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A novel synthetic material for spinal fusion: A prospective clinical trial of porous bioactive titanium metal for lumbar interbody fusion

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A novel synthetic material for spinal fusion: A prospective clinical trial of porous bioactive titanium metal for lumbar interbody fusion

Abstract

Object. To establish the efficacy and safety of porous bioactive titanium metal for use in a spinal fusion device, based on a prospective human clinical trial.

Methods. A high-strength spinal interbody fusion device was manufactured from porous titanium metal. A bioactive surface was produced by simple chemical and thermal treatment. Five patients with unstable lumbar spine disease were treated surgically using this device in a clinical trial approved by our Ethics Review Committee and the University Hospital Medical Information Network. Clinical and radiological results were reported at the minimum follow-up period of one year.

Results. The optimal mechanical strength and interconnected structure of the porous titanium metal were adjusted for the device. The whole surface of porous titanium metal was treated uniformly and its bioactive ability was confirmed before clinical use. Successful bony union was achieved in all cases within 6 months without the need for autologous iliac crest bone grafting. Two specific findings including an anchoring effect and gap filling were evident radiologically. All clinical parameters improved significantly after the operation and no adverse effects were encountered during the follow-up period.

Conclusions. Although a larger and longer-term follow-up clinical study is mandatory to reach any firm conclusions, we consider this porous bioactive titanium metal is promising material for a spinal fusion device.

Key Words: porous titanium metal, spinal fusion, biomaterial, clinical trial

Introduction

Osteoconductive synthetic materials including sintered hydroxyapatite ($\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$ or HA), $\text{Na}_2\text{O}-\text{CaO}-\text{SiO}_2-\text{P}_2\text{O}_5$ system (Bioglass[®]) and glass ceramics containing apatite and wollastonite (AW-GC) are widely used clinically as bone substitutes [7,12,16]. Because application for load-bearing conditions such as the spine or long bones requires high mechanical strength, solid materials are usually used. However, such materials are brittle against shearing forces and bond to the surrounding bone only at their surface. Porous materials have advantages over solid materials in terms of bone bonding, because they can demonstrate both osteoconductive bonding and mechanical interlocking through bone tissue ingrowth into the pores. Conventional porous synthetic materials such as granules of HA and AW-GC have been applied clinically as bone graft expanders for lumbar posterolateral fusion or bone void fillers after tumor excision [8]. However, because of their poor mechanical strength, porous body of such materials cannot be applied in load-bearing conditions. Thus, achieving both high bone-bonding ability and high mechanical strength is quite difficult for porous materials. To overcome this problem, we have developed porous bioactive titanium metal, which possesses both high bone-bonding ability and high mechanical strength simultaneously [24]. Titanium metal and its alloys can be changed to bioactive materials by simple chemical and thermal surface treatment [9,18]. This can be applied to porous titanium metal as well [15]. Several experiments on animal models showed the safety and efficacy of porous bioactive titanium metal as a synthetic bone under load-bearing conditions. Our preclinical study [26] demonstrated that bioactive treatment effectively enhanced the fusion ability of the porous titanium implants in a canine model of spinal interbody fusion .

Instrumented spinal fusion with autologous iliac crest bone grafting (ICBG) is a gold-standard surgical procedure for the treatment of unstable spinal diseases. However, grafts harvested from the iliac crest are still a major source of autologous bone and the harvesting process is associated with graft site morbidities including residual pain, long operative times and significant blood loss [1].

To accelerate the fusion rate and alleviate donor site problems, several effective osteoinductive agents including recombinant human bone morphogenetic protein-2 (rhBMP-2) and osteogenic protein-1 (OP-1/BMP-7) have been introduced and are widely used clinically [3,20]. Excellent clinical results have been documented, although some serious adverse effects have been reported such as osteolysis around the cage implant, massive bleeding and soft tissue swelling [19,27,31]. Porous bioactive titanium metal is not only osteoconductive but also has osteoinductive ability without the need for additional osteogenic cells or agents [10,25]. Although the osteoinductive ability of porous bioactive titanium metal is limited and the actual mechanism has not been clarified, the osteogenesis it induces is believed to guarantee the high osteoconductive ability of this material.

We conducted a clinical trial of porous bioactive titanium metal for lumbar interbody fusion. Here, we report our preliminary results and discuss the safety and efficacy of porous bioactive titanium metal as one of a new generation of synthetic device materials. This trial was based upon extensive experiments in animal models and clinical success in cementless total hip prosthesis using porous bioactive titanium metal [14,26].

Methods

1. Preparation of porous implants

Porous titanium metal was manufactured from a mixture of commercially pure titanium powder less than 45 μm in particle size (Osaka Titanium Tech. Co. Ltd, Osaka, Japan) and ammonium hydrogen carbonate as spacer particle [32]. Sintering was carried out at 1400 $^{\circ}\text{C}$ for 2 h in Argon gas. Three types of implants, 7, 8 and 9 mm thick and 30 mm wide, were prepared for the clinical trial (Fig. 1). To improve the safety of handling during surgery, a thin outer frame was placed around the porous body and sintered. These implants were supplied by Osaka Yakin Co. (Osaka, Japan). Micro-computed tomography (CT) analysis demonstrated that more than 99% of the porous structures were interconnected and more than 80% of pores were connected through channels more than 52 μm in diameter (Fig.2). The average porosity was 60% and the average pore size was 250 μm .

2. Mechanical properties of the porous titanium implants

The compressive strength of the porous titanium body was measured using a universal testing machine (Model EHF-LV020K1-010, Shimadzu Corp., Kyoto, Japan) at a crosshead speed of 1 mm/min. 0.2% yield compressive strength and Young's modulus of a typical 60% porous body were 53.0 MPa and 4.2 GPa, respectively. The stiffness was 91.5 kN/m, and this increased to 458.3 kN/m with the outer frame. The porous body combined with the outer frame proved stable against a cyclic load of 10,000 N at 4 Hz for 1,000,000 cycles.

