

Incidence of ossification of the spinal ligaments in acromegaly patients

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ABSTRACT

Some previous case reports have implied a relationship between acromegaly and ossification of the spinal ligaments. However, there have been no reports of a case series exploring the incidence of ossification of the spinal ligaments in patients with acromegaly. To this end, computed tomography (CT) of the spine in 10 consecutive patients with acromegaly was examined in this study. Five out of 10 patients had ossification of the spinal ligaments. Among them, two patients had ossification of the posterior longitudinal ligament (OPLL), which was noticeably higher than the prevalence of OPLL in the general adult population (1.9–4.3 %). Body mass index was significantly higher in the group with spinal ligament ossification ($p = 0.03$), but there were no significant differences in age, sex, serum phosphate, albumin-adjusted calcium, growth hormone (GH), standard deviation of insulin-like growth factor-1 (IGF-1), or the incidence of diabetes mellitus between the groups with or without ossification of the spinal ligaments. The ossification index (OS index) was used to determine the severity of spinal ligament ossification, and there were no significant correlations between the OS index and GH or IGF-1 ($p = 0.51$ and 0.75 , respectively). This study was the first to report a high prevalence of spinal ossification in patients with acromegaly. In conclusion, this study suggested a possible association between acromegaly and ossification of the spinal ligaments, although the number of patients was insufficient to draw a conclusion. Acromegaly patients should be tested to confirm, or rule out, spinal ossification, and further studies to clarify the underlying mechanism of spinal ossification in acromegaly patients are warranted.

1. Introduction

Acromegaly is a disorder caused by the development of growth hormone (GH)-producing pituitary adenoma, and results in an increase in GH and insulin-like growth factor-1 (IGF-1). The oversecretion of GH and IGF-1 not only causes hypertrophic changes, including swelling of the soft tissue in the hands and feet, characteristic facial appearance, and cardiac hypertrophy but also causes various metabolic symptoms, such as hypertension and glucose intolerance, and has a predisposition toward some malignancies (Vilar et al., 2017). Osteoarticular involvement is also a well-known complication of acromegaly, which is associated with narrowing of the joint space, osteophytes, and has other characteristic symptoms of osteoarthritis in the chronic phase (Barkan, 1997).

Ossification of the posterior longitudinal ligament, anterior longitudinal ligament, and ligamentum flavum are called ossification of the posterior longitudinal ligament (OPLL), ossification of the anterior longitudinal ligament (OALL), and ossification of the ligamentum

flavum (OLF), respectively, because spinal ligaments are thickened, ossified, or elongated and sometimes unified with each other. In particular, OPLL is associated with severe symptoms due to spinal compression and often interferes with daily life. The prevalence of spinal ligament ossification varies widely by race and region (Stapleton et al., 2011). The prevalence of OPLL in Japanese individuals was reported to be 1.9–4.3 % (Sasaki et al., 2014; Shingyouchi et al., 1996; Stapleton et al., 2011; Yoshimura et al., 2014). Although the prevalence of OALL in the whole spine was not available, the incidence of cervical spine OALL in late middle-aged males was reported to be 23.1 % (Shingyouchi et al., 1996). Diffuse idiopathic skeletal hyperostosis (DISH), a complication associated with OALL and bone fragility, was found in 25 % of OPLL patients (Ehara et al., 1998). The prevalence of OLF in Japanese patients ranges from 12 % to 34 % (Fujimori et al., 2016; Kim et al., 2018; Mori et al., 2013).

