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High whole-body bone mineral density in ossification of the posterior longitudinal ligament

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2 **ligament**

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Abbreviations: BMI, body mass index; BMD, body mineral density; CT, computed tomography; DXA, dual-energy X-ray absorptiometry; OLF, ossification of the ligamentum flavum; OPLL, ossification of the posterior longitudinal ligament

Abstract

BACKGROUND CONTEXT

Recent studies suggest that ossification of the posterior longitudinal ligament (OPLL) is exacerbated by systemic metabolic disturbances, including obesity. However, although an increase in bone mineral density (BMD) measured at the lumbar spine has been reported in patients with OPLL, no studies have investigated the systemic BMD of patients with OPLL in detail.

PURPOSE

We investigated whether patients with OPLL develop increased whole-body BMD.

STUDY DESIGN

Single institution cross-sectional study.

PATIENT SAMPLE

Data were collected from Japanese patients with symptomatic OPLL (OPLL [+]; n = 99). Control data (OPLL [-]; n = 226) without spinal ligament ossification were collected from patients who underwent spinal decompression, spinal fusion, or hip replacement surgery.

OUTCOME MEASURES

Demographic data, including age, body mass index (BMI), comorbidities, history of treatment for osteoporosis, and history of vertebral and non-vertebral fractures, was obtained from all participants. In addition, whole-body BMD, including the lumbar spine, thoracic spine, femoral neck, skull, ribs, entire upper extremity, entire lower extremity, and pelvis, were measured in all participants using whole-body dual-energy X-ray absorptiometry (DXA).

METHODS

Patient data were collected from 2018 to 2022. All participants were categorized based on sex, age (middle-aged [<70 years] and older adults [≥70 years]), and OPLL type (localized OPLL [OPLL only in the cervical spine], diffuse OPLL [OPLL in regions including the thoracic spine]), and OPLL [-]) and each parameter was compared. The factors associated with whole-body BMD were evaluated via multivariable linear regression analysis.

RESULTS

Compared with the OPLL (-) group, the OPLL (+) group of older women had significantly higher BMD in all body parts ($P < 0.01$), and the OPLL (+) group of older men had significantly higher BMD in all body parts except the ribs, forearm, and skull ($P < 0.01$). The factors associated with increased BMD of both the femoral neck (load-bearing bone) and skull (non-load-bearing bone) were age, BMI, and co-existing diffuse OPLL in women and BMI and co-existing localized OPLL in men.

CONCLUSIONS

Patients with OPLL have increased whole-body BMD regardless of sex, indicating that it is not simply due to load-bearing from obesity. These findings suggested that OPLL is associated with a systemic pathology.

Keywords: ossification of the posterior longitudinal ligament, whole-body bone mineral density, dual-energy X-ray absorptiometry, systemic bone metabolism, obesity, osteoporosis, vertebral fracture, non-vertebral fracture

Introduction

Ossification of the posterior longitudinal ligament (OPLL) is a disease characterized by progressive heterotopic ossification of the spinal ligament, and it often occurs in the cervical spine of middle-aged to older men of the East Asian race [1-5]. The exact pathogenesis of the development and exacerbation of OPLL remains unknown. Several risk factors have been reported, including aging, genetic predisposition, chronic inflammation, abnormal glucose metabolism, dietary habits, and focal mechanical stress [6-11].

Recent studies further clarified the etiology of OPLL. The disease is broadly classified into thoracic and cervical OPLL subtypes, each with varying clinical characteristics. Thoracic OPLL is a relatively rare subtype; patients tend to have diffuse ossification of ligaments throughout the spinal ligament, including ossification of the ligamentum flavum (OLF) and OPLL, compared to those with cervical OPLL [6-10]. Furthermore, lifestyle-related diseases such as obesity and fatty liver are notable risk factors for the exacerbation of OPLL, especially in patients with thoracic OPLL [12]. These accumulated findings suggest that an abnormality in systemic bone metabolism underlies the etiology of OPLL.

Patients with OPLL have higher bone mineral density (BMD) levels measured at the lumbar spine than controls [13, 14], suggesting that increased osteogenic activity correlates with OPLL development. However, BMD at the lumbar spine, considered one of the common parameters of systemic bone metabolism, raises concerns that it may be overestimated in patients with OPLL because of the coexistence of ossification of spinal ligaments. Moreover, actual “whole-body” BMD in patients with OPLL has not been studied in detail. In this study, we hypothesized that patients with OPLL may have increased systemic BMD. To address this unresolved interpretation, we compared, for the

first time, the whole-body BMD of patients with symptomatic OPLL and those without spinal ligament ossification.

