Inspiratory muscle training

After admission, patients were trained with preoperative inspiratory muscle training (Threshold IMT) by an inspiratory muscle trainer (Fig. 1, 2) for 6 weeks prior to surgery, according to the protocol described by our previous study.[13] Training was performed with the patient in the sitting position, and the nose was usually used. They were also encouraged to continue after surgery and at home after discharge. The pulmonary trainer resistive exercise intervention was based on previously published protocols.[14]

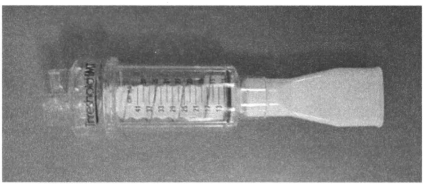

Fig. 1. Pulmonary trainer (Threshold IMT, Philips Respironics, Murrysville, PA, USA) used for preoperative and postoperative pulmonary muscle training. This device provides consistent and specific pressure for inspiratory muscle strength and endurance training and incorporates a flow-independent one-way valve to ensure consistent resistance; it features an adjustable specific pressure setting (in cm H_20) to be set by a healthcare professional. A spring-loaded valve in the Threshold IMT provides resistance that exercises respiratory muscles through conditioning when a patient inhales through the device

Fig. 2. A 13-year-old girl with Fukuyama congenital muscular dystrophy being trained using the Threshold IMT

Assessment of clinical and radiological results

Patients were reviewed clinically and questioned about whether they had difficulty sitting and if they had back pain and breakdown of the skin the day before surgery, at 6 weeks, and at 1 and 2 years after surgery. Back pain was measured by the visual analogue scale (VAS). All patients were assigned pain-scale scores prospectively the day before surgery and at 6 weeks and 1 and 2 years after surgery. Radiographic assessments were performed on sitting anteroposterior (AP) and lateral spinal radiographs covering the whole spinal column with the patient in sitting position. These assessments were made the day before surgery, during the postoperative week, at 1 and 2 years after surgery, and at the last follow-up. The Cobb angles of the curves and spinal pelvic obliquity (SPO) on the coronal plane, thoracic kyphosis between T3 and T12, and lumbar lordosis between L1 and L5 on the sagittal plane were measured. Preoperative radiographic evaluation included best-effort spine side-bending radiographs. The preoperative AP radiograph and side-bending films were examined, and Cobb angles of the curves were needed to determine flexibility.

Surgical procedure and anesthetic technique

The primary aim of this surgery was to obtain a solid fusion, a level pelvis, and a balanced spine. All the patients had standard posterior spinal fusion and pedicle-screw-alone fixation from T3 or T4 to L5. Fixation of the spine was carried out with pedicle screws in the thoracic and the lumbar spine. Screws with diameters of 5 and 6 mm were used in the thoracic and lumbar spine. Not all of the thoracic vertebrae of the curve were instrumented, just every second or third vertebra. All of the lumbar vertebrae were instrumented (Fig. 3).

All operations were performed under general anesthesia, mainly with propofol and remifentanil. These agents are recently marked in Japan, and their rapid onset and emergence characterize their best advantages. The depth of sedation was adjusted with a bispectral index (BIS) monitor. Therefore, the anesthesia with these agents under an appropriate depth of anesthesia enables rapid emergence and recover from anesthesia, resulting in early extubation.

All patients underwent posterior spine fusion and segmental pedicle screw instrumentation from the upper thoracic spine (T3 or T4) to the lower lumber spine (L5) for scoliosis. No anterior surgery was performed in any of the patients in this consecutive series. The rods were contoured to create a sagittal profile. Correction was performed with rod insertion, rod rotation, translation of the rod, and adequate distraction and compression to level the distal and proximal end verte-

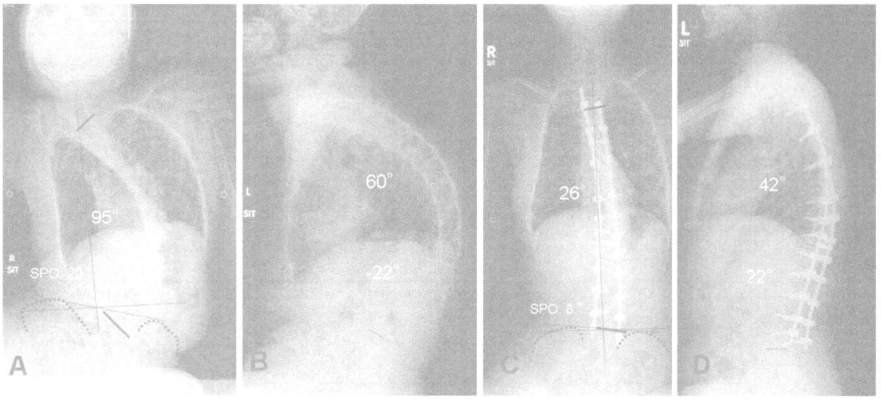

Fig. 3. A, B A 13-year-old boy with Fukuyama congenital muscular dystrophy. Sitting preoperative anteroposterior radiograph shows a severe (95°) thoracolumbar curve. **C, D** Surgical correction of scoliosis was performed successfully. Fixation of the spine was carried out with pedicle-screw-alone fixation. Postoperative sitting views show significant coronal correction of 26°, with normalization of the sagittal plane

brae. Fluoroscopy was employed to confirm acceptable screw position. Autograft bone was obtained from the spinous process, laminae, and transverse process. The posterior elements were decorticated. Autograft bone was packed onto the prepared surfaces and placed carefully in each facet. Autotransfusion via both preoperative storage and intraoperative collection was used. Intraoperatively, spinal cord function was monitored by somatosensory/motor-evoked potentials. The wound was sutured in three layers with two drainage tubes.

Perioperative/postoperative management

When the ability to breathe spontaneously was documented in the patient, he or she was extubated in the operating room. All patients received supplemental oxygen on the operative day and were weaned off with monitoring of pulse oximetry as a feedback to maintain adequate alveolar ventilation. Pulse oximetry monitoring was used to evaluate pulmonary function for all patients during the immediate postoperative period. Alveolar ventilation was considered adequate when baseline oxyhemoglobin saturation (SpO_2) remained normal ($SpO_2 > 94\%$). Frequent expulsion of debris was performed by nurses during the immediate postoperative period. The patients were encouraged to sit up in bed on the operative day and sit in the wheelchair on postoperative day (POD) 1, with discharge occurring on POD 14. The patients were encouraged to continue inspiratory muscle training after surgery and even at home after discharge.

Patient/parent satisfaction of surgery

At the last follow-up, patients/parents were interviewed by a blinded observer and asked to complete an outcome satisfaction questionnaire. They were asked to rate the outcome as very satisfactory, satisfactory, neither satisfactory nor unsatisfactory, or very unsatisfactory.

Results

A total of 10 consecutive patients were enrolled in this study. No patient was lost to follow-up. The mean age at surgery was 13 years (range 11 years 2 months to 17 years 3 months). Demographic details and surgical parameters of all the patients are shown in Table 1. Radiographic parameters for the coronal and sagittal planes are shown in Table 2. Changes in %FVC are shown in Fig. 4. All patients were alive at the last follow-up. The mean follow-up period was 3 years 5 months (range 2 years to 5 years 5 months). The cardiac function of the patients was normal in all patients preoperatively. The mean %FVC at the time of admission was 30% (range 25%–35%). %FVC increased in all patients after

Table 1. Details of the patients and operative parameters in the study group

Patient no.	Diagnosis	Age (years)	Follow-up (months)	Preoperative cardiac function	Operating time (min)	Intraoperative blood loss (ml)	Total blood loss (ml)	Complication
1	MNCMD	11	65	Normal	246	1220	2000	—
2	FCMD	13	64	Normal	278	970	1980	Paralytic ileus
3	MNCMD	12	52	Normal	289	920	1960	Paralytic ileus
4	FCMD	14	44	Normal	287	900	2150	—
5	UCMD	13	40	Normal	262	670	1260	—
6	FCMD	14	40	Normal	236	730	1540	—
7	UCMD	11	32	Normal	257	680	1450	—
8	UCMD	17	30	Normal	277	560	1150	—
9	MNCMD	11	28	Normal	308	950	1320	—
10	MNCMD	13	24	Normal	247	470	1090	—
Mean		13	41		269	810	1590	