Several disorders were reported to be associated with spinal ligament ossification, such as diabetes mellitus (Bakhsh et al., 2019; Kobashi

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et al., 2004), obesity (Kobashi et al., 2004), hypoparathyroidism (Ichinose et al., 2020; Sohail et al., 2018), hereditary fibroblast growth factor (FGF) 23-related hypophosphatemic rickets/osteomalacia (Karaplis et al., 2012; Kato et al., 2022; Kato et al., 2021) (previously known as vitamin D-resistant rickets (Lee et al., 2012)), and myotonic dystrophy (Ishizawa et al., 2014; Kinoshita et al., 1997). Regarding multifactorial inheritance, in 2014, a genome-wide association study (GWAS) revealed several susceptibility genes for OPLL (Nakajima et al., 2014). There have been some case reports that implied an association between acromegaly and spinal ligament ossification (Kamakura et al., 2021; Schmidt et al., 2013). However, there was no method to ascertain whether the reported co-occurrence of these two conditions was a coincidence or causal association, as there has been no report of consecutive cases. To this end, in the current study, 10 consecutive patients with acromegaly underwent spinal CT to explore comorbidity of spinal ligament ossification.

2. Methods

A total of 10 consecutive acromegaly patients who visited the University of Tokyo Hospital from December 2020 to December 2021 were included. The patients were eligible to be included regardless of the treatment status of acromegaly and other comorbidities, including diabetes mellitus and obesity.

The diagnosis of acromegaly was made according to the official criteria in Japan (bottom value of growth hormone being 0.4 µg/L and more during the 75 g oral glucose tolerance test).

Ossification of the spinal ligaments was evaluated with plane CT conducted for the entire spine. Two experienced orthopedic surgeons (HK & YT) evaluated the CT images and calculated the ossification of the posterior/anterior/yellow ligament indices (OP/OA/OF indices) described below. The OP index was adopted to quantitatively evaluate the extent of ossified lesions of OPLL as previously reported (Kawaguchi et al., 2013; Kawaguchi et al., 2016; Kawaguchi et al., 2017). This index represents the sum of the vertebral bodies and intervertebral discs with OPLL. Similarly, the OA index and OF index were adopted to evaluate

the severity of OALL and OLF, respectively, according to a previous report (Kato et al., 2021). The total ossification index (OS index) was calculated by the sum of the OA, OP and OF indices. The OS index was used as the representative value for the severity of spinal ligament ossification in each patient.

A two-sample *t*-test was adopted to compare the means of two independent groups. The chi-square test was used to test the relationships between categorical variables.

All procedures involving the participants in the current study were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study protocols were approved by the institutional review board of the University of Tokyo (approval number: 2879-(7)).

3. Results

The basic characteristics of 10 consecutive acromegaly patients are shown in Table 1. Five out of 10 patients (50 %) had ossification of the spinal ligaments (Table 1, Fig. 1). Two patients (Nos. 1 and 5) had OPLL, and one (No. 1) underwent decompression surgery for thoracic OPLL. Patient No. 1 and Patient No. 5 had OALL and OLF in addition to OPLL (Table 2, Fig. 1). The other three patients (Nos. 2–4) had both OALL and OLF. There was no significant difference in the correlation between the OS index and GH or IGF-1 ($p = 0.51$ and 0.75 , respectively). Representative CT images of the cervical, thoracic, and lumbar spine of the patients with spinal ligament ossification are presented in Fig. 1.

Of the five patients with ossification of the spinal ligaments, four were yet to be treated for acromegaly, and the other patient (patient No. 3) underwent surgery for pituitary adenoma. Patient No. 1 underwent laminectomy from Th7 to L2 and posterior spinal fusion from Th5 to L2 for OPLL. Of the five patients without ossification of the spinal ligaments, four were undergoing pretreatment, and the other patient (patient No. 7) was treated with a monthly injection of octreotide acetate for five years (Table 1).

Table 1
Characteristics of 10 consecutive acromegaly patients.

