including osteoporotic fragility fracture and vertebral collapse at least one vertebra on whole spine radiograph.
2. Lumbar spondylolysis
3. Degenerative spondylolisthesis of Myerding (Meyerding, 1932) grade 2 or higher
4. Cervical kyphosis of 10 degree or more
5. Knee joint osteoarthritis of Kellgren-Lawrence (Kellgren & Lawrence, 1957) grade 2 or higher
6. History of malignant tumor
7. History of infections in the spine or knee joint

As a control, 909 patients (464 males, 440 females, mean 76.5 ± 6.0 years) with no history of fracture or pain among 2,390 elderly sarcopenia research database using DXA at the National Center for Geriatrics and Gerontology were recruited.

Statistical Analysis

The data are presented as mean ± standard deviation. Differences between the control group and the chronic pain groups was tested with one-way analysis of covariate (ANCOVA) and χ^2 test with adjustment for age and sex. Receiver operator characteristic (ROC) curves were constructed, and the area under curves (AUCs) were determined. The optimal cut-off value was obtained by maximizing the sum of sensitivity and specificity. DeLong test was used to compare the AUCs of evaluated parameters. The level of statistical significance was set at $p < .05$. All statistical analyses were performed using the EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan).

Results

Of the 412 patients in non-specific chronic pain, 280 cases were CLBP, 65 were CCP, and 67 were CKP. Patients with CLBP were significantly younger shorter in height, and lower in weight than the control group. No significant difference in bone mineral density was observed in any chronic pain group compared to the control group; however, a significantly lower SMI and higher body fat percentage were observed in chronic pain group excluding CCP. (Table 1) Therefore, we defined the value obtained by dividing by the skeletal muscle mass by the fat mass as the muscle fat ratio (MFR), and compared the MFRs of the upper and lower extremities. MFR was significantly lower than the control group in all chronic pain groups (Figure 1).

Table 1. Characteristics of Each Chronic Pain Group and Control Group.

	CLBP	CCP	CKP	Control	*p* Value[1]	*p* Value[2]	*p* Value[3]
N	280	65	67	909			
Age (years)	78.71 ± 6.20	76.97 ± 6.58	79.87 ± 5.28	75.72 ± 6.03	<.0001	.1088	.1604
Sex (m:f)	103:177	27:38	20:47	464:440	.7394	.9999	.1340
Affected periods (months)	66.38 ± 52.50	54.41 ± 65.26	42.74 ± 39.41				
VAS (mm)	6.64 ± 2.04	6.07 ± 2.25	6.24 ± 2.07				
Height (cm)	152.91 ± 9.59	154.28 ± 8.82	151.98 ± 9.01	155.15 ± 9.36	.0006	.4755	.0089
Weight (kg)	55.96 ± 11.62	58.41 ± 11.91	56.00 ± 11.65	59.06 ± 11.62	.0001	.6688	.0423
BMI	23.80 ± 3.65	24.37 ± 3.57	24.15 ± 3.93	24.39 ± 3.53	.0163	.9588	.5944
L2–4 BMD (YAM)	99.47 ± 25.88	101.37 ± 26.20	100.37 ± 25.82	102.16 ± 22.94	.1002	.7915	.5099
SMI (kg/m^2)	6.26 ± 1.09	6.40 ± 1.10	6.17 ± 0.97	6.59 ± 1.02	<.0001	.1583	.0016
Body fat ratio (%)	32.22 ± 6.96	32.75 ± 7.28	32.91 ± 7.40	28.25 ± 7.81	<.0001	<.0001	<.0001

Note. Average ± *SD*. Differences between the control group and the chronic pain groups was tested with one-way analysis of covariate (ANCOVA) and χ^2 test with adjustment for age and sex. CLBP = chronic low back pain; CCP = chronic cervical pain; CKP = chronic knee pain; VAS = visual analog scale; BMI = body mass index; BMD = bone mineral density; YAM = young adult mean; SMI = skeletal muscle mass index.
p value[1]: CLBP versus Control, *p* value[2]: CCP versus Control, *p* value[3]: CKP versus Control.