CMD, congenital muscular dystrophy; MNCMD, merosin-negative (nonsyndromic) CMD; FCMD, Fukuyama CMD; UCMD, Ulrich CMD

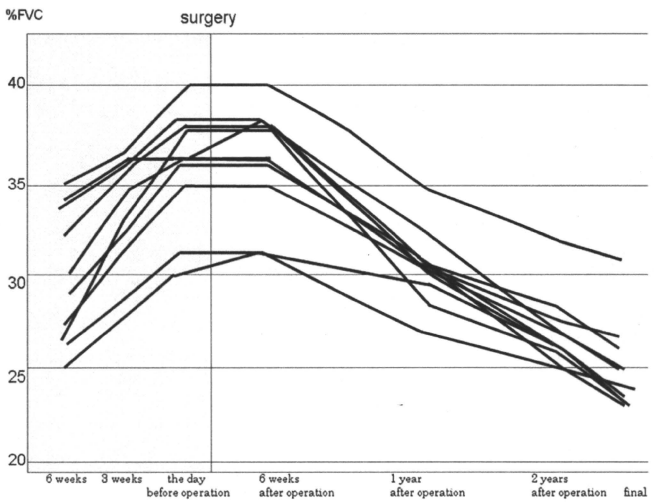

Fig. 4. Changes in the forced vital capacity (FVC) expressed as the percent of the predicted value (%FVC). After preoperative IMT for 6 weeks, the %FVC increased in all patients. All patients underwent surgical correction of spinal deformity successfully without postoperative pulmonary complications. At 6 weeks after operation, the %FVC remained stable or increased slightly. The %FVC decreased in all patients at 1 year and 2 years after operation and at the final follow-up

inspiratory muscle training. The mean %FVC was 34% (range 30%–40%) the day before surgery.

The day before surgery, all patients reported difficulty sitting due to back pain. All patients reported back pain, and the mean VAS was 5.5 (range 4–7) the day before surgery. No one reported breakdown of the skin, preoperatively.

The mean operating time was 269 min (range 236–308 min). The mean intraoperative blood loss was 810 ml (range 470–1220 ml). The mean total blood loss was 1590 ml (range 1090–2000 ml). All patients in our series recovered well following the surgery with no major complications or deaths. There was a smooth transition from no spontaneous breathing to spontaneous breathing during the immediately postoperative period in the operating room in all patients. All of the patients were successfully extubated in the operation room. None showed abnormal pulse oximetry monitoring values during the immediate postoperative period. None developed any respiratory complications including postoperative pneumonia or required reincubation or tracheotomy.

The %FVC remained stable or increased slightly in all patients at 6 weeks after surgery. After that, however,

Table 2. Radiological measurements in the study group

Patient no.	Scoliotic curvature (°) Preop	Side-bend	Immed. postop	2 Years postop	Last	Thoracic kyphosis (°) Preop	Immed. postop	2-Years postop	Last	Lumbar lordosis (°) Preop	Immed. postop	2-Years postop	Last	Pelvic obliquity (°) Preop	Immed. postop	2 Years postop	Last
1	90	22	18	19	19	20	25	26	26	15	33	35	34	18	7	7	8
2	93	28	28	25	27	5	20	20	22	45	38	37	38	18	4	6	6
3	71	15	12	12	13	10	25	26	24	33	35	34	33	17	5	7	7
4	81	18	16	17	16	6	28	28	28	–5	38	38	40	15	8	8	9
5	73	11	10	11	12	8	28	29	27	19	32	35	33	16	5	6	6
6	81	19	18	20	19	8	27	26	24	27	37	35	37	14	7	7	8
7	88	26	25	27	27	–5	26	28	29	48	35	36	35	18	9	9	10
8	61	13	10	11	12	–6	24	26	28	6	36	35	37	19	6	7	7
9	85	15	12	12	13	7	28	30	31	18	38	38	37	15	4	5	4
10	95	27	25	26	27	12	22	23	22	30	37	33	36	20	5	6	6
Mean	75	19 (75%)	18 (76%)	18	19	7	25	26	26	24	36	36	36	17	6 (65%)	7	7

Preop, preoperatively; Immed, immediately; postop, posteroperatively; Last, final follow-up

the %FVC continuously decreased: to 31% (range 27%–35%) at 1 year after surgery, to 27% (range 25%–32%) at 2 years after surgery, and to 26% (range 23%–31%) at the last follow-up.

All patients reported difficulty sitting, and their back pain was diminished at 6 weeks after surgery. The mean VAS improved from 5.5 (range 2–7) the day before surgery to 2.5 (range 1–4), 1.8 (range 0–3), and 0.8 (range 0–2) at 6 weeks, 1 year, and 2 years after surgery. No patient reported breakdown of the skin after surgery. Alleviation of the difficulty sitting and back pain was maintained over the follow-up period.

The mean preoperative scoliotic curvature was 75° (range 61°–95°). The mean scoliotic curvature on preoperative side-bending films was 19° (range 11°–28°). The postoperative scoliotic curvature was 18° (range 10°–25°). The mean scoliotic curvature was 19° (range 12°–27°) at 1 year after surgery, 19° (range 12°–27°) at 2 years after surgery, and 19° (range 12°–27°) at the last follow-up. The pelvic obliquity improved from a mean of 17° preoperatively to a mean of 6° (range 4°–9°) postoperatively to 7° (range 4°–10°) at the last follow-up. There was no significant loss of correction of the scoliotic curvature or pelvic obliquity between the postoperative measurements and the last follow-up. Balanced sitting posture was achieved and maintained in all patients.

On the sagittal plane, the mean preoperative thoracic kyphosis was 13° (range–6° to +60°) and lumbar lordosis was 16° (range–42° to +48°). The mean immediate postoperative thoracic kyphosis was 27° (range 22°–42°) and lumbar lordosis 34° (range 22°–38°). The mean thoracic kyphosis was 28° (range 23°–43°) and lumbar lordosis 34° (range 22°–8°) at 2 years after surgery. The mean thoracic kyphosis was 28° (range 22°–42°) and lumbar lordosis 34° (range 23°–40°) at the last follow-up. No significant loss of correction on the sagittal plane alignment was noted between the postoperative measurements and the last follow-up.

Two (20%) complications occurred immediately after surgery, both of which were paralytic ileus. It was treated with observation without oral intake and cleared in at least 48 h. No respiratory complications, such as postoperative pneumonia, reintubation, tracheotomy, or prolonged respiratory dependence, were observed. Also, we did not observe any cardiac problems in any of the patients. There were no neurological complications, infections, or instrumentation failures during the study period.

Patients' and parents' satisfaction was surveyed by a self-completed questionnaire at the last follow-up. All patients/parents completed the outcome satisfaction questionnaire. Eight patients/parents were very satisfied and two were satisfied.

Discussion

This is the only reported series of consecutive cases of neuromuscular scoliosis in CMD treated surgically with pedicle-screw-alone fixation. Most previous research has been in patients with DMD of the most common and severe form of muscular dystrophies (CP and SMA). Excellent 2-year results are shown in this study, with no reoperations for nonunion, infection, or instrumentation failure. There were no major complications or mortality. Radiographically, coronal curves were flexible (75% correction) on side-bending films preoperatively, and there was 76% coronal curve correction, normalization of the sagittal plane, and 62% correction of pelvic obliquity postoperatively. Loss of correction was minimal. Thus, the results of this study indicated that segmental pedicle screw instrumentation and fusion only to L5 was safe and effective in patients with CMD scoliosis of <95° and pelvic obliquity of <20°.