Patient no.	Acromegaly patients with spinal ligament ossification					Acromegaly patients without spinal ligament ossification				
	1	2	3	4	5	6	7	8	9	10
Age/sex	38 M	50 M	54 M	59 M	66 F	23 M	52 M	60 M	67 M	71 M
Condition	Before Tx	Before Tx	23 years after surgery	Before Tx	Before Tx, under hemodialysis	Before Tx	5 years Tx with octreotide acetate	Before Tx	Before Tx	Before Tx
Estimated disease duration (years)	9	7	3	1	11	5	3	5	1	8
Height (cm)	178.8	175.0	183.5	174.0	141.0	191.0	175.0	175.0	172.5	160.0
Weight (kg)	79.2	76.0	98.2	83.0	61.0	80.9	80.0	78.2	68.5	55.0
BMI (kg/m ²)	24.8	24.8	29.2	27.4	30.7	22.2	26.1	25.5	19.7	21.5
P (mg/dL) (RR 2.7–4.6)	N/A	4.2	2.8	3.4	6.4	4.2	3.8	5.1	4.2	4.3
cCa (mg/dL) (RR 8.8–10.1)	9.3	9	9.2	9.2	11.2	9.8	8.6	9.6	9.3	9.4
Cre (mg/dL) (RR 0.65–1.07)	0.49	0.67	0.82	0.51	6.45	0.95	0.63	0.79	0.57	1.01
ALP (U/L) (RR 38–113)	127	124	148	104	142	70	75	92	96	18 ^a
Intact PTH (pg/mL) (RR 25.8–75.7)	N/A	98	N/A	29	467	30	30	24	N/A	29
GH (ng/mL)	41.6	19.0	0.18 ^b	6.98	9.40	18.8	3.33 ^c	47.0	16.9	6.89
IGF-1 (SD)	+18.6	+7.5	+1.9 ^b	+9.0	+6.4	+7.1	+1.7 ^c	+7.0	+6.0	+5.2
Pituitary MRI T2WI	Low	Low	N/A	N/A	Iso	Iso	N/A	Low	Low	N/A
Diabetes mellitus	+	–	+	+	–	–	+	–	–	+

Estimated disease duration: period between onset of symptoms and the moment of conducting CT scan, or period between onset of symptoms and initiation of treatment for acromegaly, whichever is shorter.

BMI: body mass index, P: serum phosphate, cCa: albumin adjusted calcium, Cre: serum creatinine, ALP: alkaline phosphatase, intact PTH: intact parathyroid hormone, GH: growth hormone, IGF-1: insulin-like growth factor-1, SD: standard deviation, MRI T2WI: T2 weighted magnetic resonance image of the GH producing pituitary tumor, Tx: Treatment, RR: reference range.

^a Value was normalized after thyroid hormone replacement therapy.

^b Values were measured after surgery.

^c Values were measured after the initiation of treatment with octreotide acetate.

