Visceral fat obesity predicts ossification of the posterior longitudinal ligament: Annual health examination data-based evidence[1]

[1] Abbreviations: ossification of the posterior longitudinal ligament (OPLL); Japan Society for the Study of Obesity (JASSO); genome-wide association study (GWAS); body mass index (BMI); ligamentum flavum (OLF); computed tomography (CT); hemoglobin A1c (HbA1c); triglyceride (TG); high-density lipoprotein cholesterol (HDL-C); low-density lipoprotein cholesterol (LDL-C); visceral/subcutaneous fat area ratio (V/S ratio); ossification of the anterior longitudinal ligament (OALL); odds ratio (OR); confidence interval (CI); bone mineral density (BMD)

ABSTRACT

Background context

Recent studies have demonstrated a close association between the development of ossification of the posterior longitudinal ligament (OPLL) and obesity. However, the association between OPLL and visceral fat obesity, which is prevalent in the Asian population, remains unexplored.

Purpose

To examine the impact of visceral fat obesity on the development of asymptomatic OPLL.

Study design

Single-institution cross-sectional study.

Patient sample

Between 2020 and 2021, data were collected from 249 Japanese individuals (147 men and 102 women) who underwent computed tomography (CT) to assess both the visceral fat content and OPLL.

Outcome measures

We assessed patient background information, serum data, and CT images, including the abdominal circumference (cm), total fat area (cm^2), visceral fat area (cm^2), and subcutaneous fat area (cm^2) at the umbilicus level. OPLL localization was assessed using whole-spine CT images.

Methods

The individuals were categorized into four groups based on obesity and visceral fat: non-obesity without visceral fat (n = 85), obesity without visceral fat (n = 18), non-obesity with visceral fat (n = 44), and obesity with visceral fat (n = 102). OPLL was classified as localized or diffuse when present in the cervical spine alone or in the cervical and thoracic spine, respectively. The prevalence of each type of OPLL was compared between the groups. Multivariable analysis was conducted to calculate the effect size of body mass index (BMI) on the prevalence of OPLL, comparing the high and low visceral fat groups.

Results

The obesity with visceral fat group exhibited a significantly higher proportion of diffuse OPLL than did the non-obesity without visceral fat group (27.5% vs. 7.1%, P <0.001). The effect size of BMI for the occurrence of diffuse OPLL was 2.1 times greater in the high visceral fat group (odds ratio [OR], 3.12; 95% confidence interval [CI], 1.66–5.87) than in the low visceral fat group (OR, 1.44; 95% CI, 0.64–3.22).

Conclusions

Our data show that visceral fat, in conjunction with BMI, influences the occurrence of OPLL in the Japanese population. This supports the hypothesis that systemic metabolic disorders share a disease mechanism with OPLL and indicates that the high prevalence of OPLL in Japan may be attributed to physical characteristics that promote visceral fat accumulation.

Key words: body mass index, obesity, ossification of the posterior longitudinal ligament, patients, subcutaneous fat, visceral fat

MAIN TEXT

Introduction

Ossification of the posterior longitudinal ligament (OPLL), a prevalent hyperostotic disorder affecting the spinal ligament, is relatively common in East Asian populations, such as the Japanese; however, its prevalence is rare in Western populations [1–4]. Although the etiology of OPLL has historically been unclear, recent research has extensively explored the correlation between obesity and OPLL [5–9], indicating that a distinct subgroup of OPLL is strongly correlated with obesity [6–9]. Typically manifesting in the cervical spine of middle-aged and older adults [1–4], OPLL is more likely to occur in individuals with severe obesity (body mass index [BMI] >35 kg/m^2) in certain areas, including the thoracic spine, accompanied by diffuse ossification of the entire spinal ligament, including the ligamentum flavum (OLF) [6–9]. A Japanese genome-wide association study (GWAS) confirmed that a high BMI value is a causal factor in the development of thoracic OPLL [10].

Individuals with visceral fat obesity demonstrate an elevated risk of developing stroke, atherosclerosis, and type 2 diabetes when compared with those with subcutaneous fat obesity [11–13]. Specifically, Asian races, including the Japanese population, exhibit a higher likelihood of accumulating excess visceral fat, even in individuals with mild obesity, reflecting potential ethnicity-related differences in visceral fat accumulation [14–17]. Although BMI serves as a globally accepted indicator of obesity, it lacks detailed information regarding visceral or subcutaneous fat distribution, making it an insufficient metric for assessing obesity in the Japanese population [16,17]. Considering this, the Japan Society for the Study of Obesity (JASSO) guidelines define obesity in Japanese individuals as having a BMI ≥25 kg/m^2 with concurrent visceral fat accumulation [17,18]. Alterations in lipid metabolism, including non-alcoholic fatty liver disease and dyslipidemia, have been identified as potential exacerbating factors for OPLL [8,19,20], suggesting that obesity with visceral fat may serve as a mediator in the development of OPLL. However, the association between obesity and visceral fat in patients with OPLL remains unclear. Therefore, we hypothesized that obesity with visceral fat is associated with the development of thoracic OPLL in the Japanese population.

To date, no effective treatment exists for inhibiting the onset of spinal ligament ossification or for delaying the progression of ossified lesions. To identify reliable therapeutic targets for OPLL, a comprehensive understanding of the patient's background and research on controllable

pathogenic factors underlying spinal ligament ossification are imperative. Given the rarity of OPLL, observational studies of symptomatic patients have limitations, including challenges in determining the true prevalence of visceral fat obesity owing to selection biases. Such biases can stem from the small number of enrolled patients and the exclusion of asymptomatic individuals or those who do not seek medical attention. To address these limitations, this cross-sectional study utilized extensive data from asymptomatic individuals obtained through visceral fat screening during annual health examinations at a single center, a common practice in Japan. Extensive validation is required to confirm the potential effectiveness of controlling both obesity and visceral fat accumulation to inhibit disease progression. To our knowledge, this is the first study to focus on the importance of obesity and visceral fat in the pathogenesis of OPLL in Japanese patients.

Material and Methods

Study design

This retrospective cross-sectional study was conducted in accordance with the tenets of the Declaration of Helsinki (1964) and included participants from April 2020 to May 2021. The study was approved by our institutional ethical review board (approval number: 2020-14), and the need to obtain informed consent from patients was waived owing to the retrospective nature of the study and the use of de-identified data.