3. Bioactive surface treatment

The porous implants were treated chemically and thermally to give them a bioactive surface, as described [9,18]. Briefly, the sintered porous titanium bodies were immersed in 5 M aqueous NaOH solution at 60 °C for 24 h, 0.5 mM HCl at 40 °C for 24 h, ultrapure water at 40 °C for 24 h and then heat-treated at 600 °C for 1 h. The homogeneity of the bioactive surface was confirmed by examining the topography and the chemistry of the center and the peripheral parts of several implants using a field emission scanning electron microscope (FE-SEM; Hitachi S-4300, Ibaraki, Japan), an energy dispersive X-ray microanalyzer (EDX) and X-ray diffractometry (XRD). In vitro apatite-forming ability was confirmed by soaking samples for 3 days in an acellular simulated body fluid (SBF) with ion concentrations (in mM) of Na⁺ 142.0, K⁺ 5.0, Mg²⁺ 1.5, Ca²⁺ 2.5, Cl⁻ 147.8, HCO₃⁻ 4.2, HPO₄²⁻ 1.0 and SO₄²⁻ 0.5: nearly equal to those of human blood plasma at 36.5 °C and prerequisite conditions for generating bioactive materials [17]. The implants were sterilized by 25 kGy γ -radiology exposure before surgical implantation.

4. Evaluation of implants

All devices with the same lot number destined for clinical use were analyzed *in vitro* before implantation. All parameters of mechanical strength including yield compressive strength, elastic modulus and fatigue strength were within an error of less than 5%. Mechanical testing found no failure of the device, nor any loss of titanium particles. FE-SEM, EDX and XRD studies confirmed the homogeneity of the bioactive surface both centrally and peripherally. After the surface treatment, the whole porous surface was uniformly

changed to a bioactive thin TiO₂ layer approximately 1 μm thick with sub-micron-sized pores. The walls of the porous body were completely covered with apatite within three days of soaking in SBF, indicating that the whole surface of the implant could be rendered bioactive by the chemical and thermal treatments (Fig. 3A–C).

5. Transforaminal lumbar interbody fusion (TLIF) [11]

All surgical procedures were performed by the two senior authors (S.F. and M.T.). Following a midline skin incision, the lateral aspect of facet joints were exposed through a midline subperiosteal approach or Wiltse's approach depending on the case. After bilateral pedicle screw placement, the neural foramen was exposed by excision of the ipsilateral facet joint. Disc space preparation with the removal of degenerative disc materials and cartilaginous endplate was performed carefully from the safety triangle zone between the exiting and traversing nerve roots. In the case of concomitant spinal canal stenosis, neural decompression was done using a surgical microscope. The bioactive porous titanium implant was placed into the intervertebral space through the opened safety triangle zone and small local bone chips were packed around the implant as monitoring bone material. Compressive force was applied through the pedicle screws and pre-bent rods were set on the screws bilaterally. The patients were allowed to walk while wearing a hard brace beginning on the first day after surgery.

6. Patients

This was a prospective clinical case series on five patients (three men and two women) with degenerative unstable lumbar lesion who were eligible for surgical treatment and who

were referred to our University Hospital from November 2008 to June 2009. In all cases, the patient and his or her relatives were informed about the benefits and the risks of the implant. Written informed consent was obtained from all patients and/or their relatives, in accordance with protocols approved by our Institutional Ethics Committee and in agreement with the Declaration of Helsinki.

Among the five patients enrolled there were three with degenerative spondylolisthesis and two with isthmic spondylolisthesis. Inclusion criteria for this preliminary clinical trial were symptomatic single-level unstable lumbar disc disease with or without compression of neural elements, which were refractory to adequate conservative treatments for at least three months preoperatively. Patients with multilevel diseases, a previously operated spine, osteoporosis, general inflammatory disease or a severe comorbidity such as cardiovascular disease or renal dysfunction were excluded. The average age of the enrolled patients at surgery was 51.6 years (range 36–61 years).

7. Clinical assessment

A patient self-assessed 100 mm Visual Analogue Scale (VAS) (“0mm = no pain, 100mm = worst pain imaginable”) for both low back pain (LBP) and leg pain (LP), the Japanese Orthopaedic Association (JOA) score (Table 1) and its recovery rate (Recovery rate = $\frac{\text{Postoperative score} - \text{Preoperative score}}{29 \text{ (full score)} - \text{Preoperative score}} \times 100 \text{ (\%)}$) were examined before operation and postoperatively. A self-assessed patient’s satisfaction score was examined after the surgery. For subjective assessment of the overall results of surgery, the patient was asked to select from among the options: very satisfied, satisfied,

somewhat satisfied, somewhat dissatisfied or dissatisfied. The satisfaction score was recorded as a score at all time points. All patients complained of LBP preoperatively and three complained of concomitant LP. The average preoperative JOA score was 15.8 (range 11–21). The average preoperative VAS values for LBP and LP were 37.6 mm (range 10–50 mm) and 21.4 mm (range 0–60 mm), respectively. An independent expert nurse carried out the assessment of pre- and postoperative VAS and the patient's satisfaction score. The JOA scores and VAS measures were analyzed statistically using paired *t*-tests and $P < 0.05$ was considered statistically significant.

8. Radiological assessment

Magnetic resonance imaging (MRI), multidetector-row computed tomography (MDCT) and lateral dynamic X-rays were used to assess the neural compression and dynamic situation. Preoperative dynamic lateral X-rays showed marked segmental instability in all five patients. To assess bony union postoperatively, lateral dynamic radiographs were obtained at 3, 6 and 12 months. More than 3° motion on flexion–extension was considered to indicate nonunion. In addition, radiolucent regions around the pedicle screws and the implant were defined as showing nonunion. To evaluate the placement of implant and pedicle screws, bony union and adverse effects, coronal and sagittal reconstruction views using MDCT were assessed at 1 week and at 1, 3, 6 and 12 months after surgery. Bony union was defined as complete when there was osseous continuity between bony endplate and implant on both the coronal and sagittal MDCT images. Nonunion was defined as the presence of a visible gap between the vertebral endplate and implant, or radiolucency around the pedicle screws.