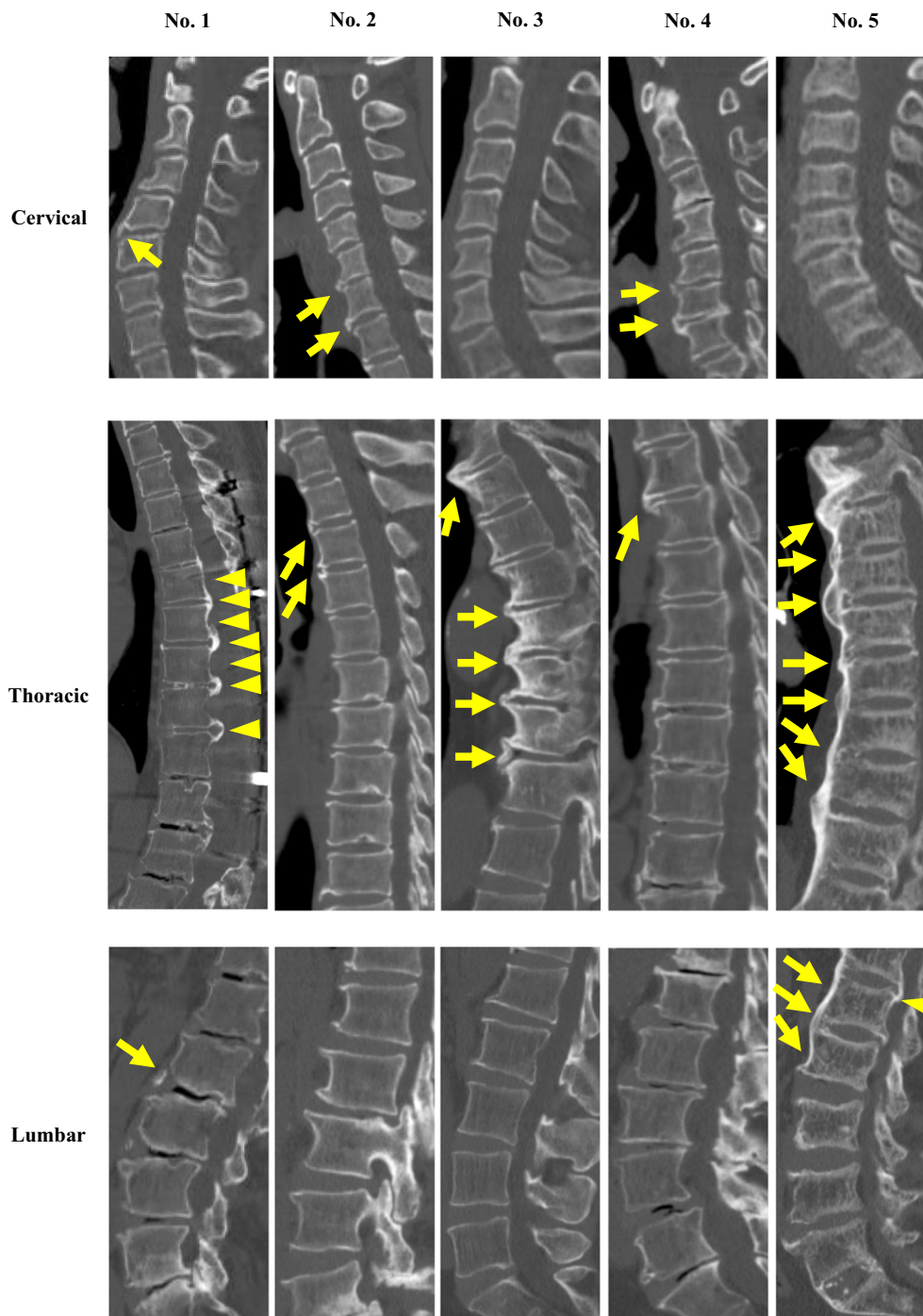


Fig. 1. CT images of the cervical, thoracic, and lumbar spine in acromegaly patients with spinal ligament ossification. Sagittal CT images demonstrated representative presentations of OALL (arrows) and OPLL (arrowheads). Patient No. 1 underwent laminectomy from Th7 to L2 and posterior spinal fusion from Th5 to L2 for OPLL.

There were no significant differences in age, sex, estimated disease duration, serum phosphate, albumin-adjusted calcium, GH, standard deviation of IGF-1, or presence of diabetes mellitus between the groups with or without ossification of the spinal ligaments. Body mass index (BMI) was the only significant difference between the groups. The patients with spinal ligament ossification had significantly higher BMIs ($p = 0.03$) (Table 3).

4. Discussion

Although some previous case reports implied an association between

acromegaly and spinal ligament ossification (Kamakura et al., 2021; Schmidt et al., 2013), they were not conclusive because there have been no reports of a consecutive case series or prospective studies. In the current study, among the 10 consecutive acromegaly patients, 5 (50 %) had spinal ligament ossification and 2 (20 %) had OPLL, so this prevalence was noticeably higher than that of the general population (1.9–4.3 %) (Sasaki et al., 2014; Shingyouchi et al., 1996; Stapleton et al., 2011; Yoshimura et al., 2014), which suggested that acromegaly might have a possible correlation with the development of spinal ligament ossification similar to other previously identified risk factors, including diabetes mellitus or obesity. Ossification was predicted to not have exclusively

Table 2

Quantitative evaluation of ossified lesions of OPLL (OP index), OALL (OA index) and OLF (OF index).