Patients

We included a cohort of 12,740 Japanese individuals who regularly underwent health examinations for screening purposes, a common practice in Japan that occurs either annually or biennially, regardless of symptomatology. Most of these individuals were community residents and employees of local companies and our hospital, representing various professions, including physicians, nurses, physiotherapists, occupational therapists, and clerical staff. Participation in body trunk computed tomography (CT) scans was voluntary, with participants choosing specific regions to be scanned (i.e., neck to chest, abdomen to pelvis, or neck to pelvis) at their discretion. From this pool, 525 patients who underwent CT from the cervical spine to the pelvis were selected. The final study cohort consisted of 249 patients (147 men and 102 women) ranging in age from 27 to 78 years who voluntarily underwent CT for abdominal visceral fat (Figure 1).

Demographics, comorbidities, and serological assessment

BMI was calculated from height and weight measurements obtained at the time of the examination. Basic demographic information was collected from all participants using a comprehensive questionnaire. This questionnaire encompassed essential parameters, including age; sex; and presence of comorbidities, such as hypertension, hyperuricemia, diabetes mellitus, and dyslipidemia, in addition to the current usage of medications. This questionnaire also ascertained whether the patients had numbness in the limbs, whether they had gained weight since the age of 20 years, and whether they engaged in at least 30 min of exercise per day. Fasting blood samples were collected for serological evaluation, which included measurements of the glucose, hemoglobin A1c (HbA1c), total cholesterol, triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) levels.

Measurement of fat area and distribution of spinal ligament ossification using CT

The abdominal circumference (cm), total fat area (cm^2), visceral fat area (cm^2), subcutaneous fat area (cm^2), and visceral/subcutaneous fat area ratio (V/S ratio) were semi-automatically quantified by technicians specializing in CT using axial CT images at the umbilicus level. Results were provided to each patient. The distribution of spinal ligament ossification, encompassing the ossification of the anterior longitudinal ligament (OALL), OPLL, and OLF, was evaluated using axial CT images spanning from the cervical spine to the pelvis. Non-contrast CT scans were conducted utilizing a CT-Aquilion ONE™/GENESIS Edition system (Canon Medical Systems Corporation, Tochigi, Japan).

JASSO criteria for obesity and visceral fat obesity

JASSO defines "obesity" as a condition requiring medical intervention for weight loss that is complicated (or predicted to be complicated) by health problems that are caused by or related to excessive fat accumulation in adipose tissues, with a BMI ≥25 kg/m^2 [17,18]. Patients who met the criteria for visceral fat obesity were classified as having “obesity” regardless of their current health status. JASSO also delineates BMI thresholds, categorizing 25≤ BMI <30 kg/m^2 as obesity I, 30≤ BMI <35 kg/m^2 as obesity II, 35≤ BMI <40 kg/m^2 as obesity III (severe obesity), and ≥40 kg/m^2 as obesity IV (severe obesity) in the Japanese population [17,18]. In addition, JASSO

defines "obesity with visceral fat" as the presence of visceral fat area ≥100 cm^2, as determined from abdominal CT images at the level of the umbilicus [17,18].

Stratification of patients according to visceral fat obesity

The participants were stratified into two groups based on the presence or absence of visceral fat, which was defined with a threshold of 100 cm^2 (Figure 2a, b). Participants were further stratified into four groups based on both the presence of visceral fat and BMI using the JASSO obesity classification [17,18]: 1) non-obesity without visceral fat (BMI <25 kg/m^2 with visceral fat area <100 cm^2), 2) obesity without visceral fat (BMI ≥25 kg/m^2 with visceral fat area <100 cm^2), 3) non-obesity with visceral fat (BMI <25 kg/m^2 with visceral fat area ≥100 cm^2), and 4) obesity with visceral fat (BMI ≥25 kg/m^2 with visceral fat area ≥100 cm^2).

Diagnostic criteria for dyslipidemia by the Japan Atherosclerosis Society

As per the 2022 guidelines of the Japan Atherosclerosis Society, dyslipidemia in adults is defined by the following criteria: TG ≥150 mg/dL, LDL-C ≥140 mg/dL, and/or HDL-C <40 mg/dL [21]. Patients meeting any of these criteria or receiving medication for dyslipidemia were categorized as having dyslipidemia.

Classifying patients according to the type of spinal ligament ossification

Patients were categorized based on the type and localization of spinal ligament ossification, including both single and multiple concomitant ossifications, as follows: 1) localized OPLL, which is primarily localized to the cervical spine, with or without concomitant OALL or OLF; 2) diffuse OPLL, predominantly involving the thoracic spine, with or without concomitant OALL, OLF, or cervical or lumbar OPLL; 3) OLF, including concomitant OALL but excluding OPLL; and 4) OALL only. This classification was guided by the following: a) the likelihood of multiple concomitant spinal ligament ossifications being higher in patients with diffuse OPLL than in those with localized OPLL [6–10], and b) the greater propensity of patients with diffuse OPLL to develop morbid obesity [6–10].

Evaluation of the presence of spinal ligament ossification

Spinal ligament ossification was assessed using CT images, with adaptations from previous methodologies (Figure 2c–f). OPLL was identified as ossification of the posterior longitudinal ligament with a thickness of ≥2 mm on axial plain images [7,19]. OLF was characterized by ossification within the ligamentum flavum, excluding facet osteophytes; specifically, cases were considered positive for OLF if the ossification thickness measured ≥3 mm on axial plane images, although ossifications <3 mm were also categorized as positive, if clearly visible [7,19]. In addition, a mushroom-shaped ossification localized at the center of the laminae was considered indicative of OLF [22]. OALL was defined as ossification of the anterior longitudinal ligament with a thickness ≥4 mm on axial plain images [7]. All CT images were independently reviewed by two board-certified spine surgeons, and any discrepancies were resolved by consensus. Before examining the CT images, the two readers evaluated the same images of 20 patients each with OALL, OPLL, and OLF, and high inter-rater reliability (intra-class correlation coefficient, 0.71–0.81) was confirmed.