Successful bony union was recorded when the assessments of radiological parameters mentioned above were complete. A change of 3 mm or more of implant migration into the vertebral endplate was defined as significant subsidence. MRI was performed at 1 week and at 1, 3, 6 and 12 months after surgery to assess neural decompression and dural tube extension, any adverse effects including inflammatory reaction around the implant such as vertebral endplate erosion, Modic change [20] and any fluid collection. Three independent experienced spinal surgeons, each with at least ten years of experience, did all the radiological assessments. Each patient's preoperative clinical and radiological data are summarized in Table 2.

9. Ethical considerations

The study was performed in accordance with the principles of the Declaration of Helsinki and of Good Clinical Practice and was registered on the University Hospital Medical Information Network Clinical Trials Registry (UMIN000001448). Approval was obtained from the relevant competent authorities and our institutional Committee of Ethics before the trial began. As clinicians, the authors played a leading role in this new type of clinical trial, which is extremely rare in the development of new medical devices in Japan. We prepared all the protocols of this study by ourselves and were supported by a translational research center in Kyoto University. The independent clinical research coordinator of the translational research center managed all clinical data, which were extracted from each patient's clinical research form. The endpoints of this clinical trial were achievement of good clinical results, bony union, no serious adverse effects (AEs) and avoidance of the need for

autologous ICBG.

Results

1. Clinical results

In all five patients, the preoperative LBP and radicular symptoms were resolved immediately after the operation. No surgery-related neurological deficit or wound breakdown was observed in any patient. The mean operating time was 164.6 min (range 154–179 min) and the mean estimated intraoperative blood loss was 192 mL (range 80–310 mL). No patient required transfusion or ICBG. No surgery-related complication was observed. The mean follow-up period was 15.2 months (range 12–19 months). The average postoperative JOA score was 25.6 at 1 month, 25.6 at 3 months, 27 at 6 months and 26.6 at 12 months (range 18–29). The mean recovery rate of the JOA score was 76.6% at 1 month, 77.5% at 3 months, 88.0% at 6 months and 85.8% at 12 months (range 38.9–100%). The postoperative JOA score improved significantly compared with the preoperative score at all times ($P = 0.002$ at 12 months). The mean VAS was 2 mm at 1 month, 2 mm at 3 months, 6 mm at 6 months and 2 mm at 12 months (range 0–30 mm) for LBP. It was 0 mm at 1 month, 0 mm at 3 months, 4 mm at 6 months and 2 mm at 12 months (range 0–20 mm) for LP. Both VAS measures were significantly improved compared with preoperative scores at all times (at 12 months; LBP $P = 0.027$; LP $P = 0.012$). All but one patient satisfied very much through the experiment periods. All clinical parameters showed rapid recovery within 1 month, which indicated a low level of invasiveness and good stabilization of the surgery (Fig. 4).

2. Radiological results

Dynamic radiological examination showed a solid bony construct without abnormal segmental motion or radiolucency around the implants in all cases after 3 months. No patient exhibited significant implant subsidence during the follow-up period. Immediate postoperative MDCT demonstrated good apposition between the vertebral endplate and implant in all but one case. These findings indicated good anchoring of the porous titanium implant to the surrounding bone. Follow-up MDCT showed good bone ingrown onto the surface of the porous titanium metal without radiolucent line. It also showed remodeling not only of the monitoring bone but also of the surrounding vertebral bone. However in Case 5, a gap was evident between porous titanium metal and surrounding vertebral endplate on the MDCT image immediately after the operation, because of a poor fit of the device surface with an irregular vertebral endplate. The gap was filled gradually and closed at the final follow-up MDCT (Fig. 5A–C). Because the radiological parameters mentioned above were complete in all cases, bony union was considered to be achieved in all cases by 6 months after the operation. Postoperative MRI scans showed no significant AE such as abnormal fluid collection or apparent change in the Modic sign. In three patients with concomitant spinal canal stenosis, successful neural tissue decompression was also confirmed. The postoperative clinical and radiological results are summarized in Table 3.

Illustrative case (Case 1)

This 54-year-old woman had complained of LBP and intractable bilateral LP for three years before surgery. These were refractory to adequate conservative treatment. She also

complained of an inability to walk for longer than 10 minutes, with intermittent claudication. A physical examination demonstrated bilateral dysesthesia on the L5 sensory dermatome. Her preoperative JOA score was 21 points and her self-reported VAS was 10 mm for LBP and 60 mm for LP. X-ray images showed degenerative spondylolisthesis at the L4–5 level with instability (Fig. 6A). Preoperative MR imaging demonstrated severe spinal canal stenosis at the L4–5 level. Transforaminal lumbar interbody fusion and spinal canal decompression using our bioactive titanium was performed. The operating time was 173 minutes and the estimated intraoperative blood loss was 140 mL. Immediate postoperative coronal imaging using MDCT demonstrated a press fit at the interface between the porous titanium metal and the vertebral endplate (Fig. 6B). Three months after the operation, dynamic X-ray imaging demonstrated no abnormal movement (Fig. 6C). Sagittal imaging using MDCT showed a stable interface without a radiolucent line or any clear zones around the pedicle screws, indicating a successful bony union (Fig. 6D). Postoperative MR imaging showed good neural decompression without any adverse effects. Her JOA score recovered to 29 points and the VAS score was 0 mm for LBP and 0 mm for LP at the final follow-up.

Discussion

Here we report the safety and efficacy of porous bioactive titanium metal for the treatment of unstable lumbar disc disease. All cases showed early bony union by 6 months without autologous ICBG and rapid recovery after the surgery. The patients' satisfaction and clinical recovery rates were both acceptable.