Congenital muscular dystrophy, among the myopathic disorders, is one form of flaccid NMD. The term of CMD refers to a group of inherited disorders in which muscle weakness is present at birth. With one limited exception, all forms of muscular dystrophy identified to date — including syndromic (Fukuyama CMD,[19] muscle-eye-brain disease,[20] Walker-Warburg syndrome,[20] congenital muscular dystrophy type I,[21] and nonsyndromic CMD[22] (both merosin positive and negative) — are inherited. The exception is Ullrich CMD,[23,24] which is normally not inherited, although two instances of inheritance have been reported. The incidence of all forms of CMDs has been estimated at 1/21 500 with a prevalence of 1/125 000.[25] The progressive character of the muscle weakness, restrictive respiratory disease, and a progressive spinal deformity are typical for flaccid neuromuscular disorders.[1,3,7,18] Management in these patients includes surgical intervention for orthopedic complications, including spinal deformity, and monitoring respiratory function.[19–25]

Spinal deformity surgery in patients with various forms of muscular dystrophies has been challenging because of the primary muscular pathology and frequently associated cardiac and pulmonary affections.[5] Severe scoliosis in NMD patients has been considered a reason to avoid surgery mainly because of the fear of cardiac and pulmonary complications.[2,8,16] We think most surgeons have been reluctant to perform scoliosis surgery in patients with CMD. Also, CMD is a rare form of NMD when compared with other forms of NMD, such as DMD, SMA, and CP.[19–25] We believe this is the reason why there have been no previous articles concerning spinal deformity surgery in CMD patients in the literature. Our patients presented for surgery with extensive spinal deformity and a low FVC either because they were referred from other clinics or centers that did not follow an early surgical intervention approach or because patients/parents were reluctant to undergo surgery until curve progression was considerable and the discomfort, sitting difficulty, and pulmonary distress were increasing to problematic levels.

Most studies on scoliosis surgery in patients with an NMD have dealt with spinal instrumentation using hooks, wires, or hybrid constructs with pedicle screws in the lumbar spine. Loss of correction has been described with these instrumentations by some authors.[26,27] There are few studies on the use of pedicle-screws-alone fixation for neuromuscular spinal deformity.

Hahn et al.[5] reported excellent results for coronal deformity with 77% correction initially and long-term, using pedicle-screw-alone fixation to the pelvis in patients with DMD. They reported 78% initial correction of pelvic obliquity and 80% final correction. Modi et al.[6] reported that in patients with neuromuscular scoliosis (including 10 DMD, 7 CP, 5 SMA, and 4 other cases), acceptable amounts of curve correction (a mean of 61% initial coronal curve correction and 58% correction at the last follow-up) can be achieved and maintained with posterior-only pedicle screw instrumentation to the pelvis. They reported 45% initial correction of pelvic obliquity and 47% final correction.

Traditional treatment recommendations for surgical treatment of neuromuscular spinal deformity has included instrumentation and fusion to the sacrum/pelvis to correct the pelvic obliquity and restore sitting balance of the trunk.[4–7] However, we have challenged the long-term belief that fusion to the pelvis can be avoided even in nonambulatory patients with NMDs. In our series, excellent coronal correction as well as good pelvic balance was achieved and maintained despite fusion only to L5. The results of our study indicate that pedicle-screw-alone fixation and fusion only to L5 appears to be equivalent to that with fusion to the sacrum/pelvis for correcting scoliotic curvature and pelvic obliquity, both initially and during long-term correction.

Sagittal plane alignment was well recreated in our series. Correction of thoracic hypokyphosis was found, with a preoperative mean of 7° improving to a postoperative mean of 25°. With a postoperative mean of 36°, an excellent reconstruction of lumbar lordosis was achieved and maintained in all our patients. The change in the sagittal plane alignment reflected the intension to recreate good sagittal profile. Adequate lumbar lordosis is important for good, balanced sitting of patients with an NMD in whom flexion contractures of the hips and knees are often present.

Peri/postoperative complications are frequent, and mortality rates of reported 2%–9% have been reported for patients with muscular dystrophy.[2,4,5–7,13] This major

surgery is accompanied by many significant complications.[2,4,6,7,14,16,18,25,28] Significant peri/postoperative complication rates in patients with neuromuscular spinal deformity ranging from 44% to 62% have been reported in some studies.[2–5,12–15,17,28] Because of poor cardiac and pulmonary function, these patients are more susceptible to postoperative pneumonia, prolonged respirator dependence, respiratory failure, cardiac failure, and even death.[4,10,15,16]

A strong association between decreased FVC and increased pulmonary complications after neuromuscular scoliosis surgery has been reported.[14,16,17,28] The limit for surgery has not been the extent of the curvature but a minimum FVC of about 30% of the predicted value.[9,16,28] Rawlins et al.[3] found a 19% rate of pulmonary complications in pediatric patients with an NMD undergoing spine surgery who had a, FVC of <40% of the predicted value. Gill et al.[17] reported that patients with rare forms of NMD and poor pulmonary function (FVC < 30%) could be safely operated on for scoliosis with no increased risk of complications. Their patients were on nocturnal respiratory support before and after surgery. In our series, 5 of 10 patients had a preoperative FVC of <30%, yet surgery was performed successfully with no respiratory complications. We believe an FVC of <30% alone does not predispose the patient to pulmonary complications.

In the literature, several authors reported that the respiratory muscle and diaphragm were trainable in terms of strength and endurance by inspiratory muscle training in patients with an NMD.[29,30] Although %FVC is usually used as a parameter for the progression of the NMD involving the entire respiratory system, it is affected by respiratory muscle function.[30] Fry et al.[29] found that inspiratory muscle training significantly increased inspiratory muscle strength in patients with an NMD; moreover, there was a clinically important positive effect on expiratory pulmonary function measures such as %FVC, forced expiratory volume at 1 s (FEV_1), and mid-expiratory flow rate ($FEF_{25-75\%}$), substantiating the indirect positive effects of training on expiratory pulmonary function.

Most of the reported peri/postoperative complications[1–11] appears to be associated with decreased expiratory pulmonary function. Fry et al.[29] showed that inspiratory muscle training (IMT) increased inspiratory muscle strength and resulted in generalized improvements in expiratory pulmonary function in patients with NMD. We suggest that expiratory pulmonary function must have improved after IMT, and the likelihood of postoperative pulmonary complications was reduced. Also, a minimal dose of anesthetics with the property of rapid onset and emergence under anesthesia depth monitor enabled early extubation in the operation room. All the patients were extubated after confirmation of spontaneous breathing in the operating room, and consequently they did not become ventilator-dependent. A minimum required dose of fentanyl was used with an SpO_2 monitor to avoid respiratory impairment due to postoperative pain.

The other reason for the excellent results is the multidisciplinary team involved with the patients' care. All the operations were performed by one well-experienced spine surgeon. The nursing and physiotherapy staff were also well experienced. Frequent expulsion of debris was performed by the nursing staff during the immediately postoperative period. Patients were encouraged to sit up in bed on the operative day and sit in a wheelchair on POD 1. We believe that all these factors helped to avoid peri/postoperative complications.

In patients with NMD, the decline in pulmonary function after surgery is mainly due to the nature of muscular dystrophy. Hence, the benefit of surgery on the long-term improvement of pulmonary function may be limited. However, prevention of pulmonary function deterioration has been one of the important goals of scoliosis surgery. Also, there has been controversy regarding the effect of scoliosis surgery on pulmonary function in patients with muscular dystrophy.[2,5,8,10,11,13,28]

In the literature, the presence of cardiomyopathy increases the peri/postoperative mortality rate among patients with NMD.[5,15] In our series, all patients had normal preoperative echocardiography. We had no peri/postoperative cardiac incidents. We believe cardiomyopathy is a determining risk factor for mortality and that surgery for these patients should be avoided.

There are some limitations in this study. There was no randomized control group.

In this study, all patients had CMD scoliosis of less than 95 degrees and pelvic obliquity of less than 20 degrees preoperatively. In all patients, instrumentation and fusion was performed to L5, resulting in excellent correction of spinal deformity and pelvic obliquity. It remains to be elucidated whether the same conclusions apply to CMD patients with greater scoliosis or greater pelvic obliquity.

The follow-up was relatively too short to comment on the adequacy of instrumentation and fusion only to L5, considering the life expectancy of CMD patients due to improved supportive care.[19–24,27] They may be expected to live more than 20 years after surgery.[19–24,27] The short-term results are encouraging, and there has been no deterioration of spinal deformity or pelvic obliquity; nor have they developed lumbosacral junctional pain or other problems. It remains to be seen whether fusion only to L5 is adequate to maintain spinal and pelvic alignment and sitting balance as well as prevent L5/S1 problems in the longer term.