Patient no.	OP index	OA index	OF index	OS index
1	11	7	16	34
2	0	6	5	11
3	0	9	9	18
4	0	16	12	28
5	3	15	3	21

The OP index, OA index and OF index ranged from 0 to 49, from 0 to 25, and from 0 to 23, respectively. The total ossification index (OS index) was determined by the sum of the OA index, OP index, and OF index. OS index ranged from 0 to 97.

Table 3

Comparison of sex and biomarkers between the acromegaly patients with or without spinal ligament ossification.

	Acromegaly patients with spinal ligament ossification	Acromegaly patients without spinal ligament ossification	<i>p</i> value
N	5	5	
Age	53.4 ± 9.4	54.6 ± 17.1	0.91
Male (%)	4 (80)	5 (100)	0.29
Estimated disease duration (years)	6.2 ± 3.7	4.4 ± 2.3	0.44
Body mass index (kg/m ²)	27.4 ± 2.3	23.0 ± 2.5	0.03
Serum phosphate (mg/dL)	4.2 ± 1.4 (n = 4) ^a	4.3 ± 0.4	0.89
Albumin adjusted calcium (mg/dL)	9.6 ± 0.8	9.3 ± 0.4	0.62
Growth hormone (ng/mL)	19.2 ± 13.7	22.4 ± 14.9	0.77
Standard deviation of IGF-1	+10.4 ± 4.8 (n = 4) ^b	+6.3 ± 0.8 (n = 4) ^c	0.31
Diabetes mellitus	3	2	0.53

Values are reported as medians ± SD.

IGF-1: insulin-like growth factor-1.

^a One patient with missing data (No. 1) was excluded.

^b One patient after surgery (No. 3) was excluded.

^c One patient treated with octreotide acetate was excluded.

developed in the posterior ligament in patients with acromegaly, because all 5 patients with spinal ligament ossification presented with at least two of the following in the current study: OPLL, OALL, or OLF.

The underlying mechanism of spinal ligament ossification in acromegaly has not been fully elucidated. However, several reports have described the relationship between GH/IGF-1 and spinal ligament ossification. A previous study suggested that GH receptors in bone osteoblasts were increased in patients with OPLL (Ikegawa et al., 1993). Another study reported that IGF-I induced osteogenic differentiation in the cells derived from OPLL lesions and that IGF-I might be the stimulant of ossification of the spinal ligaments (Goto et al., 1998). It has also been reported that 20 % of patients with acromegaly present with DISH (Scarpa et al., 2004). However, no relationship between the values of GH or IGF-1 and the severity of DISH was observed in that previous study, as was the current report. In acromegaly patients, it seems that increased GH/IGF-1 is involved in the development spinal ligament ossification; however, further studies are needed to confirm this hypothesis.

Diabetes mellitus is a well-known complication of acromegaly (Hannon et al., 2017), and a risk factor for spinal ligament ossification (Bakhsh et al., 2019; Kobashi et al., 2004). In patients with type 2 diabetes, insulin secretion is prompted due to insulin resistance, and a previous study indicated that elevated insulin secretion was positively associated with the extent of OPLL (Akune et al., 2001). Thus, in

acromegaly patients, coexisting diabetes might also accelerate the development of spinal ligament ossification, although there was no significant difference in the prevalence of diabetes mellitus between the groups with and without spinal ligament ossification in the current study.

