Circulating sclerostin level in patients with ossification of the posterior longitudinal ligament of the spine

MASAFUMI KASHII[1)], Y Matsuo[1)], T Sugiura[1)], Y. Nagamoto[2)], T. Fujimori[1)], H. Honda[1)], T. Kaito[1)], M. Iwasaki[1)], H. Yoshikawa[1)]

1) Dept. of Orthopedic Surgery, Osaka University Graduate School of Medicine, JAPAN

2) Dept. of Orthopedic Surgery, Osaka National Hospital, JAPAN

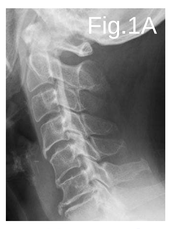
Correspondence to Masafumi Kashii, MD, PhD

Dept. of Orthopedic Surgery, Faculty of Medicine Graduate School of Medicine, Osaka University 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan e-mail: mkashii-osk@umin.ac.jp

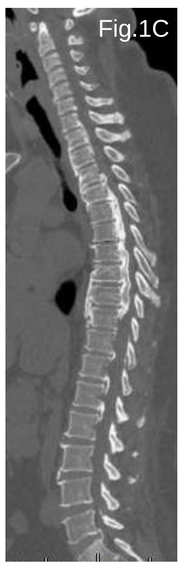
Introduction

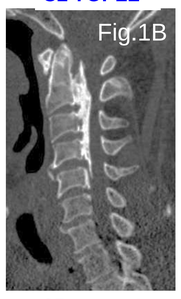
☐ *Ossification of the Posterior Longitudinal Ligament of the spine (OPLL)*

- OPLL is characterized by pathological ectopic ossification of the posterior longitudinal ligament (Fig.1A-C).
- OPLL induces compression myelopathy or radiculopathy by spinal stenosis, and the loss of spinal flexibility by ankylosing spinal hyperosteosis (ASH).
- Although the etiology of OPLL has not been fully elucidated, systemic and local bone formation factors may play an important role in its pathogenesis.



69 yrs male
C2-7OPLL



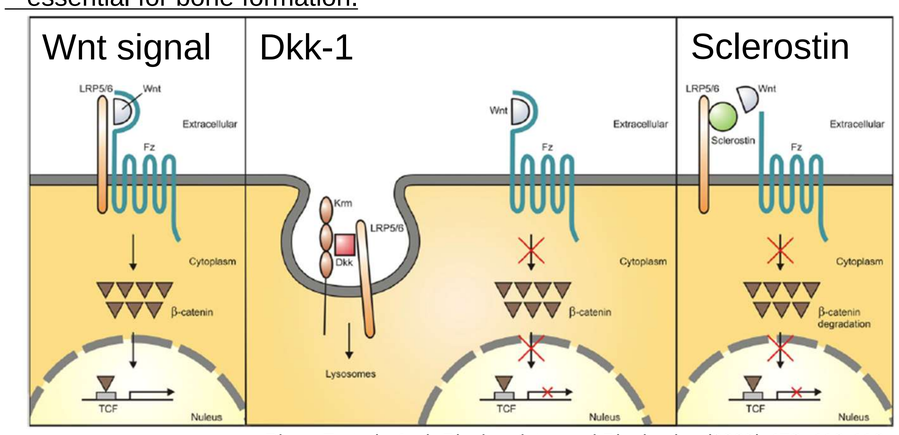


65 yrs male
C2-5 OPLL

40 yrs female
C7-L2 OPLL

☐ *Sclerostin & Dickkopf-1(Dkk1)*

- The SOST gene encoding sclerostin is an osteocyte derived negative regulator of bone formation.
- Sclerostin and Dkk-1 are the **Wnt/β-catenin signal antagonists** essential for bone formation.



Piters E et al., Arch Biochemistry and Biophysics (2008) 473: 112-116.

Objectives

To compare serum sclerostin levels between OPLL patients and controls, and to identify the relationship between serum sclerostin level, Dkk-1 level, bone turnover markers, OPLL localization and numbers of ossified vertebra

Subjects & Methods

Study Design **: Cross-sectional study**

Subjects:

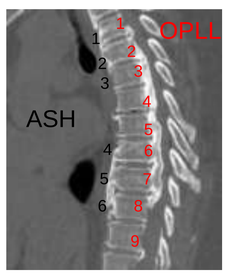
Age- and, sex-matched Control (n=38) **vs** OPLL patients (n=78)

Exception: 1) Non-ambulatory patient, 2) Person with kidney failure (≧ CKD stage 3)
3) Controls with OPLL confirmed by whole spine CT

Study Points :

☐ Serum measurements :
- **Calciotropic hormones and bone turnover markers**
- **Serum Sclerostin**（ELISA : Biomedica; Vienna, Austria)
- **Serum Dkk-1**（ELISA : R&D Systems: Minneapolis, USA)

☐ Xp/CT:
- **Localization of OPLL**
- **Numbers of ossified vertebra**
- **Presence or absence of ASH**



Results

Patients demographics

Values were shown as Means ± SD.