Conclusion

Pedicle-screw-alone fixation and fusion to L5 was safe and effective in patients with neuromuscular scoliosis in CMD with mild to moderate pelvic obliquity. Scoliosis curves were flexible (75% correction) on side-bending films preoperatively. Curve correction and maintenance of correction in the coronal and sagittal plane was excellent. The pelvic obliquity was significantly improved and maintained. A balanced sitting posture was achieved and maintained in all patients. All of our patients could be operated on safely and successfully with general anesthesia even though they had a moderately or severely decreased FVC. They were extubated in the operating room. There were no major complications or deaths. We believe a FVC of <30% alone does not predispose the patient to pulmonary complications. However, cardiomyopathy might be a determining risk factor of mortality, and surgery in these patients should be avoided. Patients' and parents' satisfaction was high.

No benefits in any form have been or will be received from a commercial party related directly or indirectly to the subject of this manuscript.

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ORIGINAL ARTICLE

Association between serum leptin and bone metabolic markers, and the development of heterotopic ossification of the spinal ligament in female patients with ossification of the posterior longitudinal ligament

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Abstract Obesity is a risk factor for ossification of the posterior longitudinal ligament (OPLL) of the spine, which is characterized by heterotopic bone formation in the posterior longitudinal spinal ligament. Hyperleptinemia is a common feature of obese people and leptin is believed to be an important factor in the pathogenesis of OPLL. However, the association between leptin and bone metabolism and the development of OPLL is not understood fully. The objective of the present study was to determine the association between serum leptin concentration and bone metabolic markers and the extent of heterotopic ossification of the spinal ligament in patients with OPLL. The serum concentrations of leptin, insulin, fructosamine, bone-specific alkaline phosphatase, and carboxyterminal propeptide of type I procollagen, urine deoxypyridinoline levels, and the number of vertebrae with OPLL involvement were measured in 125 (68 males and 57 females) patients with OPLL. The correlation between leptin and these other factors was then examined. Serum leptin and insulin concentrations were increased significantly in OPLL females compared to non-OPLL female controls. In the females with OPLL, serum leptin concentrations corrected for body mass index correlated positively with the number of vertebrae with OPLL involvement. In females, serum leptin levels were significantly higher in patients in whom OPLL extended to the thoracic and/or lumbar spine than in patients in whom OPLL was limited to the cervical spine. Our results suggest that hyperleptinemia, in combination with hyperinsulinemia, may contribute to the development of heterotopic ossification of the spinal ligament in female patients with OPLL.

Keywords Leptin · Ossification of the posterior longitudinal ligament (OPLL) · Insulin · Gender · Bone metabolic markers

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Introduction

Ossification of the posterior longitudinal ligament (OPLL) of the spine is characterized by heterotopic bone formation in the spinal canal and is considered to belong to the same pathological entity as ankylosing spinal hyperostosis. Enlarged OPLL often compresses the spinal cord and causes severe neurological disorders [33].

The Zucker fatty (*fa/fa*) rat, a model for hereditary obesity, exhibits hyperglycemia, hyperinsulinemia, hyperlipidemia, and heterotopic ossification of the spinal

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ligament [13, 20, 39]. A missense mutation (Gly269Pro) in the leptin receptor gene (Ob-R) was found in this rat where leptin-binding affinity was reduced and signal transduction was attenuated, leading to a compensatory elevation in circulating leptin levels [10, 17, 21, 28]. Since heterotopic ossification of the spinal ligament in the *fa/fa* rat is quite similar to that found in human OPLL, researchers in the field of spinal surgery consider the *fa/fa* rat as a useful animal model for studying the pathophysiology of OPLL [28, 36].

Leptin, a product of the obese (*ob*) gene, is secreted primarily by adipocytes and plays an important role in regulation of food intake and energy expenditure [30]. Peripheral administration of leptin increases bone growth and indices of bone formation [26, 37]. Leptin can also act directly on stromal cells to enhance their differentiation into osteoblasts and inhibit their differentiation into adipocytes [3]. On the other hand, intracerebroventricular infusion of leptin leads to rapid bone loss [32], implying that leptin regulates bone mass through alternate pathways, one involving a direct stimulatory effect on bone growth when administered peripherally and another acting indirectly via a hypothalamic relay that suppresses bone formation, when administered centrally [4]. As leptin has the potential to drive stromal cells into osteogenic differentiation, serum leptin may be associated with the development of heterotopic ossification of the spinal ligament. However, to date, the association between leptin and heterotopic ossification of the spine, particularly in OPLL, has been largely unstudied.

In this study, we hypothesized that serum leptin levels are elevated in patients with OPLL and may be associated with bone metabolic markers and the extent of OPLL development. We measured serum leptin concentrations in OPLL patients and non-OPLL controls and corrected these levels using individual body mass index (BMI). We then analyzed the association between the leptin/BMI ratio and bone metabolic markers, and the number of vertebrae with OPLL involvement. Based on these results, we discuss the possible role(s) of leptin in the development of OPLL.

Subjects and methods

The study subjects (Table 1) were 125 Japanese patients with OPLL (68 males and 57 females) and 62 non-OPLL control subjects (35 males and 27 females, the majority of who had spinal degenerative disorders other than OPLL). All patients were followed at the Department of Orthopedic Surgery of Chiba University Hospital between 1995 and 2008.

Based on previous data that circulating leptin concentrations are significantly higher in females than in male subjects [14, 17, 22], we subdivided the OPLL and non-OPLL groups according to gender. The mean age of OPLL females, non-OPLL females, OPLL males, and non-OPLL males was 58.6 ± 9.0, 61.7 ± 8.7, 61.2 ± 8.1, and 56.5 ± 11.2 years, respectively. The mean BMI (weight in kilograms divided by the square of height in meters) of OPLL females, non-OPLL females, OPLL males, and non-OPLL males was 25.2 ± 4.4, 22.9 ± 3.1, 24.0 ± 2.7, and 23.1 ± 2.5 kg/m^2, respectively. All the patients were informed that data on the blood or urine samples would be submitted for publication and the

Table 1 Clinical characteristics of OPLL (ossification of the posterior longitudinal ligament) patients and non-OPLL controls

	Female OPLL versus non-OPLL		
	OPLL (n = 57)	Non-OPLL (n = 27)	p (Student's t)
Age (year)	58.6 ± 9*	61.7 ± 8.7	<0.05
Height (cm)	152.9 ± 6.7	150.3 ± 6.7	N.S.
Weight (kg)	59 ± 9.8*	51.9 ± 7.8	<0.01
BMI (kg/m^2)	25.2 ± 4.4*	22.9 ± 3.1	<0.05
Serum leptin (ng/ml)	9.67 ± 5.1*	6.55 ± 3.67	<0.01
Leptin/BMI	0.368 ± 0.169*	0.275 ± 0.122	<0.01
	Male OPLL versus non-OPLL		
	OPLL (n = 68)	Non-OPLL (n = 35)	p (Student's t)
Age (year)	61.2 ± 8.1*	56.5 ± 11.2	<0.05
Height (cm)	163.8 ± 5.8*	166.6 ± 5.6	<0.05
Weight (kg)	64.6 ± 9.2	64.4 ± 7.8	N.S.
BMI (kg/m^2)	24 ± 2.7	23.1 ± 2.5	N.S.
Serum leptin (ng/ml)	3.85 ± 2.2	3.2 ± 1.4	N.S.
Leptin/BMI	0.156 ± 0.079	0.136 ± 0.055	N.S.

N.S. not significant, *BMI* body mass index

* Significantly different from non-OPLL

patients volunteered freely to participate in this study. This study was approved by the ethics committee of Chiba University Hospital.