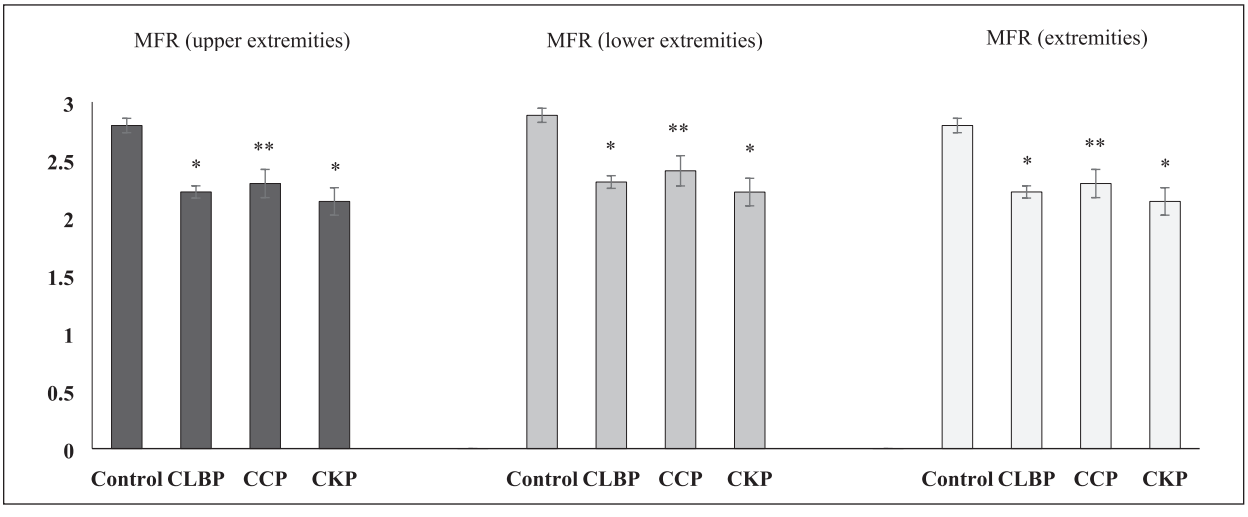


Figure 1. Comparison of muscle fat ratio of extremity in each chronic pain. MFR in chronic pain group was significantly lower compared with that in the control group. Differences between the control group and the chronic pain groups was tested with one-way analysis of covariate (ANCOVA) with adjustment for age and sex.
Note. MFR = muscle fat ratio; CLBP = chronic low back pain; CCP = chronic cervical pain; CKP = chronic knee pain.
*$p < .01$ versus Control, **$p < .05$ versus Control.

Table 2 shows the results of an ROC analysis conducted in all 1,321 patients including the control group to verify whether the threshold for the occurrence of chronic pain can be defined by skeletal muscle and fat mass. Lower extremity MFR had the highest AUC, 0.732, with a cut-off value of 2.581. Comparison of AUC between lower extremity MFR and SMI by DeLong test showed significantly higher AUC for lower extremity MFR. (Figure 2) A comparison of MFR values by gender revealed that male had significantly higher values for both the upper and lower extremities (Figure 3). Therefore, when the MFR threshold related to chronic pain was calculated by ROC analysis by gender, it was 2.984 for men and 1.867 for women (Figure 4).

Discussion

In this cohort study of geriatric non-specific chronic pain aged over 65 years, skeletal muscle and fat mass were associated with a higher risk of having chronic pain including back, neck, and knee pain. Recent research reports suggest that age-related physical change in body composition, such as skeletal muscle loss and fat accumulation, are mechanisms of senescence that occur based on chronic inflammation (Sakai et al.., 2022). The chronic inflammation associated with aging is known as SASP and is caused by the production of numerous inflammatory cytokines (Franceschi & Campisi, 2014). Previous studies (Lim et al.., 2020; Morris et al.., 2020) regarding associations between

Table 2. Area Under Curve the ROC Curve for Prediction of Chronic Pain in the Elderly.