The use of an interbody fusion cage with autologous bone grafting is a standard

procedure for lumbar spinal fusion. However, nonunion, cage subsidence, implant failure and donor site morbidity are still of concern [1]. Porous materials with adequate pore structure and appropriate mechanical properties might represent an alternative to traditional cage implants. Interconnected pores permit tissue ingrowth and thus anchor the prosthesis to the surrounding bone, preventing loosening. This concept also allows a larger support area because no graft space is required and it might be effective for the prevention of implant subsidence. In the current study, significant implant subsidence has not occurred throughout the follow-up periods. Furthermore, if bone bridging can be achieved across the whole implant through the interconnected pores from one vertebra to the other it reduces the risk of implant failure and ensures long-term stability.

The kind of material and its pore characteristics influence the mechanical strength of porous biomaterials. Porous HA implants have good biocompatibility and osteoconductivity, but their mechanical properties are not adequate for load-bearing conditions. The clinical application of such conventional porous materials is limited to non-load-bearing conditions. Therefore, the use of metal to produce porous implants with higher mechanical strength is required. By using titanium metal as a starting material, our device with high porosity and large pore size acquired a high mechanical strength that is adequate for load-bearing conditions. In a previous study, we investigated the relationship between pore structure and bone ingrowth *in vivo* using several types of porous titanium implants. We concluded that high porosity and large pore size but also high interconnectivity of the pores is effective for bone ingrowth and tissue differentiation [23]. Based on this previous study, an optimally

structured porous titanium metal was developed and used for this clinical trial. It has 60% porosity, 250 μm average pore size and more than 99% pore interconnectivity.

Another important issue associated with porous metal implants is the difficulty in producing bioactive properties on the inner surfaces of implants using conventional methods such as applying a plasma-sprayed HA coating. In the absence of a bioactive surface, the osteoconductivity of these implants and their capacity to promote fusion is limited. The thickness of a conventional HA coating layer is about 40–50 μm , which cannot be applied for critical supporting structures without changes to surface morphology [5]. Moreover, the conventional HA coating for titanium metal implants has the potential for degradation, absorption and third body wear during long-term implantation, which might be related to its poor clinical results [2,21]. Our chemical and thermal treatments ensured that bioactive properties were applied to the whole surface of the porous titanium implants without reducing the pore space available for bone ingrowth [15]. Adequate stability of the thin treated layer was confirmed both *in vitro* and *in vivo* and might assure the long-term apposition with surrounding bone [9]. This material also offers sufficient resistance to shearing forces during the implantation of treated cementless hip prostheses.

Although titanium metal and its alloys are ‘gold standard’ materials in orthopedics, one of the potential disadvantages of a metal device is a high elastic modulus. The elastic modulus of solid titanium metal is more than 100 GPa and this will lead to stress shielding around the metal device during long-term implantation. To reduce such a mechanical mismatch between the implant and host bone, several types of soft material including polyetheretherketone and carbon have been introduced clinically [6,28]. Although there are

no long-term results as yet, porous titanium metal will reduce stress shielding, because the elastic modulus of this material with 60% porosity is 4.2 GPa, close to the value of human cortical bone and much less than solid metal materials. According to Nachemson's study, loads to the human lumbar spine are between 1000 and 3000 N during most everyday activities, and increases in different body positions give possible values in excess of 3000 N during significant lifting [22]. Based upon these data, Brantigan suggested that a lumbar interbody fusion construct must bear an immediate postoperative load at the bone-implant interface of at least 2400 N during activities of daily living [4]. On the other hand, breakage of the carbon cage and dissemination of free carbon particles occurred in one case of implant nonunion [29]. A biomechanical study revealed that the carbon cage fractures at around 5800–8800 N, and concluded that at least 5000 N was required for an interbody fusion cage [13]. The fatigue strength of porous titanium metal combined with an outer frame is more than 10,000 N under a repetitive compressive load, so it can be used as a spinal interbody fusion device safely.

Another potential disadvantage of a pure metal device is the difficulty of confirming fusion status radiologically because of its high radiodensity. Usually, bony union is confirmed when the following radiological parameters are complete: visible continuous grafted bone trabeculation, no abnormal movement on dynamic study and no radiolucency around the implants. In the case of metal devices such as a titanium cage, bone trabeculation through the cage is difficult to identify on plain X-ray images. However, definitive diagnoses of bony union have become easier with the introduction of MDCT. Especially in the case of porous titanium metal, because the metal content is less than with the solid form, recognition

of fusion status such as bone–implant interface and bony trabeculation around the implant is not so difficult on MDCT images. In the current study, two specific radiological findings were evident. The first of these was the anchoring effect between the porous bioactive titanium implant and the surrounding vertebral endplate seen on the images taken immediately after surgery. This could be attributed to the optimally rough surface of the porous bioactive device. The second finding was the gap-filling effect. The radiological evidence of gap filling as shown in Figure 6 resembles the results of alkali- and heat-treated total hip prostheses. Radiological gaps between alkali- and heat-treated metal shells and the acetabulum were filled within one year, which indicated the high osteoconductive ability of bioactive titanium metal [14]. The best feature of porous bioactive titanium metal is that it permits bone ingrowth through the inner pore structure. Although we reported good bone ingrowth to the pores in several studies using animal models, we could not confirm this evidence using noninvasive radiological examinations in the present study.

There are some limitations to this study, including its small sample size, short follow-up period, and preliminary nature. Our chemical and thermal treatment has been applied clinically for cementless total hip prostheses after a strict clinical trial, which was approved by the Ministry of Health, Labor and Welfare in Japan. Excellent mid-term (4.8 years) clinical results and early bone apposition were reported [14]. These results are encouraging for the efficacy and safety of this surface treatment on titanium and its alloys. Moreover, TLIF is a promising standard procedure for the treatment of patients with unstable spinal disease. Given these encouraging results, we planned this small clinical trial as much as possible to test the efficacy and safety of porous bioactive titanium metal in a spinal fusion

device. Fortunately, there was successful bony union without the need for autologous ICBG in this small series. However, implantation of metal devices has a potency to bring about several late complications such as stress shielding and adjacent segment disease during long-term implantation. Therefore, long-term clinical results are mandatory to reveal the true efficacy and safety of this device.