A blood sample was collected from each subject between 11:00 and 13:00 h after overnight fasting and the serum immediately frozen at –80°C until analysis. For a urine analysis, the 2-h morning urine after the first void urine was tested. Serum leptin concentrations were measured using a commercially available radioimmunoassay (RIA) kit (Linco Research, Inc., St. Charles, MO). As gender and adipose tissue volume influence leptin production, the serum leptin levels were corrected for BMI, a measure of obesity, and then compared within each gender group. The minimum detection limit of serum leptin levels was 0.5 ng/ml with a 4.5% coefficient of variation. Serum insulin levels were also measured using a microparticle enzyme immunoassay (EIA) (AxSYM insulin assay kit, Dainabot Co., Ltd., Tokyo, Japan). The minimum detection limit of serum insulin levels was 0.8 μU/ml with a 5.5% coefficient of variation. The serum concentrations of bone formation markers, bone-specific alkaline phosphatase (BAP) and the carboxyterminal propeptide of type I procollagen (PICP) were measured using an EIA (Takara, Tokyo, Japan) and a RIA (Orion Diagnostica, Espoo, Finland) kit, respectively. Urine deoxypyridinoline (DPD) was measured with an EIA kit (DS Pharma Biomedical, Osaka, Japan) as a marker of bone resorption.

Radiographic evaluation of the number of vertebrae and segments with OPLL involvement in individual patients was evaluated by at least two different authors, all of whom were senior spinal surgeons. Patients with ossification of the yellow ligament of the spine, which is often seen as heterotopic ossification of the spinal ligament at the thoracic spine, were excluded from the study.

Statistical methods

Previous studies have shown that circulating leptin levels correlate positively with BMI [14, 31]. To eliminate the influence of obesity, we calculated the leptin/BMI ratio for individual patients. Comparison of age, height, body weight, BMI, serum leptin levels, and leptin/BMI ratios between OPLL patients and non-OPLL controls was performed using Student's *t* test. In female OPLL patients, correlations between leptin/BMI ratios and serum BAP, PICP, insulin, and fructosamine (FRA) levels, urine DPD levels, and the number of vertebrae with OPLL involvement were analyzed using Pearson's correction analysis.

In addition, the OPLL patients were divided into two subgroups according to the extent of OPLL development, with patients in whom OPLL was limited to the cervical spine being designated as type C-OPLL, while subjects in whom OPLL extended to the thoracic and/or lumbar spine being designated as type TL-OPLL (Fig. 1). Type C-OPLL included 63 patients (48 males and 15 females) while type TL-OPLL included 62 patients (20 males and 42 females) (Table 2). Student's *t* test was then performed to analyze differences in age, height, body weight, BMI, leptin/BMI ratios, and serum insulin and FRA levels between type C-OPLL and type TL-OPLL patients. The correlation between leptin/BMI ratios and serum BAP, PICP, insulin, and FRA levels, urine DPD levels, and the number of vertebrae with OPLL involvement in both female type TL-OPLL and female type C-OPLL patients were analyzed using Pearson's correlation analysis. All these analyses were performed with the significance level being set at $p < 0.05$.

Results

Serum leptin concentrations and leptin/BMI ratios in OPLL and non-OPLL patients

The characteristics of the four subgroups are presented in Table 1. Both OPLL and non-OPLL groups exhibited

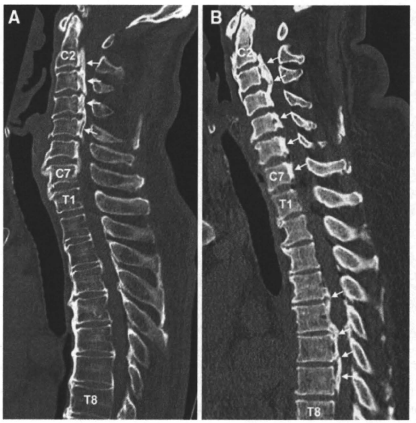

Fig. 1 Representative, mid-sagittal reconstruction images of 3-dimensional computed tomography (CT) for type C-OPLL (a type of OPLL limited to the cervical spine) and type TL-OPLL (a type of OPLL extended to the thoracic and/or lumbar spine) patients. **a** A 66-year-old male patient where OPLL is limited to the cervical spine (type C-OPLL). **b** A 54-year-old female patient where OPLL is extended to the thoracic spine (type TL-OPLL). *Arrows* indicate OPLL. *C2* 2nd cervical vertebra, *C7* 7th cervical vertebra, *T1* 1st thoracic vertebra, *T8* 8th thoracic vertebra

Table 2 Clinical characteristics of type C-OPLL (a type of OPLL limited to the cervical spine) and type TL-OPLL (a type of OPLL extended to the thoracic and/or lumbar spine) patients

	Female type C-OPLL versus type TL-OPLL		
	Type C ($n = 15$)	Type TL ($n = 42$)	p (Student's t)
Age (year)	58.6 ± 10	56.1 ± 8.6	N.S.
Height (cm)	153.1 ± 6.3	152.8 ± 6.9	N.S.
Weight (kg)	56.6 ± 10.1	59.8 ± 9.6	N.S.
BMI (kg/m^2)	24.2 ± 5	25.5 ± 4.1	N.S.
Serum leptin (ng/ml)	6.64 ± 4	10.7 ± 5*	<0.01
Leptin/BMI	0.261 ± 0.122	0.407 ± 0.168*	<0.01
Serum insulin (μU/ml)	10.1 ± 4.3	19.2 ± 22.2	N.S.
Serum FRA (μM)	511 ± 176	708 ± 418	N.S.
	Male type C-OPLL versus type TL-OPLL		
	Type C ($n = 48$)	Type TL ($n = 20$)	p (Student's t)
Age (year)	60.9 ± 8.6	61.9 ± 6.8	N.S.
Height (cm)	164.3 ± 5.6	162.5 ± 6.2	N.S.
Weight (kg)	64.7 ± 9	64.5 ± 9.8	N.S.
BMI (kg/m^2)	23.9 ± 2.6	24.3 ± 3.2	N.S.
Serum leptin (ng/ml)	3.62 ± 2.16	4.41 ± 2.33	N.S.
Leptin/BMI	0.148 ± 0.08	0.173 ± 0.075	N.S.
Serum insulin (μU/ml)	15 ± 16.7	20.1 ± 21.4	N.S.
Serum FRA (μM)	672 ± 293	739 ± 281	N.S.

N.S. not significant, *BMI* body mass index, *FRA* fructosamine

* Significantly different from type C-OPLL

significantly higher serum leptin concentrations in females than in male subjects, consistent with the findings of previous studies [14, 23]. In female subjects, serum leptin concentrations in the OPLL group were 1.5-fold higher than that in the non-OPLL group ($p < 0.01$). However, in male subjects there was no significant difference in serum leptin concentrations between the OPLL and non-OPLL groups.

In female subjects, the leptin/BMI ratio was significantly higher (1.3-fold) in the OPLL group than in the non-OPLL group ($p < 0.01$), whereas no significant difference was observed in the male subjects (Table 1).

Correlation of leptin/BMI ratios with biochemical markers of bone turnover, serum insulin and FRA concentrations, and the number of vertebrae with OPLL involvement in OPLL females

To determine the factors associated with the leptin/BMI ratio in OPLL females, we examined the correlation between leptin/BMI ratios and bone metabolic markers, circulating insulin and FRA concentrations, and the number of vertebrae with OPLL involvement (Fig. 2). There was only a relatively weak, non-significant positive correlation between the leptin/BMI ratio and both bone formation markers, BAP and PICP. In contrast, urine DPD levels, a bone resorption marker, showed a negative correlation with the leptin/BMI ratio ($r = -0.523$, $p < 0.05$). Serum insulin concentrations were correlated positively with the leptin/BMI ratio ($r = 0.344$, $p < 0.01$), whereas serum FRA levels showed no such significant relationship. It should be noted that there was a positive correlation between the number of vertebrae with OPLL involvement and the leptin/BMI ratio ($r = 0.271$, $p < 0.05$). We also examined all the above relationships in OPLL males and showed that there was no significant correlation between the leptin/BMI ratio and any other variable (data not shown).

Comparison of serum leptin, insulin, FRA concentrations, and leptin/BMI ratios between type C-OPLL and type TL-OPLL patients

The characteristics of the four subgroups of OPLL patients are presented in Table 2. In female subjects, there was no significant difference in age, height, weight, BMI, serum insulin and FRA concentrations between the groups except for serum leptin concentration which was 1.6-fold higher in type TL-OPLL than in type C-OPLL ($p < 0.01$). This difference was also found in serum leptin levels corrected by BMI, with significantly higher values in type TL-OPLL (1.6-fold, $p < 0.01$) than in type C-OPLL (Table 2). In male subjects, there were no significant differences in serum leptin concentrations and leptin/BMI ratios between the two subgroups (Table 2).