Parameter	Sensitivity	Specificity	AUC	95% CI	Cutoff
SMI	0.572	0.585	0.596	0.563–0.630	6.333
BMI	0.297	0.784	0.541	0.507–0.575	21.843
Skeletal muscle mass (upper)	0.524	0.696	0.629	0.596–0.662	3,468.000
Skeletal muscle mass (lower)	0.421	0.721	0.584	0.550–0.618	9,916.000
Skeletal muscle mass (extremities)	0.479	0.677	0.600	0.566–0.633	13,797.000
MFR (upper)	0.718	0.573	0.705	0.674–0.736	2.222
MFR (lower)	0.731	0.596	0.732	0.701–0.763	2.581
MFR (extremities)	0.487	0.831	0.727	0.696–0.758	1.861

Note. SMI = skeletal muscle mass index; BMI = body mass index; MFR = muscle fat ratio; AUC = area under curve; CI = confidential interval.

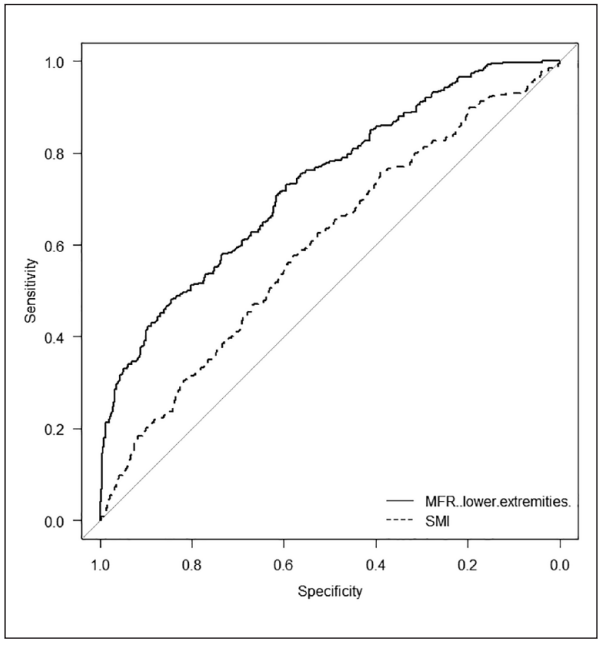


Figure 2. ROC curves illustrating the ability of MFR in lower extremities and SMI for the presence of chronic pain in the elderly. The curves should be interpreted with regard to Table 2. The highest AUC was found for a MFR in lower extremities for the presence of chronic pain in the elderly, and demonstrated statistically higher AUC (0.732) compared to those of SMI. (DeLong test: $p = .000000144$).
Note. ROC = receiver operator characteristic curve; MFR = muscle fat ratio; SMI = skeletal muscle mass index.