Materials and methods

Study design

This cross-sectional study, which was conducted in accordance with the Declaration of Helsinki (1964), included patients who underwent spine or hip surgery or received conservative treatment for OPLL from 2018 to 2022. The study was approved by the ethical review board of our institution. The need for informed consent from patients was waived because this study used de-identified data retrospectively.

Patients with OPLL

All the included patients with symptomatic OPLL regularly visited a single institution in Japan. The institution was located in a city of about 240,000 population in North Japan and was the only one with a spine center in the medical area covered by the institution. All patients were diagnosed and followed up by spine surgeons, orthopedic surgeons, and radiologists based on clinical symptoms and X-ray and computed tomography (CT) images. Of the 112 symptomatic patients with OPLL, 13 who had not undergone whole-body BMD measurement or CT in the entire spine were excluded. Hence, 99 patients with OPLL (42 men and 57 women) were included in the study.

To select controls with no spinal ligament ossification, we used preoperative data of patients who underwent spinal decompression, spinal fusion, or hip replacement surgery at the same institution. The control group was screened for the absence of neurological

deficits associated with OPLL via preoperative physical examination, stocked images, and past medical history. Of the 233 patients, 7 were excluded because of spinal ligament ossification. Eventually, 226 controls (71 men and 155 women) were included in this study. None of the OPLL and control participants had paralysis or severe walking disability, and they all visited the hospital outpatient clinic on foot.

Grouping of patients according to sex, age, and OPLL type

The participants were divided into four groups according to sex and the presence of OPLL: OPLL (+) and non-OPLL (OPLL [-]). They were further divided into middle-aged (age <70 years, 56 men and 82 women) and older adults (age ≥70 years, 57 men and 130 women) groups. The rationale for this grouping is that the incidence of osteoporosis in Japanese men and women increases in their 70s [15].

The patients with OPLL were divided into two groups according to the OPLL type: the "localized OPLL" group (OPLL only in the cervical spine) and the "diffuse OPLL" group (OPLL in the thoracic spine, regardless of co-existing OPLL in the cervical and lumbar spine) (Figure 1). This classification was based on our previous reports that patients with OPLL can be characterized into two groups based on the distribution pattern of OPLL. Most patients with cervical OPLL have localized OPLL in the cervical spine. In contrast, most patients with thoracic OPLL have diffuse ossification over the entire spinal ligament, including cervical OPLL, lumbar OPLL, and OLF [12, 16].

Clinical background and distribution of OPLL

Demographic data, including age, body mass index (BMI), comorbidities (hypertension, diabetes mellitus, and cancer), and history of treatment for osteoporosis, were obtained from all participants. The history of vertebral and non-vertebral fractures was also assessed. CT was performed using the Aquilion ONE™/GENESIS Edition system (Canon Medical Systems Corporation, Tochigi, Japan). The distribution of OPLL was assessed using sagittal reconstruction CT images of the entire spine. Two board-certified spine surgeons assessed all CT images, and disagreements were resolved by consensus to minimize intra- and inter-observer bias and errors.

Whole-body BMD

Participants received whole-body dual-energy X-ray absorptiometry (DXA) (Horizon, TOYO MEDIC, Tokyo, Japan) to measure BMD in the lumbar spine, thoracic spine, femoral neck, skull, ribs, entire upper extremity, entire lower extremity, and pelvis (Figure 2). Annual servicing and calibration of the equipment were performed according to the manufacturer's specifications, and daily quality control was performed by measuring a phantom supplied by the manufacturer.

Statistical analysis

Statistical analysis was performed using GraphPad Prism version 9 (GraphPad Software, San Diego, CA, USA). Statistical significance was set at $P < 0.05$. The normality of the data was tested using the Shapiro–Wilk test. The results are presented as median (minimum-maximum) for non-parametric variables (non-normally distributed data). The differences in continuous variables between the two groups were evaluated with the Mann–Whitney U

test. Differences in proportions were evaluated using Fisher's exact test. Three-group comparisons were conducted using the Kruskal–Wallis test to account for multiple tests. Bonferroni correction was performed to adjust the statistical significance to $P < 0.016$ (i.e., 0.05/3). To identify the independent factors on BMD of the skull and the femoral neck, we performed multivariable linear regression analysis after selecting the variables by the univariable linear regression analysis ($P < 0.10$).

Results

Higher whole-body BMD in the OPLL (+) group than in the OPLL (-) group

The patients' demographics and clinical characteristics are presented in Table 1. The OPLL (+) group shared quite similar age distribution with the OPLL (-) group, but BMI and BMD were different between the two groups. The BMI in the OPLL (+) group was significantly higher than that in the OPLL (-) group ($P < 0.001$). The incidence of history of treatment for osteoporosis and vertebral fractures was significantly lower in the OPLL (+) group than in the OPLL (-) group ($P < 0.001$ and $P = 0.009$, respectively). All the BMD values of the lumbar and thoracic spine, femoral neck, entire upper extremity, ribs, pelvis, entire lower extremity, and skull in the OPLL (+) group were significantly higher than those in the OPLL (-) group ($P < 0.001$) (Table 1).