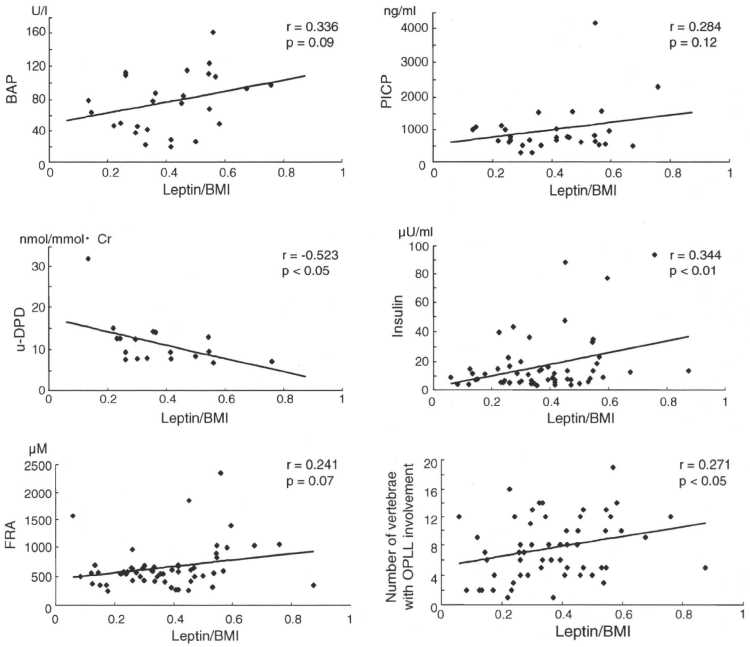

Fig. 2 Relationship between the leptin/BMI (body mass index) ratio and bone metabolic markers including serum bone-specific alkaline phosphatase (BAP), carboxyterminal propeptide of type I procollagen (PICP), and urine deoxypyridinoline (DPD), serum insulin and fructosamine (FRA) concentrations, and the number of vertebrae with OPLL (ossification of the posterior longitudinal ligament) involvement in female OPLL patients. There was a negative, significant correlation between the leptin/BMI ratio and urine DPD levels, while a positive, significant correlation between the leptin/BMI ratio and serum insulin levels, and the number of vertebrae with OPLL involvement

Correlation of leptin/BMI ratios with bone metabolic markers, serum insulin and FRA concentrations, and the number of vertebrae with OPLL involvement in females with type C-OPLL or type TL-OPLL

To investigate the factors associated with the leptin/BMI ratio in female patients with type TL-OPLL, we examined the correlation between leptin/BMI ratios and bone metabolic markers, serum insulin and FRA concentrations, and the number of vertebrae with OPLL involvement (Fig. 3). There was a strong, positive correlation between serum BAP levels and the leptin/BMI ratio ($r = 0.518, p < 0.05$), but no significant difference between PICP levels and the ratio. Urine DPD and serum FRA levels, and the number of vertebrae with OPLL involvement did not show a significant correlation with the leptin/BMI ratio. Interestingly, serum insulin concentrations correlated positively with the leptin/BMI ratio ($r = 0.324, p < 0.05$). We also carried out similar correlation analyses on type C-OPLL females, but found no significant relationship between the variables (data not shown).

Discussion

This study demonstrated that females with OPLL had significantly higher serum leptin levels compared with females without OPLL and that the levels correlated positively with serum insulin levels. These findings are consistent with those of a previous study by Shirakura et al. [24]. In the present study, we carried out further investigations to determine the factors associated with the leptin/BMI ratio in OPLL females and showed that urine DPD concentrations correlated negatively with the ratio. This

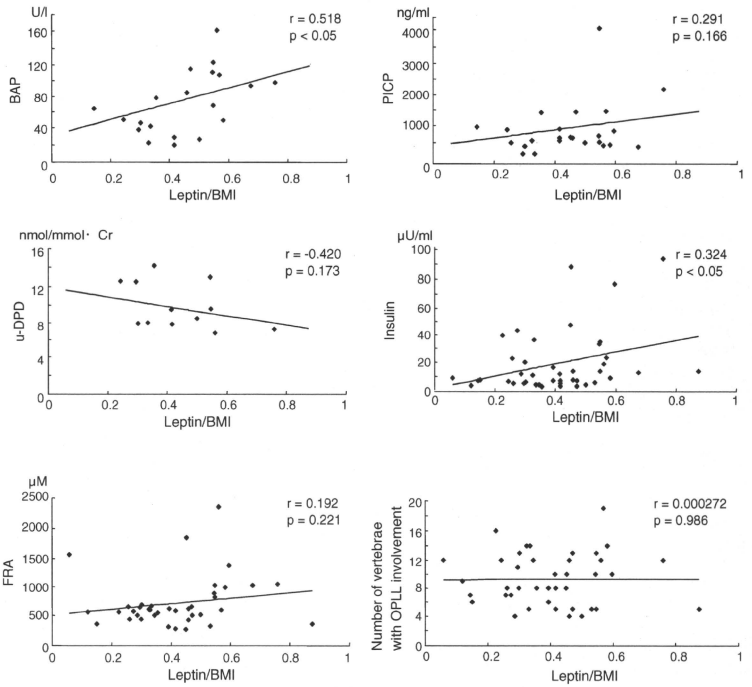

Fig. 3 Relationship between the leptin/BMI (body mass index) ratio and bone metabolic markers including serum bone-specific alkaline phosphatase (BAP), carboxyterminal propeptide of type I procollagen (PICP), and urine deoxypyridinoline (DPD), serum insulin and fructosamine (FRA) concentrations, and the number of vertebrae with OPLL involvement in female type TL-OPLL patients. There was a positive, significant correlation between the leptin/BMI ratio and serum BAP levels, and serum insulin levels

suggests a regulatory effect of leptin on bone resorption, which is in agreement with the report of Burguera et al. [2] who demonstrated in animal experiments that leptin prevented ovariectomy-induced bone loss. Taken together, these results indicate a tendency for a positive correlation between BAP levels and the leptin/BMI ratio in OPLL females and that bone anabolism may be promoted in these patients. However, a significant correlation between urine DPD levels and the leptin/BMI ratio in OPLL females may be influenced by one sample that appears to be an outlier (leptin/BMI = 0.13, u-DPD = 32) as shown in Fig. 2 because this association lost statistical significance when that one sample was excluded ($p = 0.085$, data not shown). Further studies are necessary to establish association between urine DPD levels and the leptin/BMI ratio in OPLL females.

It is interesting that the number of vertebrae with OPLL involvement correlated positively with the leptin/BMI ratio in female patients with OPLL. To the best of our knowledge, there have been no other reports demonstrating an association between serum leptin levels and the extent of OPLL development in humans. We showed previously that the A861G variant in the leptin receptor gene (Ob-R) was associated with more extensive OPLL [29]. Although the effects of the variant in Ob-R on leptin signaling are unknown, this finding suggests that altered leptin signaling in spinal ligament cells may be a factor that regulates the extent of OPLL development.

To date, a few in vitro studies have revealed the mechanisms by which leptin induces osteogenic differentiation in spinal ligament cells [6, 24]. Fan et al. [6] demonstrated that leptin caused significant increases in

mRNA expression of alkaline phosphatase (ALP) and osteocalcin in thoracic ossification of ligament flavum (TOLF) cells, but not in non-TOLF cells, and that the effect was both dose- and time-dependent. These findings suggest that TOLF cells are considerably more sensitive to leptin stimulation and that leptin has the potential to promote osteogenic differentiation in ligament flavum cells. However, this leptin-induced osteogenic differentiation was observed only in response to pharmacological doses, which are not equivalent to physiological concentrations in humans. This implies that ligand stimulation with cytokines, other than leptin, is required to induce osteogenic differentiation in spinal ligament cells.