We consider that porous bioactive titanium metal is superior to other porous metal materials in terms of safety, osteoconductive and osteoinductive abilities, mechanical strength and controllable optimum microstructure [10,24]. Another advantage of porous bioactive titanium metal is its potency for general purpose medical devices. First, our surface treatment can be applied not only to pure titanium but also to several types of titanium alloys. By changing materials, the mechanical characteristics can be optimized. Second, using our manufacturing technique, the pore structure, mechanical strength and biological characteristics can be controlled depending on the conditions. This material will be valuable not only for spinal fusion but also for reconstructive surgery to the skull, the maxillofacial region and in other orthopedic fields. Moreover, adjustments to the elastic modulus and bioactive abilities promise to produce new generations of devices for the treatment of osteoporotic bone.

Conclusions

We developed porous bioactive titanium device for spinal fusion. The optimal mechanical strength and interconnected structure of porous titanium metal were adjusted to the device. The whole surface of porous titanium was treated chemically and thermally to form the

bioactive surface. Clinical trial was successfully performed and early bony union was achieved in all cases without ICBG by 6 months. Two specific findings including an anchoring effect and gap filling were evident radiologically. Although a larger and longer-term follow-up clinical study is mandatory to reach any firm conclusions, we consider this porous bioactive titanium metal is promising material for a spinal fusion device.

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Figure legends

Fig. 1. Photograph of porous bioactive titanium device for transforaminal lumbar interbody fusion.

Fig. 2. Micro-computed tomography image showing well-connected internal porous structures.

Fig. 3. Field emission scanning electron microscope (FE-SEM) images showing surface morphological changes to the porous titanium metal. **A.** Before treatment, the surface was smooth. **B.** After chemical and thermal treatment, a thin submicron-sized pore layer was formed on the surface. **C.** Apatite formation on the whole surface of the porous bioactive titanium metal after soaking in simulated body fluid (SBF) for three days.

Fig. 4. Sequential changes in the Japan Orthopaedic Association (JOA) score of the five cases. The graph indicates a rapid recovery of the patients' clinical status within one month.

Fig. 5. Sagittal multidetector-row computed tomography (MDCT) images taken immediately postoperatively and at 3 and 12 months for Case 5. The immediate postoperative image (left) shows an apparent gap between the porous titanium metal and vertebral bone. The 3-month image (center) demonstrates bone ingrowth cranial to the porous titanium metal. The 12-month image (right) demonstrates complete gap filling and direct bone bonding to the porous titanium metal.

Fig. 6. Preoperative and postoperative radiological studies obtained from a 54-year-old woman with degenerative spondylolisthesis at L4–5 (Case 1). **A.** Plain lateral X-ray demonstrating L4 listhesis. **B.** Immediate postoperative MDCT image demonstrating a press

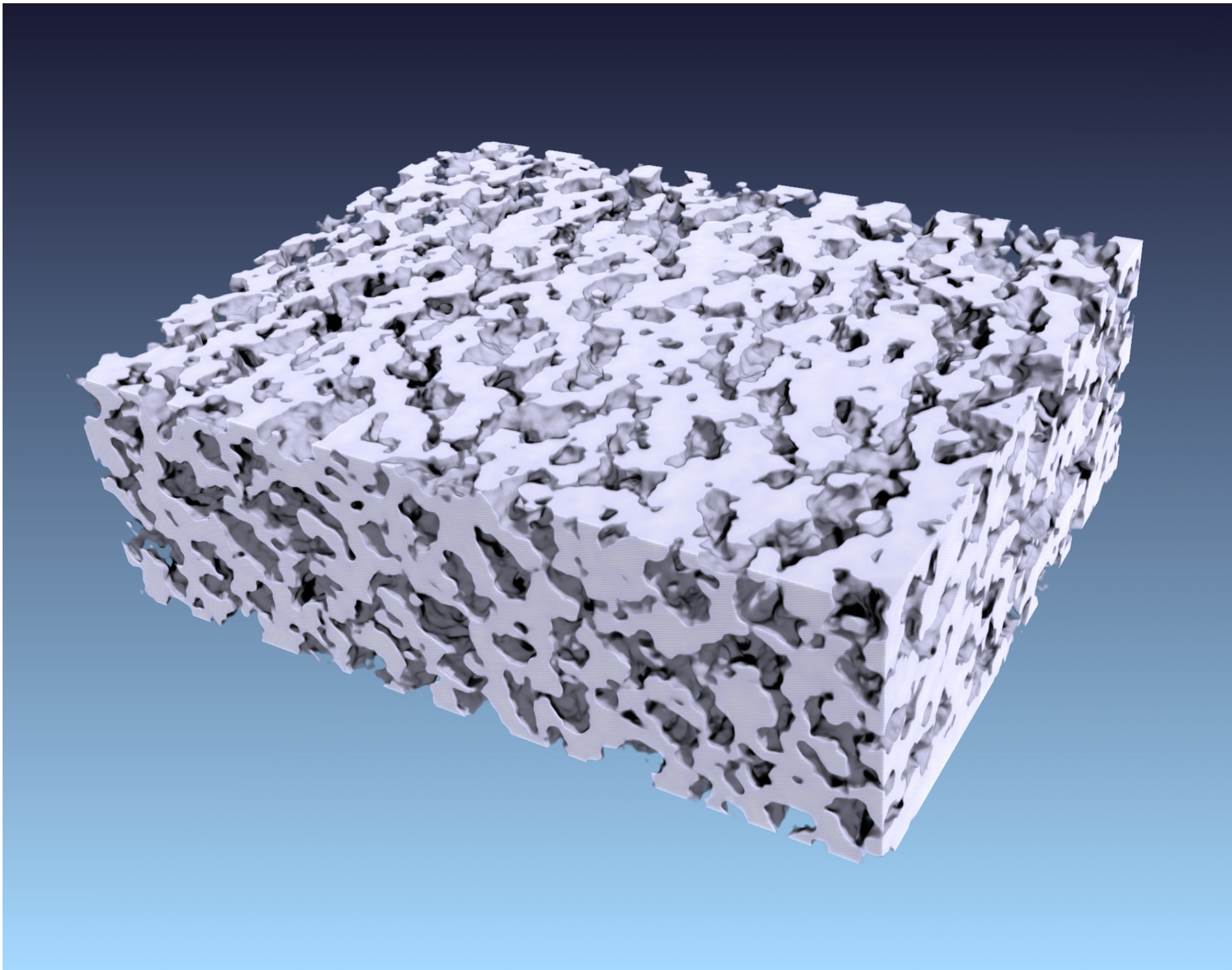
fit of the porous titanium metal implant to the vertebral endplate. **C.** Dynamic lateral radiographs at 3 months showing a solid construct without abnormal segmental motion (left, flexion; right, extension). **D.** Coronal MDCT image demonstrating solid bony union without device subsidence or any radiolucency at 3 months after surgery.