We evaluated BMD between the OPLL (+) and OPLL (-) groups by sex. Among women, BMD in all body parts was significantly higher in the OPLL (+) group than in the OPLL (-) group ($P < 0.01$) (Table 2). The incidence of a history of osteoporosis treatment and vertebral fracture was significantly lower in the OPLL (+) group than in the OPLL (-) group ($P < 0.001$ and $P = 0.001$, respectively). Among men, BMD in all body parts, except

the entire upper extremity and ribs, was significantly higher in the OPLL (+) group than in the OPLL (-) group ($P < 0.05$) (Table 3). The incidence of a history of osteoporosis treatment was significantly lower in the OPLL (+) group than in the OPLL (-) group ($P < 0.01$).

Higher whole-body BMD in the OPLL (+) group than in the OPLL (-) group in middle-aged and older patients

We also evaluated the age-specific differences in BMD between the OPLL (+) and OPLL (-) groups. Among middle-aged women, BMD of the lumbar and thoracic spine, femoral neck, pelvis, and skull was significantly higher in the OPLL (+) group than in the OPLL (-) group ($P < 0.05$) (Table 4). The incidence of a history of osteoporosis treatment among middle-aged women in the OPLL (+) group was lower than that in the OPLL (-) group ($P = 0.001$). Among the older women in the OPLL (+) group, BMD in all body parts was significantly higher ($P < 0.01$), and the incidence of a history of osteoporosis treatment and vertebral fracture was significantly lower ($P < 0.001$) than in the OPLL (-) group (Table 4). The rate of history of non-vertebral fractures among older women was also lower in the OPLL (+) group than in the OPLL (-) group, although the difference was not significant ($P = 0.09$). Among middle-aged men, BMD of the lumbar and thoracic spine was significantly higher in the OPLL (+) group than in the OPLL (-) group ($P = 0.001$ and $P < 0.001$, respectively). Among older men in the OPLL (+) group, BMD in all body parts, except the ribs, entire upper extremity, and skull, was significantly higher than that in the OPLL (-) group ($P < 0.01$) (Table 5). The number of older men in the OPLL (+) group receiving treatment for osteoporosis was lower than that in the OPLL (-) group, although the

difference was not significant (P =0.10). There was no significant difference between the two groups in the incidence of a history of fracture among middle-aged and older men, respectively.

Higher whole-body BMD in both the localized- and diffuse-OPLL groups than in the OPLL (-) group

Next, we evaluated the differences in BMI according to the OPLL type. Patients' demographics and clinical information in the localized-OPLL, diffuse-OPLL, and OPLL (-) groups are presented in Supplemental Table 1. In both men and women, the BMI was significantly higher in the diffuse-OPLL group than in the OPLL (-) group (P <0.001). The incidence of a history of vertebral fractures among women was significantly lower in the diffuse OPLL group than in the OPLL (-) group (P <0.01).

Comparisons of whole-body BMD among the localized-OPLL, diffuse-OPLL, and OPLL (-) groups are presented in Supplemental Figure 1. Regarding women, the BMD of the lumbar and thoracic spine, as well as femoral neck, rib, pelvis, and entire lower extremity, was significantly higher in the diffuse-OPLL group than in the OPLL (-) group (P <0.001 for the lumbar spine, thoracic spine, femoral neck, rib, pelvis, and skull; P <0.01 for the entire lower extremity; P <0.05 for the entire upper extremity). Regarding men, the BMD of the lumbar and thoracic spine in both the localized-OPLL and diffuse-OPLL groups was significantly higher than that in the OPLL (-) group (P <0.01). The BMD of the femoral neck in the localized-OPLL group was significantly higher than that in the OPLL (-) group (P <0.01).

OPLL as a factor associated with BMD of the femoral neck and skull

To investigate factors associated with whole-body BMD, excluding the spine, we performed multivariable linear regression analysis in all participants on the association of factors with the BMD of the femoral neck (load-bearing bone) and skull (non-load-bearing bone). We selected these two parts of the body for the following reasons: 1) to minimize overestimation of BMD due to the influence of arthropathy, which may be included in the measurement area, and 2) to evaluate whether BMD is affected by the overweight of patients with OPLL or by OPLL itself. The analysis was performed separately for women and men. Among women, age, BMI, and co-existing diffuse OPLL were associated with the BMD of both the skull and the femoral neck (Tables 6 and 7). Among men, BMI and co-existing localized OPLL were associated with the BMD of both the skull and the femoral neck (Tables 6 and 7).