Multivariable logistic regression analysis of the risk for spinal ligament ossification

We used a visceral fat area of 100 cm^2 as the cut-off and divided the data into the high- and low-visceral-fat groups. Then, we calculated the effect size of BMI for the development of each type of spinal ligament ossification in the high- and low-visceral-fat groups using multivariable logistic regression analysis; those without ossification were included as controls and those with each type of ossification comprised the cases. Based on previous reports, diabetes mellitus and dyslipidemia are considered lifestyle-related diseases associated with OPLL [2,4,8,9,23–27]. Age, sex, and the presence of diabetes mellitus and dyslipidemia were used as covariables in this analysis. We performed similar analyses for subcutaneous fat and the V/S ratio, using the median values of the present data (163.9 cm^2 and 0.69, respectively) as references. For these analyses, we defined cutoff lines of 160 cm^2 for subcutaneous fat and 0.7 for the V/S ratio to distinguish between high and low groups. Continuous variables were standardized prior to analysis.

Statistical analysis

Data analysis was conducted using Bell Curve for Excel (version 4.02; Social Survey Research Information Co. Ltd., Tokyo, Japan). The normality of the data distribution was assessed using the Shapiro–Wilk test. Results are presented as means ± standard deviations or medians (minimum–

maximum). Differences in continuous variables among groups were assessed using Student's *t*-test (for normally distributed data) and the Mann–Whitney *U* test (for non-normally distributed data). Proportional differences in categorical variables among groups were examined using Fisher's exact test. Statistical significance was defined as P <0.05 for two-group comparisons; P <0.016 (0.05/3) for three-group comparisons; and P <0.008 (0.05/6) for four-group comparisons, with Bonferroni correction for multiple testing. The association between factors influencing the presence of the four types of spinal ligament ossification (OALL, cervical OPLL, thoracic OPLL, and OLF) was evaluated using multivariable logistic regression analysis. Statistical significance was set at P <0.012 (0.05/4) with Bonferroni correction for multiple tests, considering participants with multiple concurrent types of ossifications. The inter-rater reliability for the presence of spinal ligament ossification was assessed by calculation of the intra-class correlation coefficient.

Sample size calculation

In the absence of similar previous studies, the prevalence of OPLL was prespecified as the primary endpoint by comparing the groups with and without visceral fat. As the study included asymptomatic individuals, the occurrence of OPLL was expected to be slightly higher than the prevalence of symptomatic OPLL in the Japanese population (6.9%) [28]. The study was designed to achieve a power of 80% and an alpha value of 0.05. The primary endpoint was set at 25% for the group with visceral fat and 10% for the group without visceral fat, with a 1:1 ratio for both groups. Accordingly, the sample size was calculated to be 200 patients. Based on previous reports, diabetes mellitus was a confounding factor in the development of OPLL [10]. Multivariable logistic regression analysis was performed to adjust for confounding factors.

Missing data

The following items had missing data: presence of weight gain since the age of 20 years, 3.6% (9/249); presence of exercise for at least 30 min per day, 3.2% (8/249); fasting blood glucose levels, 7.6% (19/249); HbA1c levels, 11.6% (29/249). In group comparisons, missing data were treated as blanks. In the multivariable analysis, a full case analysis was conducted, as patients currently being treated for diabetes were included as having diabetes mellitus.

Results

Baseline characteristics of all patients

The baseline characteristics of patients with any spinal ligament ossification (OPLL, OLF, or OALL) (ossification group) and the control group are presented in Table 1. The proportion of patients with BMI ≥25 kg/m^2 was significantly higher in the ossification group than in the control group (55.7% vs. 6.6%, respectively, P <0.001). Furthermore, the proportion of patients in each high BMI category (i.e., BMI ≥27.5 kg/m^2, BMI ≥30 kg/m^2, and BMI ≥35 kg/m^2) was greater in the ossification group than in the control group. The abdominal circumference, total fat area, visceral fat area, subcutaneous fat area, and V/S ratio were significantly higher in the ossification group than in the control group (all P <0.05). The visceral fat area was approximately 48.7% higher in the ossification group than in the control group (130.6 cm^2 vs. 87.8 cm^2, respectively).

High occurrence of OPLL and OLF in patients with visceral fat accumulation

To investigate the effect of visceral fat accumulation on the occurrence of spinal ligament ossification, we first divided all patients into two groups according to the presence or absence of visceral fat accumulation and compared the proportions of patients with ossification. The proportions of patients with localized OPLL, diffuse OPLL, and OLF were significantly higher in the group with a visceral fat area ≥100 cm^2 than in the group with visceral fat area <100 cm^2 (P = 0.008, P <0.001, and P <0.001, respectively) (Supplemental Figure 1A–D).

The highest BMI values were observed in the diffuse OPLL group

The baseline data for each ossification group was compared with that for the control group (Table 2). The proportion of patients with comorbid hypertension was significantly higher in the localized and diffuse OPLL groups than in the control group (P = 0.045 and P = 0.010, respectively). The proportion of patients with comorbid diabetes mellitus was significantly higher in the localized OPLL and OALL-only groups than in the control group (P = 0.046 and P = 0.007, respectively). The proportion of patients with comorbid ischemic heart disease was significantly higher in the localized OPLL group than in the control group (P = 0.042). BMI values were significantly higher in the localized OPLL, diffuse OPLL, OLF, and OALL-only groups than in the control group (P <0.001). Notably, adults in the diffuse OPLL group exhibited the highest mean BMI value (29.3 kg/m^2) among the groups, with 28.9% of patients having a BMI ≥30.0 kg/m^2 and 10.5% having a BMI ≥35.0 kg/m^2.

A high prevalence of visceral fat obesity was observed in the localized OPLL and diffuse OPLL groups

Table 2 also presents a comparison of the visceral fat area, subcutaneous fat area, and V/S ratio between patient groups with spinal ligament ossification and the control group. The total fat area in both the localized and diffuse OPLL groups was significantly higher than that in the control group (P = 0.005 and P <0.001, respectively). Visceral fat area was also significantly higher in the localized and diffuse OPLL groups than in the control group (both P <0.001). The subcutaneous fat area was significantly larger in the diffuse OPLL group than in the control group (P <0.001). In addition, the V/S ratio was significantly higher in the localized OPLL and OLF groups than in the control group (P <0.001 and P = 0.025, respectively). The proportion of patients with visceral fat obesity (BMI ≥25 kg/m^2 with visceral fat area ≥100 cm^2) was significantly higher in both the localized and diffuse OPLL groups than in the control group (52.9% vs. 25.2% and 73.7% vs. 25.2%, respectively, P <0.001) (Supplemental Figure 2).