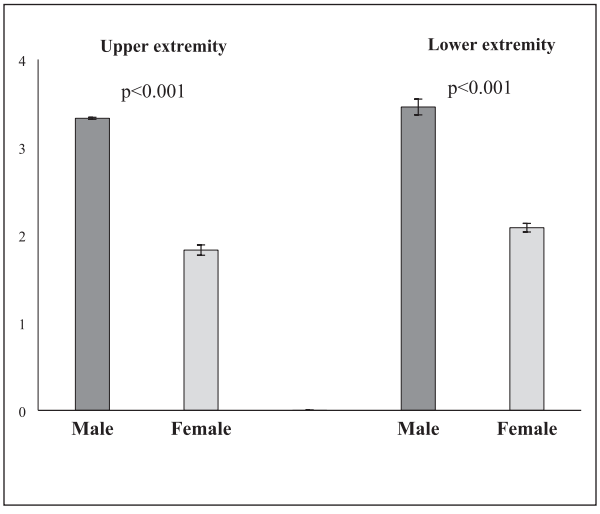
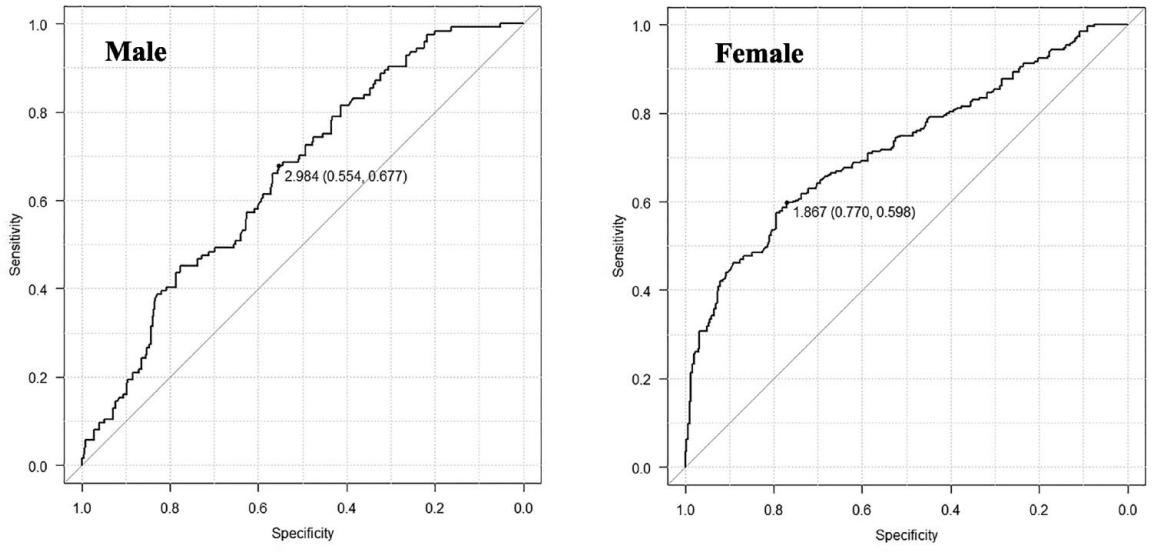


Figure 3. Comparison of MFR in upper and lower extremities by gender. MFR is significantly higher in male than in female in both upper and lower extremities.
Note. MFR = muscle fat ratio.

inflammatory cytokines such as TNF-α or IL-6 and non-specific LBP support the intervention of inflammatory changes in chronic pain in the elderly. While sarcopenia is defined by the amount and strength of skeletal muscle, myosteatosis, ectopic fat deposit in skeletal muscle occurs with aging, and age-related obesity and muscle atrophy are intimately connected (Li et al.., 2022). Thus, we should search for indices including adipose tissue that better than muscle mass to evaluate age-related changes in body composition. Adipose tissue is an endocrine organa as skeletal muscle, and adipocyte and infiltrating macrophages release adipokines such as TNF-α, IL-6, and leptin, and act as IMAT to replace depleted skeletal muscle for fat accumulation (Li et al.., 2022). Thus, obesity involves various endocrine changes, leading to a large volume of evidence pointing to the concurrence of obesity and pain complaints (Okifuji & Hare, 2015). Potential mechanisms underlying the obesity-pain link have been shown to include the increased loading due to weight gain, involvement of the inflammatory mediators, and decreased pain threshold associated with obesity; however, exact nature of the relationship between pain and obesity is not fully known (Okifuji & Hare, 2015). Considering the fact that myosteatosis is directly and strongly related to muscle strength and performance (Stenholm et al.., 2008), in order to understand the age-related skeletal muscle changes, in addition to quantitative evaluation such as a decreased muscle mass, qualitative assessment is necessary. Since age-related skeletal muscle mass reduction and fat accumulation occur in the common pathological basis of chronic inflammation associated with senescence, the fact that the ratio of skeletal muscle mass to fat mass in the lower extremities was most strongly related to geriatric non-specific chronic pain is a very interesting result from the viewpoint of the pathogenesis of sarcopenic pain.