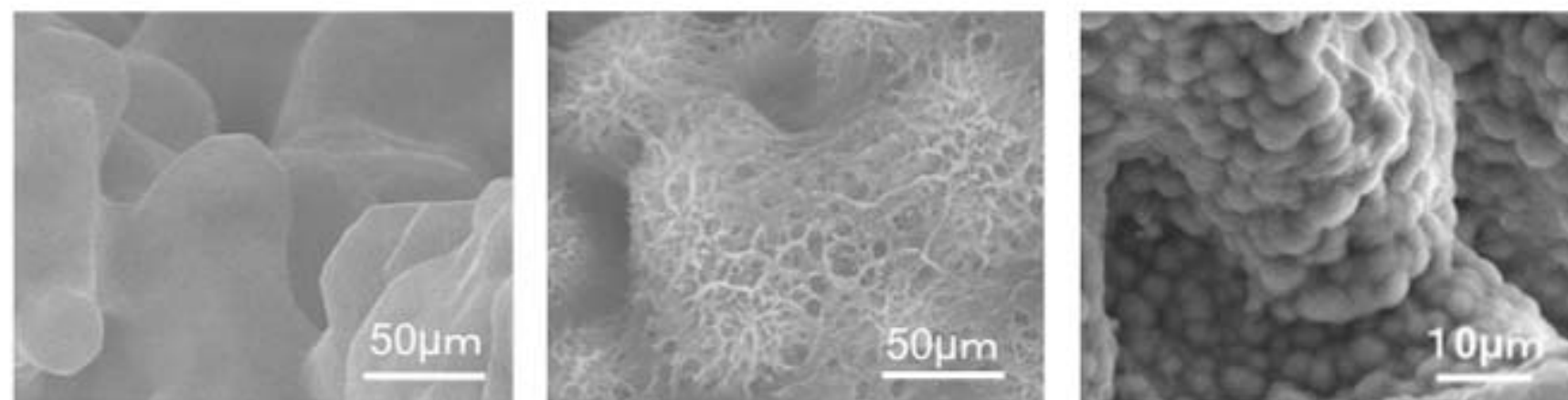
Table 1. JOA score classifications for low back pain.

Table 2. Summary of patients' preoperative data.

Table 3. Summary of patients' postoperative data.