Effect of visceral fat obesity on the prevalence of OPLL

When comparing the occurrence of spinal ligament ossification among the four groups classified based on both visceral fat area and BMI, both the non-obesity with visceral fat and obesity with visceral fat groups exhibited significantly higher rates of localized OPLL than did the non-obesity without visceral fat group (20.5% vs. 5.9%, P = 0.01; 17.6% vs. 5.9%, P = 0.02, respectively) (Figure 3A). The proportion of patients with localized OPLL was lower in the obesity without visceral fat group than in the obesity with visceral fat group, although this difference was not statistically significant. In addition, the proportion of diffuse OPLL was significantly higher in the obesity with visceral fat group than in the non-obesity without visceral fat group (27.5% vs. 7.1%, respectively, P <0.001) (Figure 3B). The proportion of patients with diffuse OPLL was 0% in the obesity without visceral fat group.

Impact of high visceral fat on the effect size of BMI for spinal ossifications

Finally, we used multivariable logistic regression analysis to compare the effect size (odds ratio [OR]) of BMI for the occurrence of localized OPLL, diffuse OPLL, OLF, and OALL only against the background of the presence of visceral fat or subcutaneous fat accumulation. Except for the

occurrence of OALL only in the low subcutaneous fat group, BMI had positive effect sizes for the occurrence of each ossification type. The effect of BMI for the occurrence of overall ossification tended to be greater in the high visceral fat group (OR, 1.95; 95% confidence interval [CI], 1.19–3.18) than in the low visceral fat group (OR, 1.53; 95% CI, 0.97–2.41) (Figure 4A). The effect of BMI on the occurrence of overall ossification tended to be greater in the high subcutaneous fat group (OR, 2.02; 95% CI, 1.23–3.34) than in the low subcutaneous fat group (OR, 1.48; 95% CI, 0.81–2.68) (Figure 4B). The effect size of BMI for the occurrence of diffuse OPLL was 2.1 times greater in the high visceral fat group (OR, 3.12; 95% CI, 1.66–5.87) than in the low visceral fat group (OR, 1.44; 95% CI, 0.64–3.22) (Figure 4A). The effect of BMI on the occurrence of diffuse OPLL was 1.9 times greater in the high V/S ratio group (OR, 7.36; 95% CI, 2.51–21.5) than in the low V/S ratio group (OR, 3.74; 95% CI, 1.84–7.61) (Figure 4C).

Discussion

We investigated the association between visceral obesity and prevalence of spinal ligament ossification using data from a comprehensive annual health examination in Japan. Our results revealed that individuals with visceral obesity had a 2–3-fold higher prevalence of localized or diffuse OPLL than did those without visceral fat obesity. Notably, the prevalence of obesity with high visceral fat was particularly pronounced in patients with diffuse OPLL (73.7%), with the mean visceral fat area on CT imaging being 72.4% higher than that in patients without ligamentous ossification (150 cm^2 vs. 87 cm^2, respectively). A pivotal finding was the stronger association between visceral fat obesity and the development of spinal ligament ossification, compared to the association between obesity and non-visceral (subcutaneous) fat. Our results provide the first evidence of a significant association between obesity, visceral fat, and OPLL in the Japanese population, suggesting that systemic endocrine metabolic disorders may underlie the pathogenesis of OPLL.

The hypothesis that thoracic OPLL is more likely to be associated with a high BMI in conjunction with visceral fat accumulation than with a high BMI alone is supported by the observation that individuals with a high BMI value without visceral fat accumulation had a lower prevalence of diffuse OPLL. This was further supported by a relative comparison of the effect size of BMI with and without visceral fat accumulation in the multivariable logistic regression analysis. In addition, individuals with visceral-fat obesity showed a higher prevalence of diffuse OPLL than

did individuals with subcutaneous-fat obesity. A recent Mendelian randomization analysis, using a causal inference approach with GWAS data from nationwide Japanese patients, indicated that a high BMI value is a potential causal factor for diffuse-type OPLL [10]. The fact that patients with OPLL often present with comorbidities of metabolic syndrome, including hypertension, diabetes, and dyslipidemia [2,19,20,23–27,29], suggests that visceral fat may be more directly involved in the pathogenesis of OPLL than is subcutaneous fat. However, caution is warranted when interpreting this result because the paucity of individuals with subcutaneous fat obesity in the Japanese population may have affected the results. Unexpectedly, although the proportion of patients with obesity with visceral fat and localized OPLL (52.9%) was lower than that of patients with obesity with visceral fat and diffuse OPLL (73.7%), the mean visceral fat area in patients with localized OPLL was almost as high as that in patients with diffuse OPLL. The observation that patients with localized OPLL had a lower BMI value than did those with diffuse OPLL was consistent with previous findings. Patients with diffuse and localized OPLL likely share some pathophysiology with the accumulation of visceral fat.

The current findings on the association between spinal ligament ossification and visceral fat obesity help shed light on the long-standing question of why East Asians, including the Japanese, exhibit a higher prevalence of OPLL [1-4,27,28]. Previous studies have implicated genetic factors, racial differences, obesity, lifestyle factors (including diet), dynamic factors, postural abnormalities, trauma, inflammation, and sex hormones as risk factors for OPLL [2,4,8,9,23–27,29]. The notable difference between Japanese people and people of European descent can be explained by the lower tolerance of the Japanese population to visceral fat accumulation [14–18]. Japanese individuals have a higher risk of chronic diseases than did people of European descent, even among those with the same BMI or waist circumference [16,30,31]. The genetic predisposition of Asians to visceral fat accumulation and impaired pancreatic β-cell function has been widely reported [32]. The World Health Organization has recommended adopting more stringent obesity criteria tailored for Asian populations compared to those for non-Asians, recognizing that Asians generally accumulate more visceral fat, which may lead to an underestimation of health risks when using standard BMI criteria for obesity, such as a BMI of 30 kg/m^2 [33]. However, considering that the proportion of obese individuals among the Japanese is lower than the global average [34], our results should not be misinterpreted to mean that the rate of OPLL development is high because the majority or a significant proportion of the Japanese

population is obese. Rather, our findings that patients with OPLL, which is relatively rare, have excessive visceral fat accumulation provide strong evidence that visceral fat is likely related to the etiology of OPLL. At the same time, for Japanese people who have low tolerance for visceral fat accumulation and are not generally obese, the adverse health effect of excess body weight modified by visceral fat accumulation may be related to the etiology of OPLL.