BMI was the single marker in this study. There was a significant difference in BMI between the groups with and without spinal ligament ossification in acromegaly patients. High BMI was an independent risk factor for the development of OPLL (Kobashi et al., 2004), and obese patients were reported to be more prone to develop DISH (Coaccioli et al., 2000; Kiss et al., 2002). High BMI is a risk factor for type 2 diabetes and concomitant elevation of insulin secretion, which would have some effect on the development of spinal ligament ossification. However, the precise mechanism by which obesity causes spinal ligament ossification is unclear. The association between obesity and acromegaly in the context of the development of spinal ligament ossification also remains unclear.

We reported elevated FGF23 in patients with acromegaly as the counteraction for hyperphosphatemia (Ito et al., 2007). As mentioned above, some types of hereditary FGF23-related hypophosphatemic rickets/osteomalacia have been identified as an intensive disposition for the development spinal ligament ossification (Kato et al., 2022; Kato et al., 2021). However, since FGF23 is known to be exponentially elevated in patients with end-stage renal disease (Wolf, 2010) and there have been no reports suggesting an association between spinal ligament ossification and end-stage renal disease, it is unlikely that FGF23 is a direct stimulant of spinal ligament ossification.

Our study had several limitations. First, the sample size was not large enough to accurately estimate the prevalence of spinal ligament ossification. Second, this was a retrospective study, and some data were missing. Finally, CT scans were not conducted at the same time for the diagnosis or treatment of acromegaly. In the future, larger prospective cohort studies are warranted.

5. Conclusions

In conclusion, this study increased the possibility of an association between acromegaly and ossification of the spinal ligaments compared to previous case reports. However, to clarify whether there is a significant association, a larger-scale prospective study with a larger number of recruited acromegaly patients is warranted.

CRediT authorship contribution statement

Yoshitomo Hoshino: Conceptualization, Methodology, Software, Data curation, Writing – original draft, Visualization, Validation, Writing – review & editing. **Naoko Hidaka:** Investigation. **Hajime Kato:** Investigation, Methodology, Data curation. **Minae Koga:** Investigation. **Yuki Taniguchi:** Investigation, Data curation. **Hiroshi Kobayashi:** Investigation, Data curation. **Masaomi Nangaku:** Supervision. **Noriko Makita:** Supervision. **Nobuaki Ito:** Conceptualization, Methodology, Supervision, Writing – review & editing.

Declaration of competing interest

None of the authors have any potential conflicts of interest associated with this study.

Data availability

Data will be made available on request.