Discussion

In this study, we focused on whole-body BMD as the primary indicator reflecting the effects of systemic bone metabolism and compared these in patients with OPLL and non-OPLL. Our results showed that in both men and women, patients with OPLL had a higher whole-body BMD than non-OPLL patients. A sub-analysis showed that middle-aged (age <70 years) women and older (age ≥70 years) men and women with OPLL had higher whole-body BMD than non-OPLL patients. The lower proportion of osteoporosis and vertebral fractures in patients with OPLL than in non-OPLL patients also supports the finding of high whole-body BMD in patients with OPLL.

Multivariable linear regression analysis showed that the BMD of the femoral neck and skull was significantly associated with the presence of diffuse OPLL in women and localized OPLL in men, suggesting that the increase of BMD is not simply owing to load-bearing from obesity in patients with OPLL but owing to increase in systemic bone formation. Previous studies showed that the BMD of the lumbar spine and femur was significantly higher in patients with cervical OPLL than in those with non-ligamentous ossification in the spine [14, 17, 18]. One study also found that lumbar spine BMD in patients with OPLL was positively correlated with the number of intervertebral segments affected by OPLL in the cervical spine [17]. A recent study reported that female patients with symptomatic OPLL had greater bone strength than non-OPLL patients, as shown by quantitative CT-based finite element analysis [19]. Regarding patients with OPLL, the value of lumbar spine BMD measured using DXA would sometimes be exaggerated by OPLL itself and may not represent the actual BMD of the spine.

Therefore, we needed to measure whole-body BMD in patients with OPLL. In the present study, high whole-body BMD in patients with OPLL was prominent among older women, who generally had significant osteoporosis. High BMD was also observed in older men with OPLL in most parts of the body, supporting the idea that OPLL is associated with systemic bone metabolism. Diffuse OPLL has a strong tendency toward ossification in the entire spinal ligament [16]. Therefore, we thought it reasonable that the results of this study showed that diffuse OPLL was significantly associated with BMD of the femoral neck and skull in women. However, it was contrary to our expectations that localized but not diffuse OPLL was significantly associated with BMD of the femoral neck and skull in men. It was difficult to explain clearly why the results differed between men and women at this time.

Further studies are needed to investigate the differences in risk factors between the sexes, which may be due to the multifactorial nature of OPLL.

This study showed that obesity is also likely to increase whole-body BMD. Obesity is traditionally considered beneficial for increased BMD and protects against osteoporosis, and the incidence of bone fragility fractures decreases with increasing BMI. Physiological mechanical loading associated with weight stimulates bone formation by decreasing the apoptosis of osteoblasts and osteocytes and increasing their proliferation and differentiation through the Wnt/β-catenin signaling pathway [20, 21]. In contrast, recent reports indicate that excessive fat mass may not protect humans from osteoporosis. As adipocytes and osteoblasts are derived from common multi-potential mesenchymal stem cells, promoting their differentiation into adipocytes due to obesity would relatively suppress osteoblast differentiation and decrease bone formation [22].

Furthermore, obesity is significantly associated with musculoskeletal degeneration and inflammation and may increase bone resorption by upregulating the levels of inflammatory cytokines such as interleukin-6 and tumor necrosis factor-α [23]. These inflammatory cytokines can stimulate osteoclast activity by modulating the receptor-activator of nuclear factor kappa beta ligand/receptor-activator of nuclear factor kappa beta/osteoprotegerin pathway [24, 25]. Some studies suggest that high body weight and BMI are independent risk factors for fractures apart from BMD [26, 27], and no complete consensus remains about the relationship between obesity and fractures.

The interpretation of the fact that patients with OPLL sometimes have decreased vertebral bone density requires some caution. Hyperostosis, as represented by OPLL and diffuse idiopathic skeletal hyperostosis, results in stress-shield-induced osteoporosis of the

vertebral bones due to ankylosis associated with heterotopic ossification of the spinal ligaments, with or without obesity [28]. A recent nationwide cohort study in Korea showed that OPLL was significantly associated with osteoporosis [29]. However, the participants in that study did not receive whole-body DXA and were enrolled as having osteoporosis based on whether the disease was listed in the database. Although decreased BMD in ankylosed vertebral bones can cause fractures and other serious problems, we emphasize that osteoporosis in patients with OPLL does not necessarily result from decreased BMD in the whole body.