At present, whether visceral fat directly induces heterotopic ossification in the body, including in the spinal ligaments, remains uncertain; however, several studies have suggested this possibility. Previous studies comparing Japanese patients with OPLL (mean BMI, 24–25 kg/m^2) to control patients with degenerative spine disease (mean BMI, 22–23 kg/m^2) have suggested an association between obesity-related factors, particularly leptin, and the development of OPLL [35,36]. Leptin, which is primarily secreted by the adipose tissue, including bone marrow adipocytes, has a direct effect on osteoblasts and chondrocytes by stimulating their proliferation and differentiation [37,38]. In non-diabetic Japanese Americans, higher levels of leptin are associated with greater accumulation of visceral fat [39]. Another recent report showed that patients with OPLL, who have a strong tendency to develop ossification of their entire spinal ligaments, have a lower serum adiponectin/leptin ratio and higher serum osteocalcin levels than do patients with a weak tendency for ligament ossification [40]. Leptin levels are also positively correlated with bone mineral density (BMD) in humans [38]. Increased BMD throughout the body, including the spine, extremities, and skull, have been reported in patients with OPLL [41]. Potential pathways of genetic variants associated with OPLL identified by GWAS studies include the Wnt signaling pathway, which plays an important role in maintaining homeostasis in both endocrine and bone metabolism [10]. A study of the dietary habits of patients with OPLL showed that patients with early-onset thoracic OPLL (<50 years of age) had insufficient vitamin A intake and low serum vitamin A levels compared with those in age- and sex-matched control patients without ossification. In addition, serum vitamin A levels in men were negatively correlated with both their BMI and the severity of thoracic OPLL classification [9]. Insufficient vitamin A intake has been shown to be closely related to bone metabolism, obesity, and lipid metabolism [42,43]. These molecular findings suggest that the pathogenesis of OPLL is not only due to the mechanical stress of obesity but is also related to metabolic and endocrine factors.

Our study has certain limitations. First, owing to the cross-sectional nature of the study, we could not conclusively determine whether visceral fat obesity was a cause or consequence of spinal

ligament ossification. Experimental animal models and longitudinal studies are required to draw definitive conclusions. Second, all data were collected from a Japanese database; therefore, the results may not be generalizable to other populations, including people of European or African descent. Third, there were missing data for fasting blood glucose and HbA1c, which were important variables in this study. However, in the questionnaire, the diagnostic criterion for diabetes mellitus was ongoing treatment for the same, and all cases were included in the multivariable analysis; therefore, we believe that the impact on the interpretation of the results was minimal. Fourth, in this study, the patients underwent a physical examination but had not been previously diagnosed with OPLL. Therefore, symptomatic patients with OPLL and myelopathy were not included in this study. Additionally, while all eligible patients voluntarily underwent CT, most ineligible patients who did not undergo CT of the trunk and neck or visceral fat screening did not meet other eligibility criteria. Therefore, selection bias could not be completely excluded.

Conclusions

This study demonstrated that visceral fat obesity is associated with the development of diffuse OPLL in the Japanese population. This study explored, for the first time, the possibility that the high prevalence of spinal ligament ossification in Japanese individuals may be attributed to physical characteristics that predispose them to the accumulation of visceral fat. These findings suggest that visceral fat could serve as a modifiable factor with therapeutic implications for preventing spinal ligament ossification.

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Figure Legends

Figure 1. Flowchart of patient selection in this study

OALL, ossification of the anterior longitudinal ligament; OLF, ossification of the ligamentum flavum; OPLL, ossification of the posterior longitudinal ligament

Figure 2. Representative visceral fat and subcutaneous fat obesity and criteria for the identification of OPLL, OLF, and OALL on CT images

A. Representative example of an abdominal CT image of a patient with obesity and visceral fat. BMI, 26.5 kg/m^2; total fat area, 319 cm^2; visceral fat area, 191 cm^2 (red); subcutaneous fat area, 127 cm^2 (blue); V/S ratio, 1.51.

B. Representative example of an abdominal CT image of a patient with obesity but without visceral fat. BMI, 29.1 kg/m^2; total fat area, 416 cm^2; visceral fat area, 86 cm^2 (red); subcutaneous fat area, 329 cm^2 (blue); V/S ratio, 0.26.

C. Illustration showing the anatomical location of OPLL, OLF, and OALL.

D. OPLL: small but with a thickness of ≥2 mm.

E. OLF: clearly visible but <3 mm in thickness.

F. OALL: located in the midline of the anterior vertebral body with a thickness of ≥4 mm.

BMI, body mass index; CT, computed tomography; OALL, ossification of the anterior longitudinal ligament; OLF, ossification of the ligamentum flavum; OPLL, ossification of the posterior longitudinal ligament; V/S ratio, visceral/subcutaneous fat area ratio

Figure 3. Proportion of each spinal ligament ossification compared between visceral fat obesity and non-visceral fat obesity

A. Proportion of localized OPLL.

B. Proportion of diffuse OPLL.

The cutoff line for obesity is a BMI of 25 kg/m^2 and that for visceral fat is an area of 100 cm^2. **P <0.001.

BMI, body mass index; OPLL, ossification of the posterior longitudinal ligament.

Figure 4. Effect of BMI on spinal ligament ossification modified by visceral and subcutaneous fat distribution

Bar plots represent the effect size of BMI on five types of spinal ligament ossification: localized OPLL, diffuse OPLL, OLF, OALL only, and ossification (localized OPLL + diffuse OPLL + OLF + OALL only). Error bars represent 95% confidence intervals of the effects.