References

- Akune, T., et al., 2001. Insulin secretory response is positively associated with the extent of ossification of the posterior longitudinal ligament of the spine. *J. Bone Joint Surg. Am.* 83 (10), 1537–1544. <https://doi.org/10.2106/00004623-200110000-00013>.
- Bakhsh, W., et al., 2019. Cervical ossification of the posterior longitudinal ligament: a computed tomography-based epidemiological study of 2917 patients. *Glob. Spine J.* 9 (8), 820–825. <https://doi.org/10.1177/2192568219833658>.
- Barkan, A., 1997. Acromegalic arthropathy and sleep apnea. *J. Endocrinol.* 155 (Suppl. 1), S41–S44 discussion S45.
- Coaccioli, S., et al., 2000. Diffuse idiopathic skeletal hyperostosis in diabetes mellitus, impaired glucose tolerance and obesity. *Panminerva Med.* 42 (4), 247–251.
- Ehara, S., et al., 1998. Paravertebral ligamentous ossification: DISH, OPLL and OLF. *Eur. J. Radiol.* 27 (3), 196–205. [https://doi.org/10.1016/s0720-048x\(97\)00164-2](https://doi.org/10.1016/s0720-048x(97)00164-2).
- Fujimori, T., et al., 2016. Prevalence, concomitance, and distribution of ossification of the spinal ligaments: results of whole spine CT scans in 1500 Japanese patients. *Spine* 41 (21), 1668–1676. <https://doi.org/10.1097/brs.0000000000001643>.
- Goto, K., et al., 1998. Involvement of insulin-like growth factor I in development of ossification of the posterior longitudinal ligament of the spine. *Calcif. Tissue Int.* 62 (2), 158–165. <https://doi.org/10.1007/s002239900410>.
- Hannon, A.M., et al., 2017. Diabetes in patients with acromegaly. *Curr. Diab. Rep.* 17 (2), 8. <https://doi.org/10.1007/s11892-017-0838-7>.
- Ichinose, Y., et al., 2020. A patient with ossification of the yellow ligament and ventriculomegaly with 22q11.2 deletion syndrome undiagnosed until adulthood. *Heliyon.* 6 (12), e05600 <https://doi.org/10.1016/j.heliyon.2020.e05600>.
- Ikegawa, S., et al., 1993. Increase of serum growth hormone-binding protein in patients with ossification of the posterior longitudinal ligament of the spine. *Spine (Phila Pa 1976)* 18 (13), 1757–1760. <https://doi.org/10.1097/00007632-199310000-00007>.
- Ishizawa, K., et al., 2014. Dysphagia as a result of ossification of the anterior longitudinal ligament in a patient with myotonic dystrophy. *Neurology and Clinical Neuroscience.* 2 <https://doi.org/10.1111/ncn3.70>.
- Ito, N., et al., 2007. Fibroblast growth factor (FGF)23 in patients with acromegaly. *Endocr. J.* 54 (3), 481–484. <https://doi.org/10.1507/endocrj.K06-217>.
- Kamakura, D., et al., 2021. Acromegaly presenting with myelopathy due to ossification of posterior longitudinal ligament: a case report. *BMC Musculoskelet. Disord.* 22 (1), 353. <https://doi.org/10.1186/s12891-021-04232-6>.
- Karaplis, A.C., et al., 2012. Mineralizing enthesopathy is a common feature of renal phosphate-wasting disorders attributed to FGF23 and is exacerbated by standard therapy in hyp mice. *Endocrinology* 153 (12), 5906–5917. <https://doi.org/10.1210/en.2012-1551>.
- Kato, H., et al., 2022. Identification of ENPP1 haploinsufficiency in patients with diffuse idiopathic skeletal hyperostosis and early-onset osteoporosis. *J. Bone Miner. Res.* <https://doi.org/10.1002/jbmr.4550>.
- Kato, H., et al., 2021. Incidence of complications in 25 adult patients with X-linked hypophosphatemia. *J. Clin. Endocrinol. Metab.* 106 (9), e3682–e3692. <https://doi.org/10.1210/clinem/dgab282>.
- Kawaguchi, Y., et al., 2013. Ossification of the posterior longitudinal ligament in not only the cervical spine, but also other spinal regions: analysis using multidetector computed tomography of the whole spine. *Spine (Phila Pa 1976)* 38 (23), E1477–E1482. <https://doi.org/10.1097/BRS.0b013e3182a54f00>.
- Kawaguchi, Y., et al., 2016. Characteristics of ossification of the spinal ligament; incidence of ossification of the ligamentum flavum in patients with cervical ossification of the posterior longitudinal ligament – analysis of the whole spine using multidetector CT. *J. Orthop. Sci.* 21 (4), 439–445. <https://doi.org/10.1016/j.jos.2016.04.009>.