This study had several limitations. First, the sample size was small. Second, only patients with symptomatic OPLL who regularly visited the hospital were enrolled in the study. The exclusion of asymptomatic patients from the study may have introduced selection bias. Furthermore, based on the characteristics of the institution where data sampling was conducted, we had expected that the study would include many patients with OPLL with relatively severe symptoms. As expected, many patients with diffuse type OPLL, considered even rarer than those with localized type OPLL, were enrolled (Supplementary Table 1). Unlike localized type OPLL, which is twice as common in men as in women, diffuse type OPLL is more common in women (male:female = 1:3) and is often more difficult to treat [11, 30]. Also, including a high proportion of female participants with diffuse OPLL affects the male/female ratio of all participants with OPLL. Third, this study included only patients who lived in the cold regions of northern Japan. The results do not necessarily apply to people living in regions with different sunlight conditions or of different ethnicities. Fourth, this study did not investigate bone metabolism laboratory markers or bone morphometry. Therefore, it is impossible to conclude whether the increase

in whole-body BMD in patients with OPLL was due to the increased bone formation capacity. Finally, we could not completely rule out the possibility of patients with OPLL in the control group because we could not perform whole-spine CT scans on patients in the control group due to ethical considerations. Based on an epidemiological study reporting the prevalence of OPLL in the Japanese population (cervical OPLL: 1.9–4.3%, thoracic OPLL: 0.8%) [1-5, 11], it seems unlikely that the risk of including participants with OPLL in the control group would affect the interpretation of the present findings.

In conclusion, the present study revealed elevated whole-body BMD in patients with OPLL. Diffuse OPLL, characterized by obesity and a strong tendency toward ossification of spinal ligaments, in women, and localized OPLL in men were significantly associated with elevated whole-body BMD. These findings strongly suggest that OPLL is associated with systemic pathology as well as local stress. The results of this study will help to elucidate further the pathophysiology of OPLL.

Competing Interests

The authors declare no competing interests.

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Figure Legends

Figure 1. Representative examples of OPLL types evaluated using whole-spine CT. OPLL existing only in the cervical spine is defined as localized-OPLL (a), and that existing in the entire spine, including the thoracic spine, with or without cervical OPLL, is defined as diffused-OPLL (b) (arrowheads indicate OPLL and arrows indicate OLF).

OPLL, ossification of the posterior longitudinal ligament; CT, computed tomography; OLF, ossification of the ligamentum flavum.

Figure 2. Images of whole-body BMD obtained by DXA. A 68-year-old woman with a BMI of 24.5 kg/m^2 in the OPLL (-) group (a). A 72-year-old woman with a BMI of 27.8 kg/m^2 in the OPLL (+) group (b). Patients with OPLL have higher whole-body BMD and spine BMD than control individuals.

BMD, bone mineral density; BMI, body mass index; DXA, dual-energy X-ray absorptiometry; OPLL, ossification of the posterior longitudinal ligament; T,thoracic; L, lumbar

Supplemental Figure 1. Comparison of the whole-body BMD among OPLL (-), localized-OPLL, and diffuse-OPLL groups. *: P <0.001 vs. OPLL (-) group. †: P <0.01 vs. OPLL (-) group. ‡: P <0.05 vs. OPLL (-) group

BMD, bone mineral density; OPLL, ossification of the posterior longitudinal ligament

Table 1. Comparison of the characteristics between the OPLL (-) and OPLL (+) groups

Variable	OPLL (-) (n = 226)	OPLL (+) (n = 99)	P-value
Age (years)	72 (37－89)	72 (35－87)	0.71
Years (%):			
30–39	2	1	0.99
40–49	12	5	0.99
50–59	27	11	0.99
60–69	54	25	0.78
70–79	75	33	0.99
80–89	54	24	0.99
BMI (kg/m^2)	23.4 (15.3－39.9)	26.1 (17.0－42.8)	<0.001
Male (%)	31.4	42.4	0.06
Comorbidities (%):			
Hypertention	52.2	63.6	0.06
Diabetes mellitus	19.0	32.3	0.01
Past history (%):			
Osteoporosis treatment	55.3	12.1	<0.001
Vertebral fracture	15.4	5.0	0.009
Non-vertebral fracture	10.1	4.0	0.08
BMD (g/cm^2):			
Lumbar spine	0.93 (0.26－2.03)	1.15 (0.55－1.86)	<0.001
Thoracic spine	0.75 (0.50－1.65)	0.99 (0.52－1.81)	<0.001
Femoral neck	0.61 (0.36－1.18)	0.73 (0.40－1.85)	<0.001
Entire upper extremity	0.64 (0.37－0.99)	0.70 (0.52－1.66)	<0.001
Rib	0.57 (0.39－0.97)	0.64 (0.43－1.06)	<0.001
Pelvis	0.96 (0.62－1.51)	1.13 (0.64－1.60)	<0.001
Entire lower extremity	0.95 (0.63－1.90)	1.07 (0.78－1.48)	<0.001
Skull	1.77 (0.68－2.90)	1.97 (1.21－2.74)	<0.001
Total	0.93 (0.49－1.41)	1.10 (0.77－2.41)	<0.001

Data are shown as median (minimum–maximum) or as percentage.