A. Comparison of the effect size of BMI on visceral fat between the high- and low-fat groups.

B. Comparison of the effect size of BMI between high and low subcutaneous fat groups.

C. Comparison of the effect size of BMI between the high and low groups on the V/S ratio.

*P <0.05

BMI, body mass index; CT, computed tomography; OALL, ossification of the anterior longitudinal ligament; OLF, ossification of the ligamentum flavum; OPLL, ossification of the posterior longitudinal ligament; V/S ratio, visceral/subcutaneous fat area ratio

Supplemental Figure 1. Prevalence of each type of spinal ligament ossification in groups with low- and high-visceral-fat accumulation

A. Proportion of localized OPLL.

B. Proportion of diffuse OPLL.

C. Proportion of OLF.

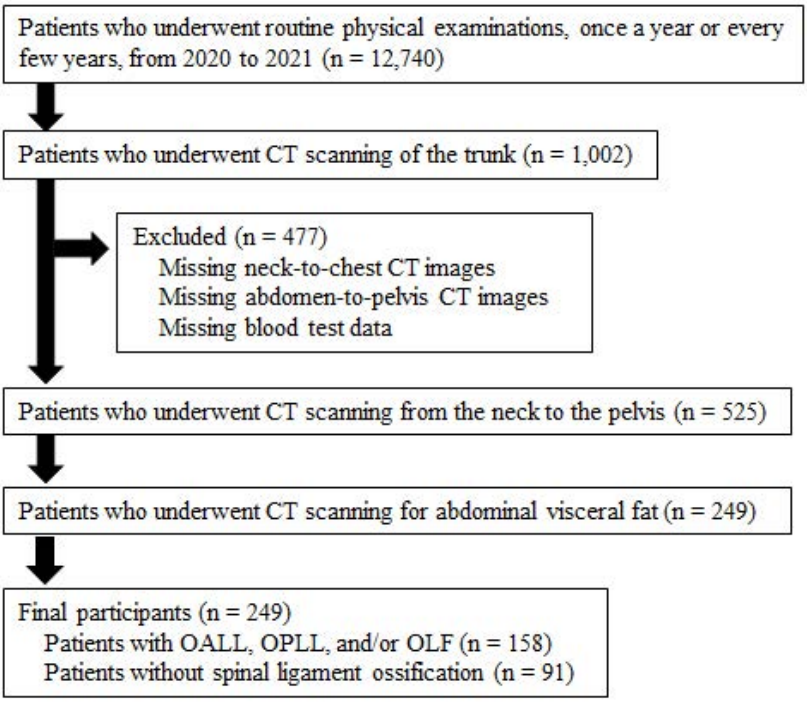
D. Proportion of OALL only.

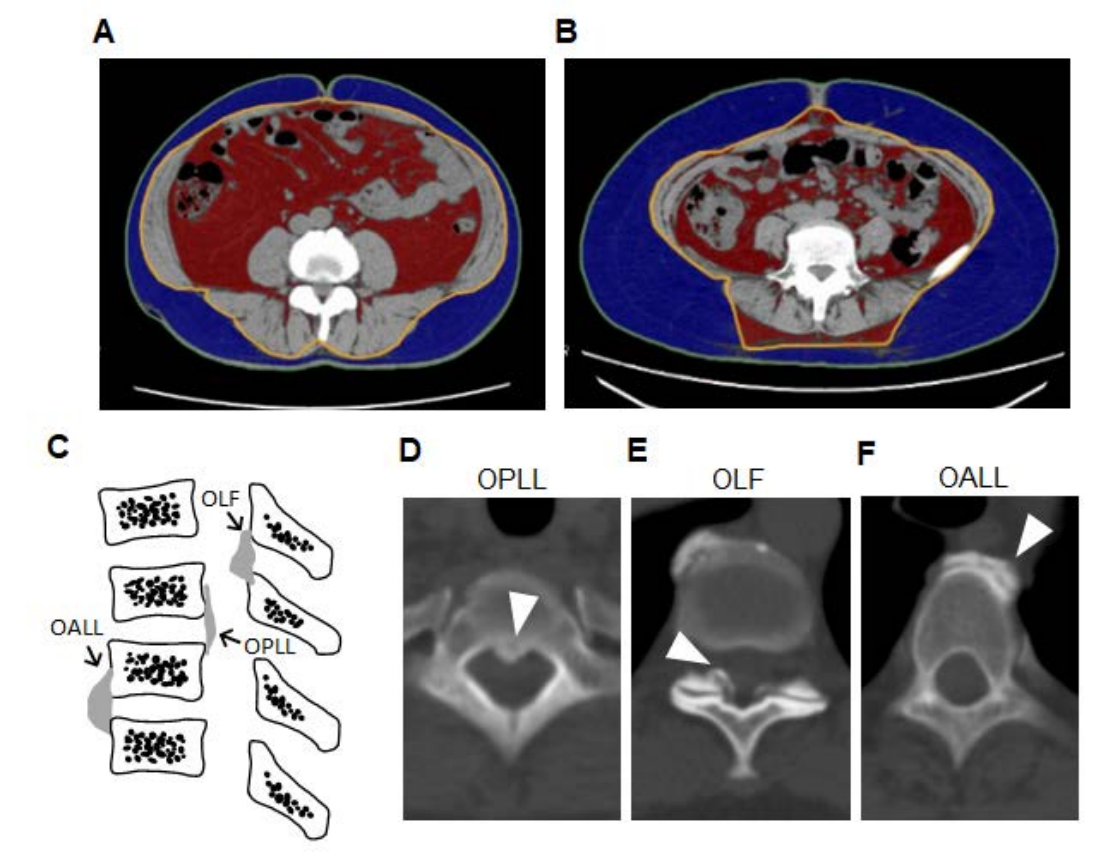
Low indicates a visceral fat area <100 cm^2; high indicates a visceral fat area >100 cm^2. *P <0.05; **P <0.001.