	Sensitivity	Specificity	AUC	95% CI	Cutoff
Male	0.677	0.554	0.655	0.604-0.706	2.984
Female	0.598	0.770	0.723	0.680-0.765	1.867

Figure 4. ROC analysis of MFR in lower extremity in male and female. The cut-ff value for MFR in lower extremity for the development of chronic pain is 2,984 for male and 1.867 for female.
Note. ROC = receiver operator characteristic curve; MFR = muscle fat ratio; AUC = are under curve; CI = confidential interval.

It is novel finding that the MFR, which is the ratio of skeletal muscle mass to fat mass, was shown as statistical threshold for the occurrence of chronic pain in the elderly in this study with gender differences. Exercise therapy, which has relatively high evidence as a treatment for CLBP, skeletal muscle plasticity is limited in response to high-intensity resistance training in the elderly (Raue et al.., 2009). In addition, the recommended high-intensity exercise is often difficult for sarcopenic patients. In the response to a bout of exercise for hypoalgesia, while exercise induced hypoalgesia (EIH) is characterized by a decrease in sensitivity to pain, which is associated with the endogenous opioid (Koltyn, 2000) and endocannabinoid system (Dietrich & McDaniel, 2004), and the effect of exercise induced pro-inflammatory mediators act as the interaction between the immune and the nervous systems (Rice et al.., 2019). Furthermore, in relationship between skeletal muscle and fat tissue, the exercise-induced IL-6 on fat metabolism is well supported findings enhancing lipolysis and fat oxidation through muscle-adipose crosstalk (Pedersen & Febbraio, 2008), and irisin reported as a myokine has browning effects of white fat leading to increases of mitochondrial activity in white adipose tissue (Boström et al.., 2012). Given the possibility that age-related senescence occurs on the basis of chronic inflammation and causes chronic pain as a geriatric syndrome (Sakai et al.., 2022), it could be beneficial for the elderly to find usefulness to investigate the pathological mechanisms of skeletal muscle and related pain through the therapeutic tool of exercise from the viewpoint of anti-inflammatory and immune function. However, in the current exercise therapy approach, the type and intensity of exercise that are effective or preventive indicators for chronic pain have not been elucidated (Kool et al.., 2004). When exercise is recommended for elderly people as a countermeasure against sarcopenia, the results of this study suggest that the skeletal muscle mass of the lower extremities should be approximately three times greater foe men with fat mass, and two for women, as an index to prevent geriatric chronic pain. It is expected that the criteria for MFR obtained from the present study may be considered as new criteria for exercise therapy outcomes by longitudinal evaluation whether it is a factor associated with pain control or prevention in the elderly.

A limitation of this study is that it cannot be concluded that the decrease in skeletal muscle and the increase in fat mass are necessarily the causes of chronic pain because of a cross-sectional study. In addition, since the evaluation of fat mass in this study was not limited to within skeletal muscle, it does not mean that all of fat mass increases are caused in parallel with decreases in skeletal muscle. This study is data on the

body composition of Japanese people, and further research is required for applicability in other races.

Conclusions

As a result of evaluating the body composition of elderly patients with non-specific chronic pain, it was found that lower extremity skeletal muscle fat mass ratio (MFR) was useful as an index related to chronic pain. We propose lower extremity MFR of 2.984 for men and 1.867 for women as an indicator of exercise therapy for the elderly.

Declaration of Conflicting Interest

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Institutional funds were received in support of this work.

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.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethical Approval

Ethical approval was given by National Center for Geriatrics and Gerontology Ethics Committee (Approval Number 1229).