A

B

C

Fig3

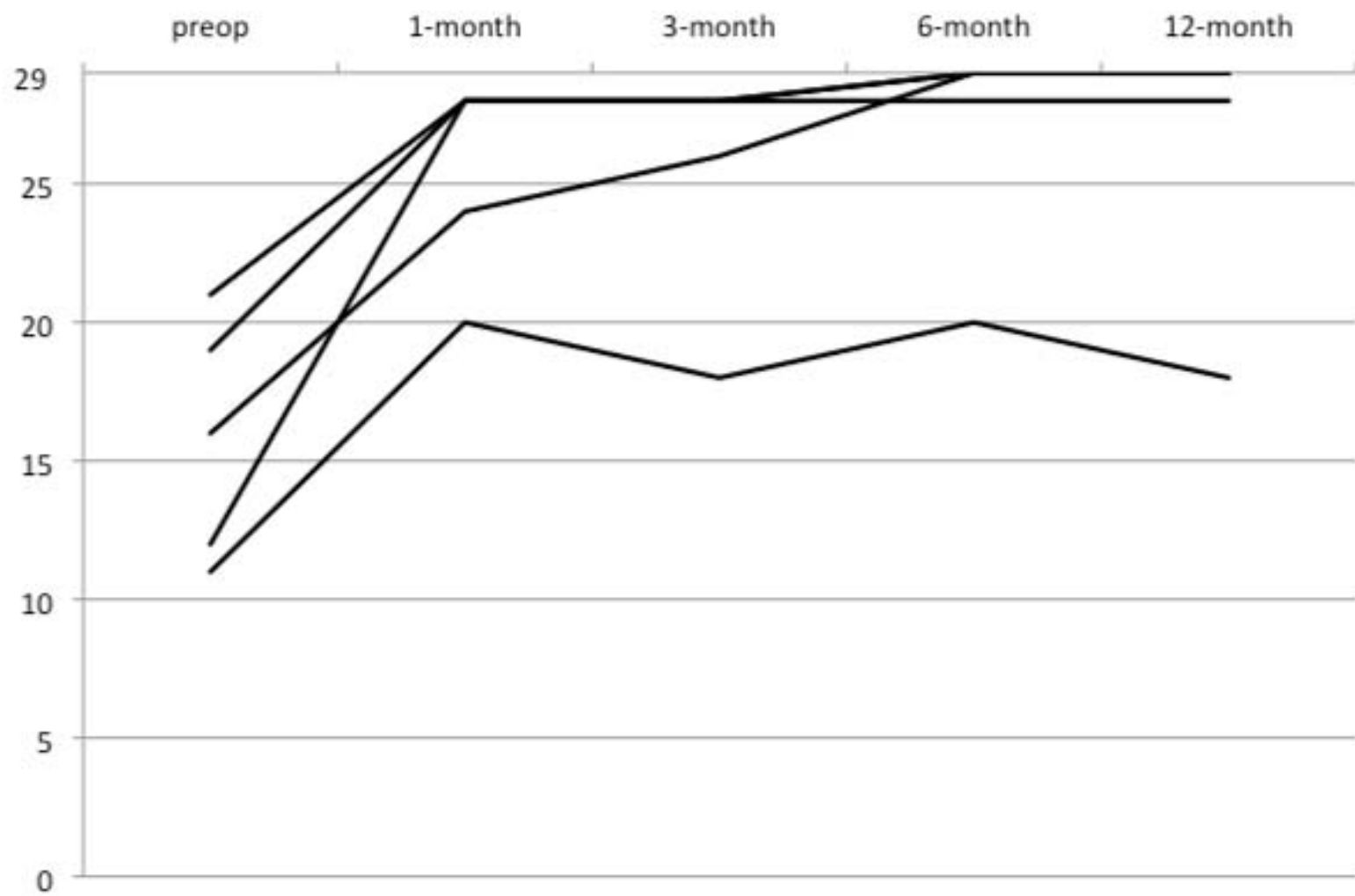


Fig4



Fig5



Fig6-A

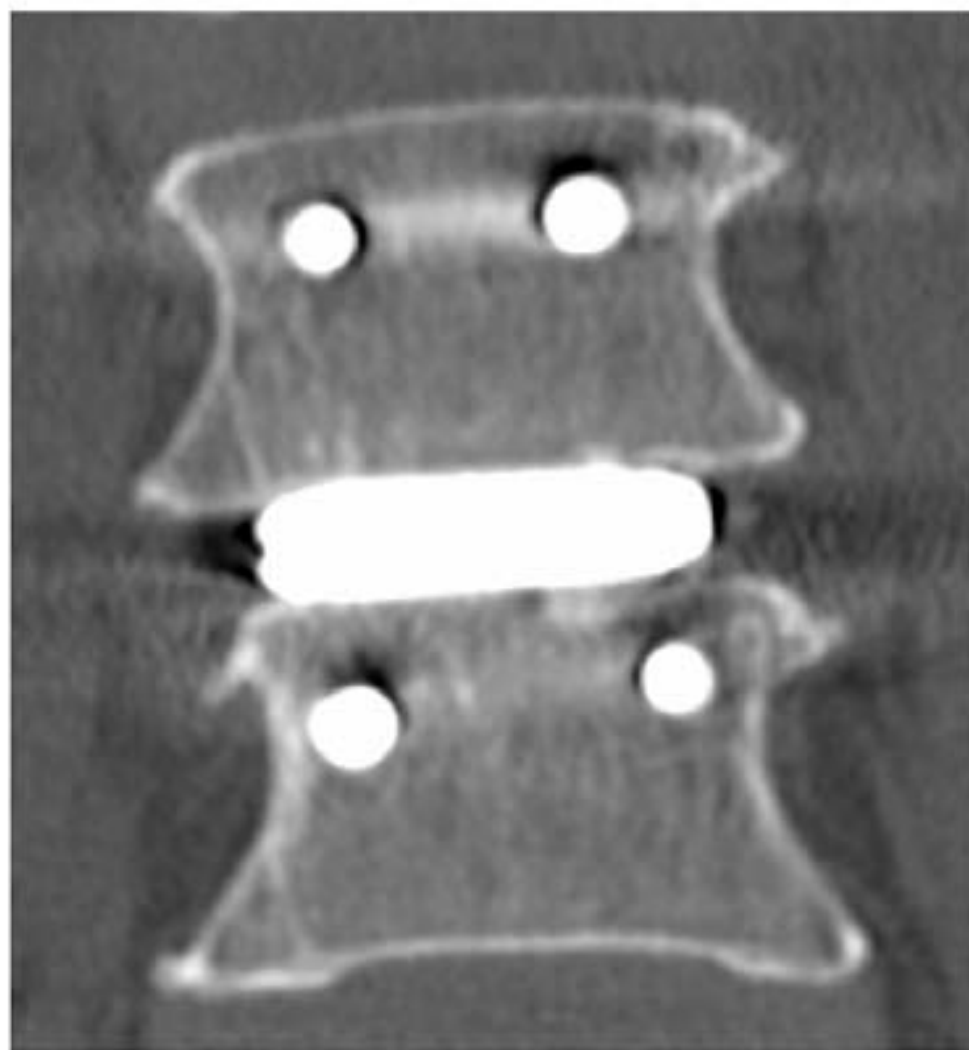