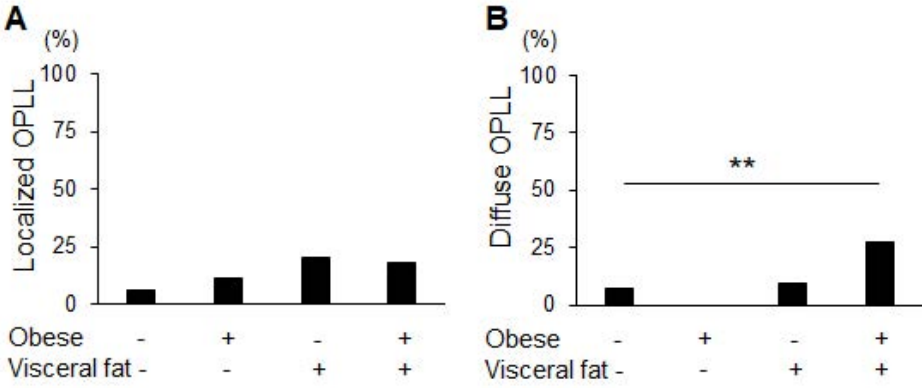
OALL, ossification of the anterior longitudinal ligament; OLF, ossification of the ligamentum flavum; OPLL, ossification of the posterior longitudinal ligament

Supplemental Figure 2. Percentage of patients with visceral fat area ≥100 cm^2 and BMI ≥25 kg/m^2 in each spinal ligament ossification group.

**P <0.01; ***P <0.001


Patients who underwent routine physical examinations, once a year or every few years, from 2020 to 2021 (n = 12,740)
Patients who underwent CT scanning of the trunk (n = 1,002)
Excluded (n = 477)
Missing neck-to-chest CT images
Missing abdomen-to-pelvis CT images
Missing blood test data
Patients who underwent CT scanning from the neck to the pelvis (n = 525)
Patients who underwent CT scanning for abdominal visceral fat (n = 249)
Final participants (n = 249)
Patients with OALL, OPLL, and/or OLF (n = 158)
Patients without spinal ligament ossification (n = 91)


A
B
C
OLF
OALL
OPLL
D
OPLL
E
OLF
F
OALL


A
(%)
Localized OPLL
100
75
50
25
0
Obese - + - +
Visceral fat - - + +
B
(%)
Diffuse OPLL
100
75
50
25
0
**
Obese - + - +
Visceral fat - - + +

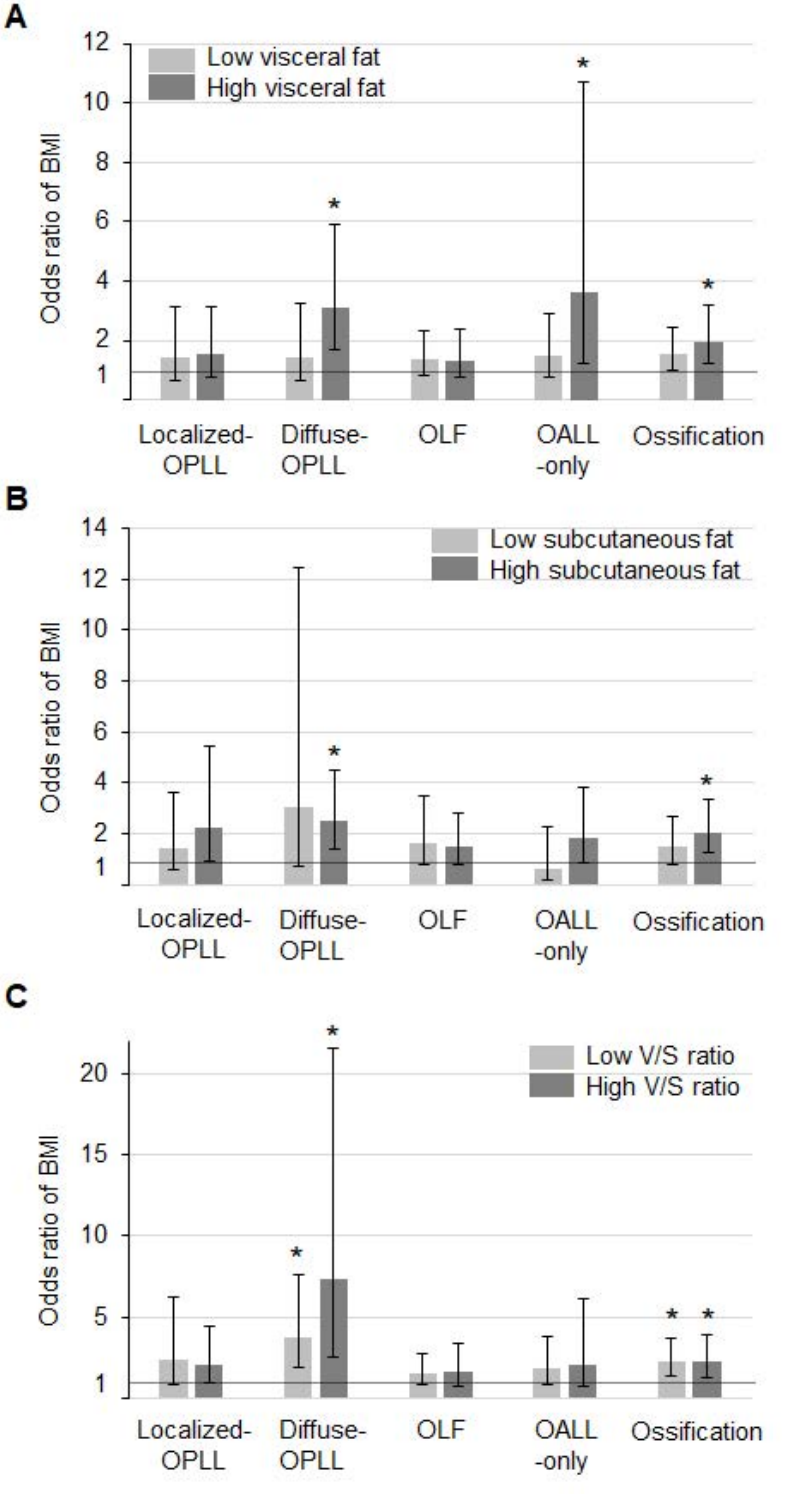

A
Low visceral fat
High visceral fat
Odds ratio of BMI
12
10
8
6
4
2
1
*
*
*
Localized-OPLL
Diffuse-OPLL
OLF
OALL-only
Ossification
B
Low subcutaneous fat
High subcutaneous fat
Odds ratio of BMI
14
12
10
8
6
4
2
1
*
*
Localized-OPLL
Diffuse-OPLL
OLF
OALL-only
Ossification
C
Low V/S ratio
High V/S ratio
Odds ratio of BMI
20
15
10
5
1
*
*
*
*
Localized-OPLL
Diffuse-OPLL
OLF
OALL-only
Ossification