OPLL, ossification of the posterior longitudinal ligament; BMI, body mass index; BMD, bone mineral density.

Table 2. Comparison of the BMD between the OPLL (-) and OPLL (+) groups in women

Variable	OPLL (-) (n = 155)	OPLL (+) (n = 57)	P-value
Age (years)	73 (42－89)	73 (42－87)	0.56
BMI (kg/m^2)	23.0 (15.3－39.9)	25.7 (17.0－42.8)	0.001
Past history (%):			
Osteoporosis treatment	67.0	17.5	<0.001
Vertebral fracture	27.1	4.3	0.001
Non-vertebral fracture	17.7	6.5	0.08
BMD (g/cm^2):			
Lumbar spine	0.85 (0.26－1.54)	1.09 (0.54－1.85)	<0.001
Thoracic spine	0.71 (0.49－1.23)	0.88 (0.52－1.61)	<0.001
Femoral neck	0.57 (0.35－1.18)	0.67 (0.39－0.97)	<0.001
Entire upper extremity	0.60 (0.36－0.87)	0.63 (0.52－1.66)	<0.01
Rib	0.54 (0.41－0.81)	0.58 (0.42－1.05)	<0.001
Pelvis	0.90 (0.62－1.36)	1.03 (0.63－1.56)	<0.001
Entire lower extremity	0.95 (0.62－1.90)	0.97 (0.77－1.37)	<0.001
Skull	1.69 (0.68－2.89)	1.93 (1.28－2.73)	<0.001
Total	0.88 (0.49－1.25)	1.01 (0.77－1.82)	<0.001

Data are shown as median (minimum–maximum) or as percentage.

OPLL, ossification of the posterior longitudinal ligament; BMI, body mass index; BMD, bone mineral density.

Table 3. Comparison of the BMD between the OPLL (-) and OPLL (+) groups in men

Variable	OPLL (-) (n = 71)	OPLL (+) (n = 42)	P-value
Age (years)	68 (37－86)	71 (35－87)	0.56
BMI (kg/m^2)	24.0 (17.4－31.2)	26.2 (18.8－42.5)	0.001
Past history (%):			
Osteoporosis treatment	23.9	4.7	<0.01
Vertebral fracture	4.2	4.7	0.99
Non-vertebral fracture	2.8	2.3	0.99
BMD (g/cm^2):			
Lumbar spine	1.08 (0.42－2.02)	1.38 (0.85－1.78)	<0.001
Thoracic spine	0.94 (0.64－1.65)	1.18 (0.67－1.80)	<0.001
Femoral neck	0.72 (0.39－1.04)	0.79 (0.60－1.84)	<0.01
Entire upper extremity	0.79 (0.59－0.98)	0.81 (0.58－1.00)	0.27
Rib	0.69 (0.39－0.97)	0.72 (0.48－0.99)	0.19
Pelvis	1.08 (0.62－1.51)	1.19 (0.79－1.60)	<0.01
Entire lower extremity	1.16 (0.86－1.50)	1.21 (0.84－1.48)	0.02
Skull	1.85 (1.21－2.35)	2.01 (1.21－2.46)	0.02
Total	1.09 (0.86－1.40)	1.18 (0.85－2.41)	<0.01

Data are shown as median (minimum–maximum) or as percentage.

OPLL, ossification of the posterior longitudinal ligament; BMI, body mass index; BMD, bone mineral density.

Table 4. Comparison of the BMD between the OPLL (-) and OPLL (+) groups in women

Variable	Middle-aged adults (age <70 years)			Older adults (age ≥70 years)		
	OPLL (-) (n = 59)	OPLL (+) (n = 23)	P-value	OPLL (-) (n = 96)	OPLL (+) (n = 34)	P-value
Age (years)	63.0 (42－69)	60.0 (42－69)	0.46	78 (70－89)	78 (70－87)	0.76
BMI (kg/m^2)	23.8 (15.3－39.9)	26.4 (17.0－42.8)	0.06	22.4 (15.3－33.8)	25.0 (17.1－34.4)	0.007
Past history (%):						
Osteoporosis treatment	45.7	8.6	0.001	80.2	23.5	<0.001
Vertebral fracture	0	0	NA	33.3	5.8	<0.001
Non-vertebral fracture	3.3	0	NA	19.7	8.8	0.09
BMD (g/cm^2)						
Lumbar spine	0.93 (0.49－1.54)	1.12 (0.55－1.86)	<0.001	0.82 (0.26－1.41)	1.06 (0.55－1.47)	<0.001
Thoracic spine	0.75 (0.58－1.23)	0.93 (0.52－1.61)	<0.001	0.68 (0.50－1.13)	0.88 (0.64－1.25)	<0.001
Femoral neck	0.62 (0.41－1.18)	0.69 (0.43－0.98)	<0.001	0.54 (0.36－0.96)	0.63 (0.40－0.90)	<0.001
Entire upper extremity	0.64 (0.48－0.88)	0.68 (0.53－1.66)	0.30	0.58 (0.37－0.71)	0.62 (0.52－0.72)	0.006
Rib	0.56 (0.43－0.81)	0.59 (0.43－1.06)	0.08	0.53 (0.41－0.81)	0.58 (0.44－0.80)	<0.001
Pelvis	1.00 (0.66－1.37)	1.15 (0.64－1.57)	<0.001	0.87 (0.68－1.25)	0.97 (0.68－1.45)	<0.001
Entire lower extremity	0.95 (0.78－1.90)	1.02 (0.80－1.38)	0.07	0.86 (0.63－1.20)	0.94 (0.78－1.23)	0.003
Skull	1.86 (0.77－2.79)	2.08 (1.29－2.65)	0.04	1.61 (0.68－2.90)	1.80 (1.44－2.74)	<0.001
Total	0.96 (0.49－1.25)	1.05 (0.77－1.14)	0.08	0.86 (0.68－1.02)	0.97 (0.83－1.82)	<0.001