	Control (n=39)	OPLL (n=78)	*p* value
Age (years)	68.0 ± 12.4	65.5 ± 10.4	N.S.
Gender（male/female ratio)	1.35	1.67	N.S.
Height (cm)	157.8 ± 9.9	162.2 ± 8.3	0.013
Body weight (kg)	59.8 ± 12.3	66.5 ± 11.6	0.004
BMI (kg/m^2)	23.9 ± 3.6	25.2 ± 3.8	0.06
eGFR (ml/min./1.73m^2)	72.3 ± 16.6	72.1 ± 26.1	N.S.
Presence of Hypertension	47.5%	32.3%	N.S.
Presence of Hyperlipidemia	17.5%	20.0%	N.S.
Presence of DM	15%	35%	0.022
HbA1c (%)	5.26 ± 0.56	5.72 ± 0.78	0.002

Statistical analysis using unpaired Student's t test or Mann-Whitney U test, $p<0.05$: significant difference (+)

Result.1

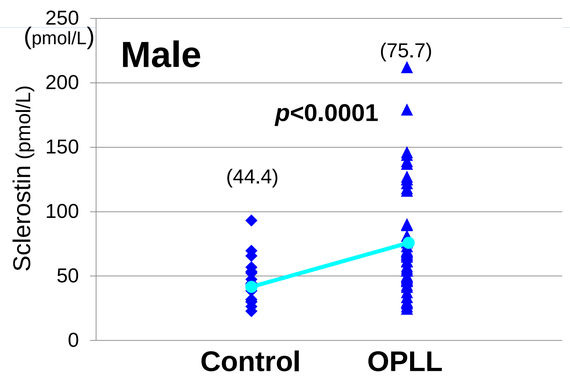
Serum sclerostin levels in OPLL patients were significant higher than controls. Conversely, serum Dkk1 levels in OPLL patients were significant lower than controls.

	Standard value	Control (n=39)	OPLL (n=78)	*p* value
Serum Ca	(8.6-10.1 mg/dL)	8.94 ± 0.26	8.84 ± 0.40	0.15
Serum P	(2.5-4.6 mg/dL)	3.42 ± 0.41	3.2 ± 0.50	0.06
BAP	(3.7-22.6 μg/L)	12.9 ± 4.2	15.1 ± 7.2	0.08
P1NP	(14.9-109.3 μg/L)	48.4 ± 22.8	38.0 ± 16.2	0.006
Osteocalcin	(2.5-13 ng/mL)	3.48 ± 1.66	3.99 ± 1.69	0.13
TRACP5 b	(120-760 mU/dL)	414 ± 174	363 ± 146	0.10
PTH	(10-60 pg/mL)	43.7 ± 12.4	52.9 ± 18.6	0.006
1.25(OH)D	(20-60 pg/mL)	61.7 ± 23.6	57.2 ± 18.3	0.26
Sclerostin	(0-240 pmol/L)	**44.9 ± 17.7**	**64.0 ± 39.3**	**0.005**
Dkk-1		**2394 ± 959**	**2016 ± 836**	**0.03**

Statistical analysis using unpaired Student's t test or Mann-Whitney U test, $p<0.05$: significant difference (+)

Result.2

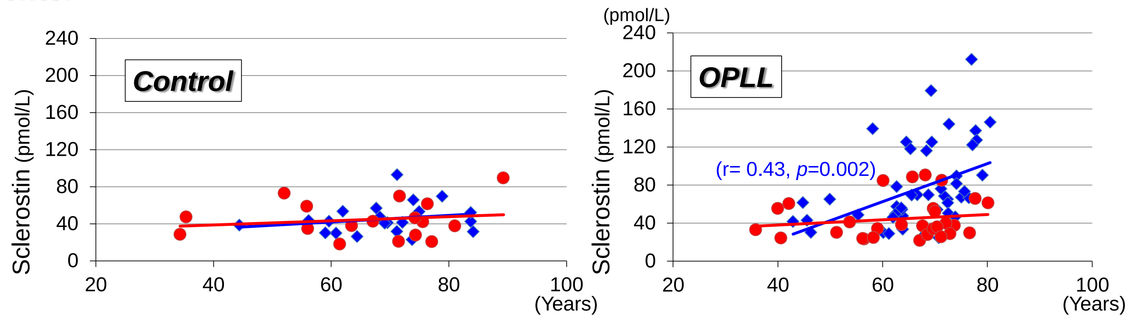
Serum sclerostin levels in OPLL male patients were significant higher than controls.



Statistical analysis using unpaired Student's t test, $p<0.05$: significant difference (+)

Result.3

The positive correlation between age and sclerostin levels was found in OPLL male patients.