Table 1. Comparison of clinical characteristics between patients without spinal ligament ossification (control group) and those with OPLL, OLF, and/or OALL

Variable	**Control (n = 91)**	**OPLL + OLF + OALL (n = 158)**
Age (years)	49.0 (34–78)	55.0 (27–75)
30–39	11.0	4.4
40–49	39.6	28.5
50–59	35.2	42.4
60–69	9.9	20.3*
70–79	4.4	4.6
Male (%)	50.5	63.9*
Coexisting spinal ligament ossification (%):		
OPLL		
Localized OPLL	0	20.5
Diffuse OPLL	0	25.3
OLF	0	37.3
OALL only	0	17.1
Total	0	100
BMI (kg/m^2)	23.3 (17.2–34.1)	25.8 (16.3–39.8)*
BMI ≥25.0 kg/m^2 (%)	19.8	55.7*

BMI ≥27.5 kg/m^2 (%)	8.8	34.8
BMI ≥30.0 kg/m^2 (%)	8.8	15.8
BMI ≥35.0 kg/m^2 (%)	0	3.2
Abdominal circumference (cm)	84.8 ± 10.0	91.5 ± 10.7*
Fat area (cm^2)		
Total fat	251.0 (15.3–569.5)	307.7 (22.2–770.4)*
Visceral fat	87.8 (5.1–322.4)	130.6 (14.0–359.0)*
Subcutaneous fat	155.8 (9.4–437.6)	176.6 (8.3–581.5)*
V/S ratio	0.6 (0.1–1.9)	0.8 (0.1–2.2)*

Data are shown as means ± standard deviations (for normally distributed variables), medians (minimum–maximum) (for non-normally distributed variables), or percentages.

*P <0.05 vs. the control group.

BMI, body mass index; CT, computed tomography; OALL, ossification of the anterior longitudinal ligament; OLF, ossification of the ligamentum flavum; OPLL, ossification of the posterior longitudinal ligament; V/S ratio, visceral/subcutaneous fat area ratio

Table 2. Comparison of clinical characteristics among patients with each type of spinal ligament ossification

Variable	Control (n = 91)	Localized OPLL (n = 32)	Diffuse OPLL (n = 40)	OLF (n = 59)	OALL only (n = 27)
Age (years)	49 (34–78)	52 (38–73)	53 (35–74)*	54 (27–72)*	59 (38–75)*
30–39	11.0	6.3	2.5	3.4	7.4
40–49	39.6	34.4	30.0	25.4	11.1*
50–59	35.2	40.6	45.0	35.6	33.4
60–69	9.9	12.5	17.5	28.8*	37.0*
70–79	4.4	6.3	5.0	5.1	11.1
Male (%)	50.5	81.3*	57.5	62.7	55.6
Comorbidity (%):					
Hypertension	15.4	31.3	37.5*	27.1	33.4
Diabetes mellitus	3.3	9.4	10.0	5.1	18.5*
Dyslipidemia	52.7	71.9	55.0	54.2	63.0
IHD	6.6	21.9*	10.0	11.9	7.4

Stroke	0	3.1	0	1.7	0
Renal disease	0	0	0	0	0
Smoking (%)	33.0	34.4	27.5	20.3	18.5
Fasting glucose (mg/dL)	97 (78–218)	113 (83–256)	106 (85–166)	102 (69–173)	103 (84–161)*
HbA1c (%)	5.5 (4.9–7.7)	6.2 (5.3–11.5)*	5.9 (4.8–8.3)*	5.7 (5.1–8.2)	5.8 (4.9–8.1)*
Weight gain since the age of 20 years (%)	49.5	75.9	62.5	42.4	48.1
Exercise for at least 30 min/day (%)	14.3	16.7	20.0	27.1	44.4*
BMI (kg/m^2)	23.3 (17.2–34.1)	26.0 (19.1–31.5)*	28.7 (20.4–38.2)*	24.9 (19.6–39.8)*	25.1 (16.3–31.1)*
BMI ≥25.0 kg/m^2 (%)	33.0	59.4*	72.5*	44.1	51.9*
BMI ≥27.5 kg/m^2 (%)	15.4	31.3	62.5	17.0	37.0
BMI ≥30.0 kg/m^2 (%)	6.6	12.5	37.5	3.4	14.8
BMI ≥35.0 kg/m^2 (%)	0	0	10.0	1.7	0

Abdominal circumference (cm)	84.8±10.0	91.8±10.9*	97.6±10.1*	88.2±9.4*	89.6±11.1*
Fat area (cm^2)					
Total fat	251.0 (15.3–569.5)	323.7 (22.2–552.4)*	404.3 (142.2–752.1)*	285.7 (80.5–770.4)	285.3 (67.4–493.8)
Visceral fat	87.8 (5.05–322.4)	150.8 (14.0-327.4)*	164.3 (46.7–359.0)*	118.5 (18.4–275.4)*	87.1 (16.2–241.6)
Subcutaneous fat	155.8 (9.41–437.6)	172.9 (8.3–367.7)	239.9 (68.2–581.5)*	167.2 (32.6–513.2)	178.5 (13.7–379.4)
V/S ratio	0.6 (0.1–1.9)	1.0 (0.3–1.9)*	0.78 (0.3–1.9)*	0.8 (0.2–1.9)*	0.7 (0.1–2.2)

Data are shown as means ± standard deviations (for normally distributed variables), medians (minimum–maximum) (for non-normally distributed variables), or percentages.

*P <0.05 vs. control group.

BMI, body mass index; IHD, ischemic heart disease; OALL, ossification of the anterior longitudinal ligament; OLF, ossification of the ligamentum flavum; OPLL, ossification of the posterior longitudinal ligament; V/S ratio, visceral/subcutaneous fat area ratio