- Kawaguchi, Y., et al., 2017. Serum biomarkers in patients with ossification of the posterior longitudinal ligament (OPLL): inflammation in OPLL. *PLoS One.* 12 (5), e0174881. <https://doi.org/10.1371/journal.pone.0174881>.
- Kim, S.I., et al., 2018. Prevalence and related clinical factors of thoracic ossification of the ligamentum flavum—a computed tomography-based cross-sectional study. *Spine J.* 18 (4), 551–557. <https://doi.org/10.1016/j.spinee.2017.08.240>.
- Kinoshita, M., et al., 1997. Abnormal calcium metabolism in myotonic dystrophy as shown by the Ellsworth-Howard test and its relation to CTG triplet repeat length. *J. Neurol.* 244 (10), 613–622. <https://doi.org/10.1007/s004150050155>.
- Kiss, C., et al., 2002. Risk factors for diffuse idiopathic skeletal hyperostosis: a case-control study. *Rheumatology (Oxford)* 41 (1), 27–30. <https://doi.org/10.1093/rheumatology/41.1.27>.
- Kobashi, G., et al., 2004. High body mass index after age 20 and diabetes mellitus are independent risk factors for ossification of the posterior longitudinal ligament of the spine in Japanese subjects: a case-control study in multiple hospitals. *Spine (Phila Pa 1976)* 29 (9), 1006–1010. <https://doi.org/10.1097/00007632-200405010-00011>.
- Lee, S.H., et al., 2012. Paravertebral ligament ossification in vitamin D-resistant rickets: incidence, clinical significance, and genetic evaluation. *Spine (Phila Pa 1976)* 37 (13), E792–E796. <https://doi.org/10.1097/BRS.0b013e31824a3dc8>.
- Mori, K., et al., 2013. Prevalence, distribution, and morphology of thoracic ossification of the yellow ligament in Japanese: results of CT-based cross-sectional study. *Spine (Phila Pa 1976)* 38 (19), E1216–E1222. <https://doi.org/10.1097/BRS.0b013e31829e018b>.
- Nakajima, M., et al., 2014. A genome-wide association study identifies susceptibility loci for ossification of the posterior longitudinal ligament of the spine. *Nat. Genet.* 46 (9), 1012–1016. <https://doi.org/10.1038/ng.3045>.
- Sasaki, E., et al., 2014. Prevalence and symptom of ossification of posterior longitudinal ligaments in the Japanese general population. *J. Orthop. Sci.* 19 (3), 405–411. <https://doi.org/10.1007/s00776-014-0552-0>.
- Scarpa, R., et al., 2004. Acromegalic axial arthropathy: a clinical case-control study. *J. Clin. Endocrinol. Metab.* 89 (2), 598–603. <https://doi.org/10.1210/jc.2003-031283>.
- Schmidt, R.F., et al., 2013. Ossified ligamentum flavum causing spinal cord compression in a patient with acromegaly. *J. Clin. Neurosci.* 20 (11), 1599–1603. <https://doi.org/10.1016/j.jocn.2012.10.033>.
- Shingyouchi, Y., et al., 1996. Ligamentous ossification of the cervical spine in the late middle-aged Japanese men. Its relation to body mass index and glucose metabolism. *Spine (Phila Pa 1976)* 21 (21), 2474–2478. <https://doi.org/10.1097/00007632-199611010-00013>.
- Sohail, A.H., et al., 2018. Isolated ligamentum flavum ossification in primary hypoparathyroidism. *Surg. Neurol. Int.* 9, 4. https://doi.org/10.4103/sni.sni_364_17.
- Stapleton, C.J., et al., 2011. Ossification of the posterior longitudinal ligament: genetics and pathophysiology. *Neurosurg. Focus.* 30 (3), E6. <https://doi.org/10.3171/2010.12.Focus10271>.
- Vilar, L., et al., 2017. Acromegaly: clinical features at diagnosis. *Pituitary* 20 (1), 22–32. <https://doi.org/10.1007/s11102-016-0772-8>.
- Wolf, M., 2010. Forging forward with 10 burning questions on FGF23 in kidney disease. *J. Am. Soc. Nephrol.* 21 (9), 1427–1435. <https://doi.org/10.1681/asn.2009121293>.
- Yoshimura, N., et al., 2014. Prevalence and progression of radiographic ossification of the posterior longitudinal ligament and associated factors in the Japanese population: a 3-year follow-up of the ROAD study. *Osteoporos. Int.* 25 (3), 1089–1098. <https://doi.org/10.1007/s00198-013-2489-0>.