Insulin has been implicated in the development of heterotopic ossification of spinal ligaments [8, 12, 15]. Spinal ligament cells express insulin receptor substrate (IRS)-1, a common major substrate for both insulin and insulin-like growth factor (IGF)-I receptor tyrosine kinase [12]. We have reported previously that IGF-I stimulates proliferation and collagen type I synthesis in the majority of spinal ligament cells [8]. Li et al. [15] showed that both insulin and IGF-I increased proliferation and ALP activity in human spinal ligament cells. It has been reported that leptin acts through some of the components of the insulin signaling cascade by recruiting several IRSs [1, 7, 9, 19]. This implies that there is cross-talk between leptin signaling and insulin-induced pathways. Our finding that the leptin/BMI ratio correlated positively with serum insulin levels in OPLL females suggests that increased levels of both leptin and insulin may act synergistically to strengthen downstream signaling, thereby contributing to the development of OPLL.

As the number of vertebrae with OPLL involvement correlated positively with serum leptin levels in OPLL females, we hypothesized that female patients with extended OPLL may have higher serum levels of leptin than those with limited OPLL. To verify this hypothesis, we divided the OPLL females into two further subgroups; type C and type TL groups. We then compared BMI, serum leptin levels, leptin/BMI ratios, and serum insulin and FRA concentrations in these two groups. The results showed that relative to type C-OPLL, serum leptin levels and leptin/BMI ratios were increased significantly in type TL-OPLL by 1.6- and 1.9-fold, respectively. Although there were no statistical differences in serum insulin and FRA concentrations between the groups, higher levels of insulin and FRA were detected in type TL-OPLL, which supports the concept that both hyperleptinemia and hyperinsulinemia contribute to extension of heterotopic ossification of the spinal ligament in OPLL females.

It is also of interest that there was a positive, significant correlation between the leptin/BMI ratio and BAP levels in type TL-OPLL females whose serum leptin concentrations were significantly higher than type C-OPLL, whereas no significant correlation was detected in all OPLL females. These results indicate that bone anabolism is elevated substantially in female type TL-OPLL patients compared to female type C-OPLL patients. However, this is inconsistent with a previous report that serum leptin levels are negative regulators of bone mass [5]. We speculate that in OPLL females there may be a decrease in leptin sensitivity in the hypothalamus, which in turn, increases circulating leptin levels, resulting in the development of OPLL through the direct and anabolic effects of leptin on bone and spinal ligament cells.

OPLL occurs frequently at the cervical spine [33]. However, it has not been determined why OPLL is sometimes limited to the cervical spine or alternatively extends to the thoracic and/or lumbar spine. As shown in our study, higher serum leptin levels, detected in female patients with OPLL extending to the thoracic and/or lumbar spine, may be a causative factor determining the extension of OPLL. However, even if serum leptin levels or other systemic factors including serum insulin or FRA levels affect the extension of OPLL, there still remains the question as to why the limited type of OPLL is seen frequently at the cervical spine. We speculate that mechanical stress, which is supposedly a local factor, could be a prime candidate to induce heterotopic ossification in the cervical spine but is unlikely to occur in the thoracic spine. Iwasawa et al. [11] demonstrated that exposure to mechanical stress such as uniaxial stretching upregulated various genes related to bone metabolism including endothelin-1 (ET-1) and prostaglandin I_2 (PGI_2) in OPLL cells. This shows clearly the importance of mechanical stress in heterotopic ossification of the spinal ligament. Several biomechanical studies have revealed that the range of motion (extension and flexion) of the cervical spine is much larger than that of the thoracic spine [18, 27, 35]. Taken together, it is conceivable that moderately elevated levels of leptin, in combination with mechanical stress to the ligament cells, may contribute to the development of cervical OPLL, while highly elevated levels of leptin may have a role in the extension of OPLL to the thoracic and/or lumbar spine.

The important issue that is not clarified by the present study is the significant gender difference between serum leptin levels and the development of OPLL. It is likely that some gender-specific factors such as estrogen may have an important role in the development of OPLL. Recent studies on human periodontal ligament cells have shown that estrogen is capable of inducing osteogenic differentiation in ligament cells [16, 25, 38]. It has also been shown previously in the Japanese population that serum estrogen levels are elevated significantly in OPLL patients, and that the levels are related to the extent of heterotopic ligament ossification [34]. These observations suggest a pivotal role

for estrogen in heterotopic ossification of the spinal ligament. We therefore speculate that serum leptin do not regulate solely the development of OPLL, but may contribute to the development of OPLL in combination with some gender-specific factors such as estrogen.

In summary, we showed that serum leptin concentrations are elevated in females with OPLL and are associated with extension of OPLL, i.e. an increased number of vertebrae with OPLL involvement. In addition, serum leptin levels in patients with extensive OPLL (thoracic and/or lumbar type) were higher than in patients with limited OPLL (cervical type). These observations indicate that hyperleptinemia may contribute to the development of heterotopic ossification of the spinal ligament in females with OPLL. However, it is also clear that this scenario does not completely explain the entire mechanism of spinal ligament ossification in OPLL patients as other complicated pathological factors associated with OPLL such as hyperinsulinemia, hyperlipidemia, and high glucose levels coexist with hyperleptinemia. The present observations are, nevertheless, important for future work and may provide information on the mechanisms underlying the development of OPLL, and ultimately may lead to potential drug therapies for management of this disease.

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CASE REPORT

Acupuncture needle-associated prosthetic knee infection after total knee arthroplasty

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Abstract The case of a patient who previously had permanent acupuncture needles placed in the knee joint and had been doing well, with no evidence of infection, but who eventually underwent a revision total knee arthroplasty due to acupuncture needle-associated prosthetic infection is presented. The microorganism responsible for the infection was *Enterococcus faecalis*, a bacterium which rarely causes infection following arthroplasty. This case should be highlighted to increase the awareness of healthcare providers to acupuncture-associated subclinical infection that may be exacerbated by surgical manipulation.

Keywords Acupuncture · Prosthesis · TKA · Subclinical infection

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Introduction

Infection of prosthetic joints is a rare but catastrophic complication of joint arthroplasty. The prevalence of infection after total knee arthroplasty (TKA) has been reported to range from 0.5 to 5% in series ranging in scope from 821 to 13,478 arthroplasties [1–5]. *Staphylococcus* spp. are the most common pathogens causing prosthetic joint infection, [6], but *Streptococcus* and *Enterococcus* spp.-induced or culture-negative prosthetic joint infections have also been reported [7, 8].

Acupuncture is one of the most commonly applied procedures in alternative or complimentary medicine and is widely used in both Asian and Western countries. Despite controversies surrounding its effectiveness, acupuncture is generally regarded as a safe procedure. However, it may cause serious adverse events, such as pneumothorax, viral hepatitis, and human immunodeficiency virus infection [9, 10]. In the orthopaedic field, acupuncture therapy is performed as a treatment for patients with low back pain or osteoarthritis. Acupuncture-associated complications, such as subcutaneous abscess and septic arthritis of the spinal and peripheral joints, have been reported [11–14]; however, in most of the reported cases, the infection developed within a short time following the acupuncture therapy. To the best of our knowledge, there have been no reports of the development of infection many years after the end of the acupuncture treatment.

We present a patient who previously had permanent acupuncture needles placed in the subcutaneous tissue around the knee joint and eventually underwent a revision TKA due to acupuncture needle-associated prosthetic infection. This case should be highlighted in the orthopaedic community in order to increase clinicians' awareness of

acupuncture-associated subclinical infection that may be unmasked by surgical manipulation.

Our patient gave informed consent that data concerning her case could be submitted for publication.

Case report

A 60-year-old woman presented to our hospital with a chief complaint of right knee pain for 15 years. She had been treated with non-steroidal anti-inflammatory drugs and physiotherapy, but her clinical symptoms had not improved. Thirteen years previously, she had undergone acupuncture therapy with the implantation of permanent needles for treatment of her right knee pain. Preoperative radiographs of the right knee demonstrated a number of permanent acupuncture needles had been left in the subcutaneous tissue around the knee (Fig. 1, arrows). The range of motion for the right knee was 0°–30°. Preoperatively, both peripheral leukocyte count and C-reactive protein levels were within normal limits. The synovial fluid culture for her right knee was negative. She underwent a posterior stabilized (PS) type TKA (FINE Knee; Nakashima Medical, Okayama, Japan) for the right osteoarthritic knee. Cultures for intraoperative synovial tissues were also negative. The patient obtained relief from the right knee pain immediately after the surgery.