Result.4

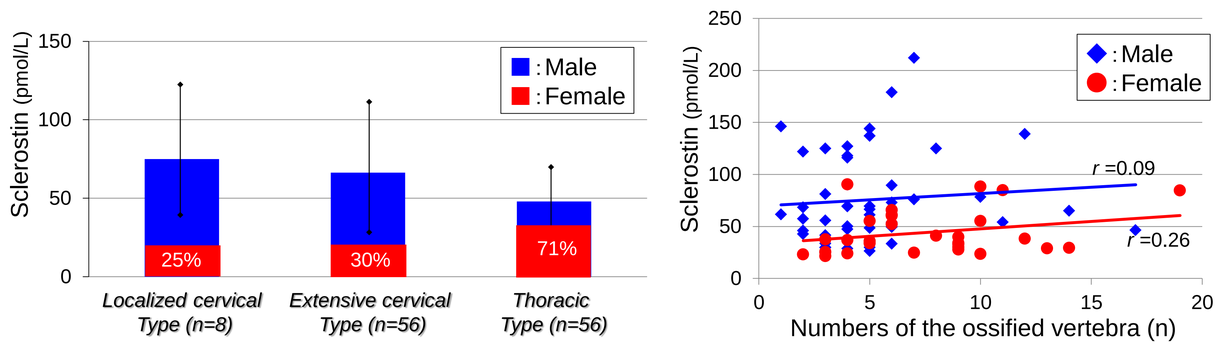
In OPLL male patients, there were no relationships between serum sclerostin levels and bone turnover markers, and was a strong negative correlation between serum sclerostin and Dkk1 levels.

Correlation coefficient (r)	***vs Sclerostin***		***vs Dkk-1***	
	Control	***OPLL***	***Control***	***OPLL***
Age	0.213	**0.430***	0.051	**-0.288***
BMI	0.317	-0.015	-0.186	0.083
HbA1c	**0.540***	0.025	-0.144	**-0.392***
BALP	0.295	-0.005	-0.153	-0.213
P1NP	**0.488***	-0.058	-0.285	**0.309***
Osteocalcin	**0.480***	0.141	-0.293	**0.263***
TRACP5b	**0.544***	0.111	-0.190	0.114
PTH	0.096	0.281	-0.014	-0.231
1.25(OH)D	**-0.441***	-0.240	0.206	0.161
Sclerostin	1	1	-0.194	**-0.506***
Dkk-1	-0.194	**-0.506***	1	1

Pearson correlation coefficient test, $p<0.05$: significant difference (+)

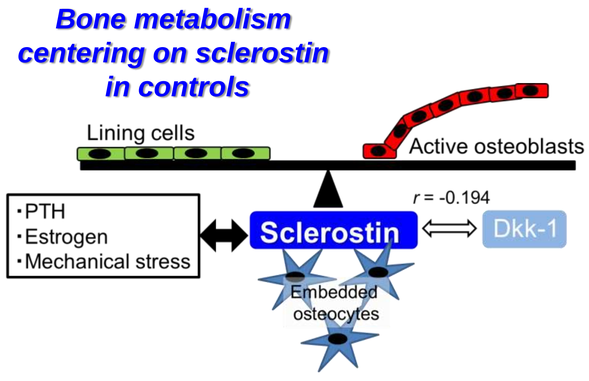
Result.5

In OPLL patients, there were no relationships between OPLL localization, numbers of ossified vertebra and ASH.

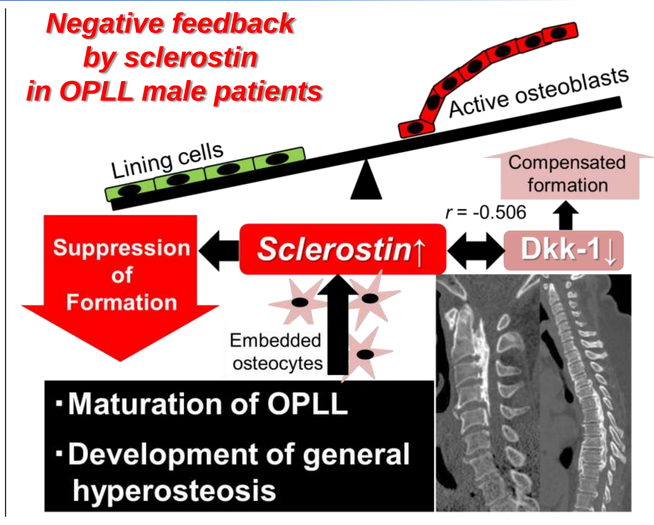


Discussions

Bone metabolism centering on sclerostin in controls



Negative feedback by sclerostin in OPLL male patients



Conclusions

- **Systemic secretion of sclerostin by osteocytes increased in OPLL male patients with advancing age.**
- **There will be a negative feedback system by sclerostin to suppress development of OPLL and hyperosteosis in OPLL male patients.**
- **The negative effects on bone formation associated with higher serum sclerostin levels are counterbalanced by the underproduction of Dkk1 in OPLL male patients.**

Disclosure

- This work was performed with the aid of the Investigation Committee on the Ossification of the Spinal Ligaments of the Japanese Ministry of Health, Labor, and Welfare.
- None of the authors has any financial interest with any of the commercial entities.
- All authors state that they have no conflicts of interest.