ORCID iD

Yoshihito Sakai https://orcid.org/0000-0001-6507-7859

References

Boström, P., Wu, J., Jedrychowski, M. P., Korde, A., Ye, L., Lo, J. C., Rasbach, K. A., Boström, E. A., Choi, J. H., Long, J. Z., Kajimura, S., Zingaretti, M. C., Vind, B. F., Tu, H., Cinti, S., Højlund, K., Gygi, S. P., & Spiegelman, B. M. (2012). A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. *Nature*, *481*, 463–468. https://doi.org/10.1038/nature10777

Brady, S. R. E., Urquhart, D. M., Hussain, S. M., Teichtahl, A., Wang, Y., Wluka, A. E., & Cicuttini, F. (2019). High baseline fat mass, but not lean tissue mass, is associated with high intensity low back pain and disability in community-based adults. *Arthritis Research & Therapy*, *21*, 165. https://doi.org/10.1186/s13075-019-1953-4

Dietrich, A., & McDaniel, W. F. (2004). Endocannabinoids and exercise. *British Journal of Sports Medicine*, *38*, 536–541. https://doi.org/10.1136/bjsm.2004.011718

Eichwald, T., & Talbot, S. (2020). Neuro-immunity controls obesity-induced pain. *Frontiers in Human Neuroscience*, *14*, 181. https://doi.org/10.3389/fnhum.2020.00181

Franceschi, C., & Campisi, J. (2014). Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *69*(Suppl 1), S4–S9. https://doi.org/10.1093/gerona/glu057

Hussain, S. M., Urquhart, D. M., Wang, Y., Shaw, J. E., Magliano, D. J., Wluka, A. E., & Cicuttini, F. M. (2017). Fat mass and fat distribution are associated with low back pain intensity and disability: Results from a cohort study. *Arthritis Research & Therapy*, *19*, 26. https://doi.org/10.1186/s13075-017-1242-z

Kellgren, J. H., & Lawrence, J. S. (1957). Radiological assessment of osteo-arthrosis. *Annals of the Rheumatic Diseases*, *16*, 494–502. https://doi.org/10.1136/ard.16.4.494

Kidd, B. L., & Urban, L. A. (2001). Mechanisms of inflammatory pain. *British Journal of Anaesthesia*, *87*, 3–11. https://doi.org/10.1093/bja/87.1.3

Koltyn, K. F. (2000). Analgesia following exercise: A review. *OA Sports Medicine*, *29*, 85–98. https://doi.org/10.2165/00007256-200029020-00002

Kool, J., de Bie, R., Oesch, P., Knüsel, O., van Den Brandt, P., & Bachmann, S. (2004). Exercise reduces sick leave in patients with non-acute non-specific low back pain: A meta-analysis. *Journal of Rehabilitation Medicine*, *36*, 49–62. https://doi.org/10.1080/16501970310020104

Li, C. W., Yu, K., Shyh-Chang, N., Jiang, Z., Liu, T., Ma, S., Luo, L., Guang, L., Liang, K., Ma, W., Miao, H., Cao, W., Liu, R., Jiang, L. J., Yu, S. L., Li, C., Liu, H. J., Xu, L. Y., Liu, R. J., Zhang, X. Y., & Liu, G. S. (2022). Pathogenesis of sarcopenia and the relationship with fat mass: descriptive review. *Journal of Cachexia, Sarcopenia and Muscle*, *13*, 781–794. https://doi.org/10.1002/jcsm.12901

Lim, Y. Z., Wang, Y., Cicuttini, F. M., Hughes, H. J., Chou, L., Urquhart, D. M., Ong, P. X., & Hussain, S. M. (2020). Association between inflammatory biomarkers and non-specific low back pain: A systematic review. *The Clinical Journal of Pain*, *36*, 379–389.

Linton, S. J., & Bergbom, S. (2011). Understanding the link between depression and pain. *Scandinavian Journal of Pain*, *2*, 47–54. https://doi.org/10.1016/j.sjpain.2011.01.005

Meyerding, H. W. (1932). Spondylolisthesis. *Surgery, Gynecology & Obstetrics*, *54*, 371–377.