Data are shown as median (minimum–maximum) or as percentage.

OPLL, ossification of the posterior longitudinal ligament; BMI, body mass index; BMD, bone mineral density; NA, not available.

Table 5. Comparison of the BMD between the OPLL (-) and OPLL (+) groups in men

Variable	Middle-aged adults (age <70 years)			Older-aged adults (age ≥70 years)		
	OPLL (-) (n = 36)	OPLL (+) (n = 20)	P-value	OPLL (-) (n = 35)	OPLL (+) (n = 22)	P-value
Age (years)	59.0 (37－68)	62.0 (35－69)	0.13	78 (70－86)	78 (71－87)	0.50
BMI (kg/m^2)	24.6 (18.1－31.2)	26.7 (20.4－42.5)	0.03	22.5 (15.3－33.8)	25.0 (17.1－34.4)	0.10
Past history (%):						
Osteoporosis treatment	19.4	0	NA	28.5	9.0	0.10
Vertebral fracture	0	0	NA	8.6	9.0	0.99
Non-vertebral fracture	2.7	5.0	0.99	2.8	0	NA
BMD (g/cm^2)						
Lumbar spine	1.04 (0.42－1.55)	1.25 (0.85－1.78)	0.001	1.10 (0.58－2.02)	1.44 (0.87－1.78)	<0.001
Thoracic spine	0.92 (0.64－1.42)	1.08 (0.71－1.80)	<0.001	0.68 (0.50－1.13)	0.88 (0.64－1.25)	<0.001
Femoral neck	0.73 (0.39－1.04)	0.79 (0.61－1.00)	0.24	0.54 (0.35－0.96)	0.63 (0.40－0.90)	0.006
Entire upper extremity	0.81 (0.59－0.98)	0.82 (0.73－1.00)	0.57	0.58 (0.37－0.71)	0.62 (0.52－0.72)	0.25
Rib	0.69 (0.40－0.97)	0.72 (0.52－1.00)	0.42	0.53 (0.41－0.81)	0.58 (0.44－0.80)	0.32
Pelvis	1.10 (0.62－1.51)	1.18 (0.84－1.60)	0.20	0.87 (0.68－1.25)	0.97 (0.68－1.45)	0.008
Entire lower extremity	1.16 (0.98－1.50)	1.19 (1.00－1.48)	0.52	0.86 (0.63－1.20)	0.94 (0.78－1.23)	0.008
Skull	1.85 (0.98－2.35)	1.92 (1.21－2.46)	0.16	1.61 (0.68－2.90)	1.80 (1.44－2.74)	0.064
Total	1.11 (0.86－1.40)	1.14 (0.91－2.41)	0.24	0.86 (0.68－1.02)	0.98 (0.83－1.82)	0.007

Data are shown as median (minimum–maximum) or as percentage.

OPLL, ossification of the posterior longitudinal ligament; BMI, body mass index; BMD, bone mineral density; NA, not available.