At the 2-month postoperative follow-up, local heat and swelling were found at the right tibial tubercle, and she was diagnosed with phlegmon of the lower thigh by a dermatologist. Osteolysis around the femoral component was suspected from radiographs of the knee (radiographs not shown), but the patient was satisfied with the results of the TKA and was able to walk 1–2 km without pain. Ampicillin (750 mg per day) was administered orally for 1 week, resulting in resolution of the phlegmon.

Ten months following the operation, however, she returned to our hospital due to severe right knee pain and swelling. Physical examination revealed considerable heat and swelling in the right knee with joint effusion. With the exception of her right swollen and tender knee, her physical examination was otherwise unremarkable. Plain radiographs revealed evidence of osteolysis around the femoral and tibial components (Fig. 2, arrows). The peripheral leukocyte count was within normal limits ($7.6 \times 10^3/\mu L$); however, C-reactive protein was highly elevated at 6.9 mg/dL (normal range <0.3 mg/dL). An initial culture of the synovial fluid from the right knee showed no growth after 4 days. The patient underwent removal of the knee prostheses and extensive synovectomy followed by implantation of a mold spacer consisting of 40 g of cement (Surgical Simplex P; Howmedica Int, Limerick, Ireland) and 2 g of vancomycin. The synovial fluid and granulation tissue taken during surgery were cultured, resulting in the growth of *Enterococcus faecalis*. After implant removal, intravenous injection of ampicillin/sulbactam (3.0 g per day) was administered for 7 days, followed by meropenem (1.0 g per day) for 5 weeks. The bacteriological cultures of the drainage sampled on post-operative days 6 and 8 were

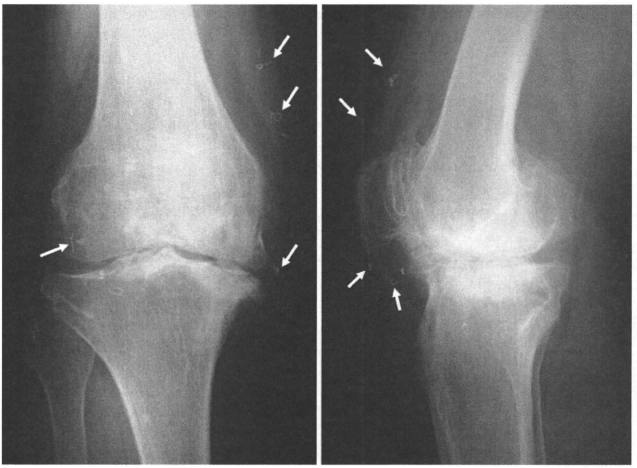

Fig. 1 Preoperative radiographs of the right knee. Note that a number of permanent acupuncture needles (*arrows*) had been left in the subcutaneous tissue around the knee

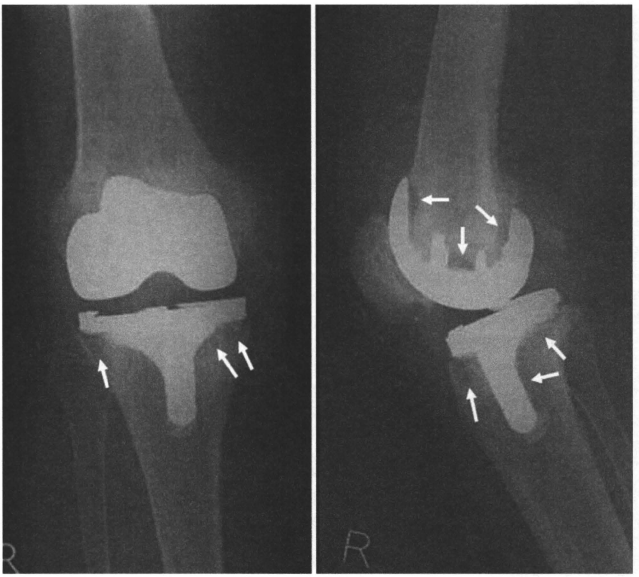

Fig. 2 Radiographs of the right knee 11 months after the primary total knee arthroplasty (TKA). Osteolysis around the femoral and tibial components is evident (*arrows*)

negative. C-reactive protein declined to 1.8 mg/dL within 1 week of implant removal, then to 0.2 mg/dL 3 weeks after implant removal.

Four months after the removal of the infected prostheses, the patient underwent a revision TKA (Legacy Constrained Chondyler Knee; Zimmer, Warsaw, IN) with 20 g of cement (Surgical Simplex P) including 1 g of vancomycin. Meropenem (1.0 g per day) was administered postoperatively for 1 week. No acute inflammation was noted following histological examination of sections from the synovial lining, and the intraoperative cultures showed no growth of the organism. One year after her right knee reimplantation, the patient was doing well, with no major clinical symptoms associated with her right knee, and the range of motion was 0°–60°. Radiographs demonstrated no evidence of osteolysis, but acupuncture needles were still present in the subcutaneous tissue around the right knee (Fig. 3).

Discussion

Our review of the literature revealed that acupuncture-associated infection following prosthetic arthroplasty has not been reported to date. To treat the prosthetic knee infection, we removed the implant of our patient and performed a revision TKA. Despite an asymptomatic period since the acupuncture needles had been placed 13 years previously, infection had developed during the early phase after the primary TKA. We report this case to highlight debate as to whether surgeons should undertake arthroplasty in patients who have permanent acupuncture needles in affected joints.

The microorganism cultured from intraoperative samples in our patient was *Enterococcus faecalis*, which only rarely causes infection following arthroplasty. Possible sources for this bacterium are the oral cavity and gastrointestinal and urogenital tracts. To date, only two cases demonstrating prosthetic joint infection caused by *E. faecalis* have been reported in the literature [15, 16]. One of these is hematogenous infection of a resurfacing hip replacement after transurethral resection of the prostate [16]. As the hip prosthesis had been inserted 7 years before surgery and had been asymptomatic with no other significant comorbidities, this case is thought to be that of a late infection.

Infections of joint prostheses can be classified as early (presenting <3 months postoperatively), delayed (3–24 months), and late (>24 months) [17]. In acute and delayed infections, the pathogens responsible are usually

Fig. 3 Radiographs of the right knee 1 year after the revision TKA. Osteolysis is not observed at all, but acupuncture needles are still present in the subcutaneous tissue around the knee

introduced during the operation, whereas late infection occurs by hematogenous seeding of the implant from the bacteraemia. In our case, infection was obvious 11 months after TKA; however, superficial infection and radiographic loosening of the femoral component were observed as early as 2 months postoperatively, suggesting an early infection that could have been introduced during the primary TKA.

Segawa et al. defined four clinical settings, namely, deep early, superficial early, late chronic, and acute hematogenous infection, and classified 81 infections after TKA. In their study, 19 of the 24 early infections (including both deep and superficial) were coagulase-positive or -negative staphylococci-induced infections [8]. *E. faecalis* is a rare causal agent of early infection; however, among the infections found after TKA, the authors demonstrated that nine were caused by *Enterococcus* spp. and that three of these were superficial early infections. Taking these facts into consideration, we cannot completely deny the possibility that the prosthetic joint infection in our patient was due to early infection.

How could the permanent acupuncture needles have been involved in the prosthetic knee infection after the TKA? We speculate that there was subclinical (or low-grade) infection due to a number of the acupuncture needles still being present before the primary TKA. Subclinical infection in patients with joint prostheses who lack prior or current evidence of infection has recently been reported [18–20]. Because microorganisms are typically present in a biofilm on the surface of the prostheses, they elude standard culture techniques as demonstrated in our case: we actually cultured preoperatively the joint fluid and synovial tissues during the primary TKA using standard techniques, but no bacteria grew from any samples. Although there have been no reports demonstrating subclinical infection in patients with permanent acupuncture needles, it is possible that the subclinical infection already existed in the knee of our