Morris, P., Ali, K., Merritt, M., Pelletier, J., & Macedo, L. G. (2020). A systematic review of the role of inflammatory biomarkers in acute, subacute and chronic non-specific low back pain. *BMC Musculoskeletal Disorders*, *21*, 142. https://doi.org/10.1186/s12891-020-3154-3

Nakamura, M., Nishiwaki, Y., Ushida, T., & Toyama, Y. (2011). Prevalence and characteristics of chronic musculoskeletal pain in Japan. *Journal of Orthopaedic Science*, *16*, 424–432. https://doi.org/10.1007/s00776-011-0102-y

Okifuji, A., & Hare, B. (2015). The association between chronic pain and obesity. *Journal of Pain Research*, *14*, 399–408. https://doi.org/10.2147/jpr.s55598

Pedersen, B. K., & Febbraio, M. A. (2008). Muscle as an endocrine organ: Focus on muscle-derived interleukin-6. *Physiological Reviews*, *88*, 1379–1406. https://doi.org/10.1152/physrev.90100.2007

Pinho-Ribeiro, F. A., Verri, W. A., & Chiu, I. M. (2017). Nociceptor sensory neuron-immune interactions in pain and inflammation. *Trends in Immunology*, *38*, 5–19. https://doi.org/10.1016/j.it.2016.10.001

Raue, U., Slivka, D., Minchev, K., & Trappe, S. (2009). Improvements in whole muscle and myocellular function are limited with high-intensity resistance training in octogenarian women. *Journal of Applied Physiology*, *106*, 1611–1617. https://doi.org/10.1152/japplphysiol.91587.2008

Rice, D., Nijs, J., Kosek, E., Wideman, T., Hasenbring, M. I., Koltyn, K., Graven-Nielsen, T., & Polli, A. (2019). Exercise-induced hypoalgesia in pain-free and chronic pain populations: State of the art and future directions. *The Journal of Pain*, *20*, 1249–1266. https://doi.org/10.1016/j.jpain.2019.03.005

Sakai, Y., Matsui, H., Ito, S., Hida, T., Ito, K., Koshimizu, H., & Harada, A. (2017). Sarcopenia in elderly patients with chronic low back pain. *Osteoporosis and Sarcopenia*, *3*, 195–200. https://doi.org/10.1016/j.afos.2017.09.001

Sakai, Y., Wakao, N., Matsui, H., Watanabe, T., Iida, H., & Watanabe, K. (2022). Clinical characteristics of geriatric patients with non-specific chronic low back pain. *Scientific Reports*, *12*, 1286. http://creativecommons.org/licenses/by/4.0/

Schrager, M. A., Metter, E. J., Simonsick, E., Ble, A., Bandinelli, S., Lauretani, F., & Ferrucci, L. (2007). Sarcopenic obesity and inflammation in the InCHIANTI study. *Journal of Applied Physiology*, *102*, 919–925. https://doi.org/10.1152/japplphysiol.00627.2006

Stenholm, S., Harris, T. B., Rantanen, T., Visser, M., Kritchevsky, S. B., & Ferrucci, L. (2008). Sarcopenic obesity: Definition, cause and consequences. *Current Opinion in Clinical Nutrition and Metabolic Care*, *11*, 693–700. https://doi.org/10.1097/MCO.0b013e328312c37d

Tanishima, S., Hagino, H., Matsumoto, H., Tanimura, C., & Nagashima, H. (2017). Association between sarcopenia and low back pain in local residents prospective cohort study from the GAINA study. *BMC Musculoskeletal Disorders*, *18*, 452. https://doi.org/10.1186/s12891-017-1807-7

Wilson, D., Jackson, T., Sapey, E., & Lord, J. M. (2017). Frailty and sarcopenia: The potential role of an aged immune system. *Ageing Research Reviews*, *36*, 1–10. https://doi.org/10.1016/j.arr.2017.01.006

Woolf, C. J., Shortland, P., & Coggeshall, R. E. (1992). Peripheral nerve injury triggers central sprouting of myelinated afferents. *Nature*, *355*, 75–78. https://doi.org/10.1038/355075a0