Table 6. Univariable and multivariable linear regression analysis for factors associated with the BMD of skull

Independent variables	Univariable		Multivariable	
	β (95% CI)	P-value	β (95% CI)	P-value
(Women)				
Age (years)	-0.014 (-0.018－0.010)	<0.001	-0.012 (-0.016－-0.008)	<0.001
BMI (kg/m^2)	0.02 (0.01－0.03)	<0.001	0.01 (0.00－0.02)	<0.001
Hypertension	0.01 (-0.08－0.11)	0.76		
Diabetes mellitus	0.06 (-0.06－0.18)	0.32		
Localized-OPLL	0.17 (-0.07－0.42)	0.16		
Diffuse-OPLL	0.07 (0.03－0.11)	<0.001	0.15 (0.04－0.26)	0.004
(Men)				
Age (years)	0.0009 (-0.0031－0.0049)	0.65		
BMI (kg/m^2)	0.012 (0.001－0.023)	0.03	0.01 (0.00－0.02)	0.04
Hypertension	0.06 (-0.03－0.16)	0.76		
Diabetes mellitus	0.03 (-0.07－0.14)	0.49		
Localized-OPLL	0.12 (0.01－0.23)	0.02	0.11 (0.00－0.22)	0.03
Diffuse-OPLL	0.01 (-0.14－0.17)	0.83		

BMD, bone mineral density; β, regression coefficient; CI, confidence interval; BMI, body mass index; OPLL, ossification of the posterior longitudinal ligament

Table 7. Univariable and multivariable linear regression analysis for factors associated with the BMD of femoral neck

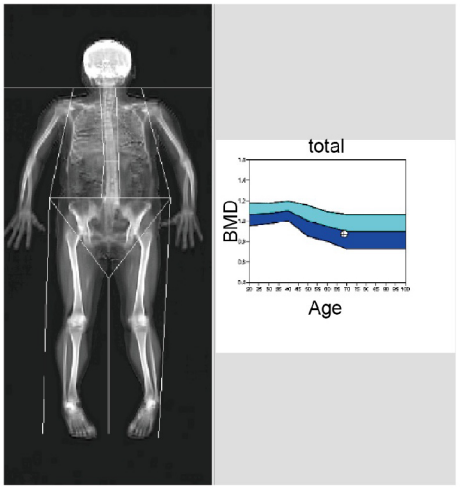
Independent variables	Univariable		Multivariable	
	β (95% CI)	P-value	β (95% CI)	P-value
(Women)				
Age (years)	-0.004 (-0.006－-0.002)	<0.001	-0.003 (-0.005－-0.002)	<0.001
BMI (kg/m^2)	0.012 (0.009－0.015)	<0.001	0.009 (0.006－0.013)	<0.001
Hypertension	-0.003 (-0.040－0.033)	0.85		
Diabetes mellitus	0.06 (0.01－0.10)	0.005	0.02 (-0.01－0.06)	0.23
Localized-OPLL	0.06 (-0.02－0.15)	0.13		
Diffuse-OPLL	0.07 (0.03－0.11)	<0.001	0.04 (0.003－0.081)	0.03
(Men)				
Age (years)	0.0001 (-0.0026－0.0029)	0.91		
BMI (kg/m^2)	0.010 (0.003－0.018)	0.006	0.008 (0.001－0.016)	0.02
Hypertension	0.070 (0.002－0.137)	0.04	0.03 (-0.02－0.10)	0.25
Diabetes mellitus	0.0005 (-0.0759－0.0769)	0.98		
Localized-OPLL	0.12 (0.05－0.19)	0.001	0.10 (0.03－0.18)	0.003
Diffuse-OPLL	0.01 (-0.09－0.12)	0.77		

BMD, bone mineral density; β, regression coefficient; CI, confidence interval; BMI, body mass index; OPLL, ossification of the posterior longitudinal ligament


a
Localized-OPLL
b
Diffuse-OPLL

a

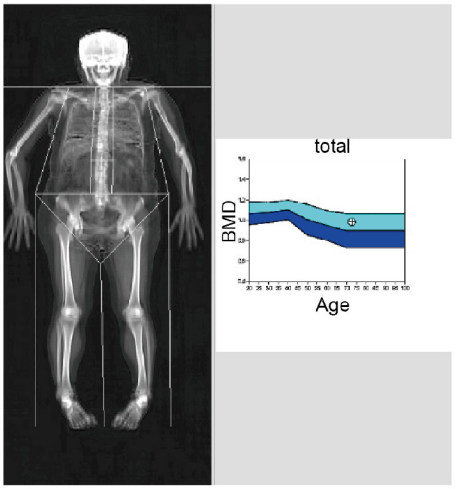
OPLL (−)



part	BMD (g/cm^3)
Lt. upper extremity	0.593
Rt. upper extremity	0.586
Lt. rib	0.572
Rt. rib	0.550
T. spine	0.791
L. spine	0.893
Pelvis	0.919
Lt. lower extremity	0.918
Rt. lower extremity	0.941
Skull	1.464

b

OPLL (+)



part	BMD (g/cm^3)
Lt. upper extremity	0.650
Rt. upper extremity	0.679
Lt. rib	0.608
Rt. rib	0.553
T. spine	0.964
L. spine	1.400
Pelvis	1.047
Lt. lower extremity	0.939
Rt. lower extremity	0.980
Skull	1.754