Fig6-B

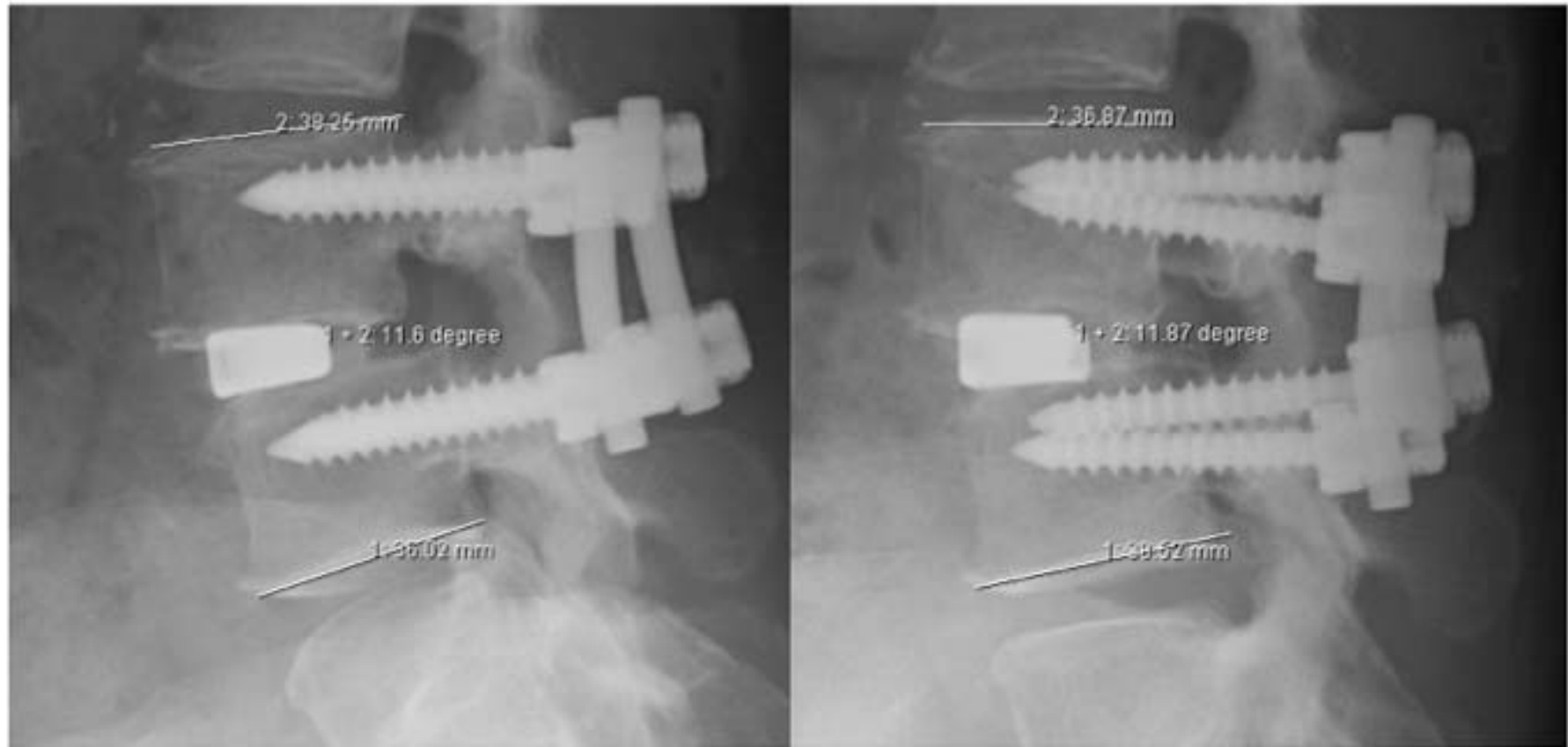


Fig6-C

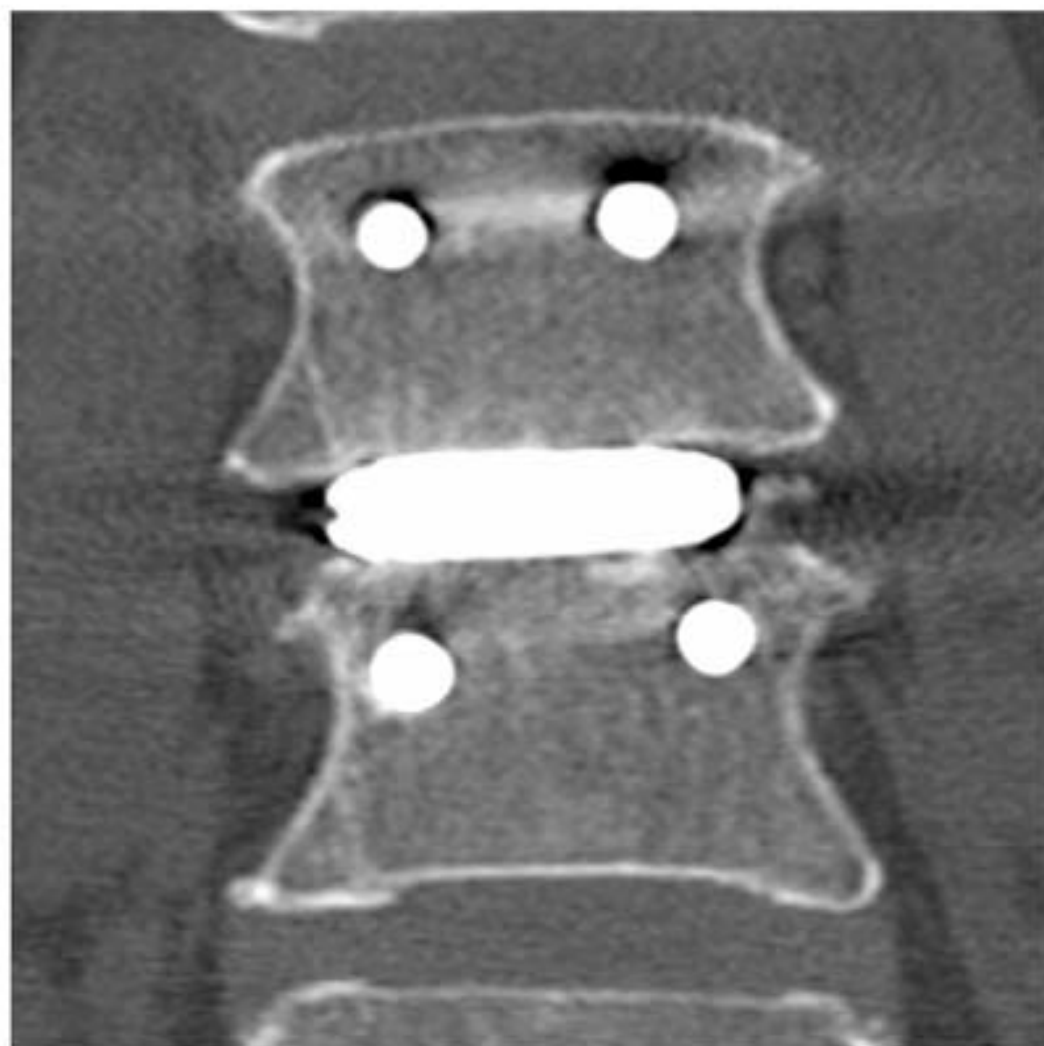


Fig6-D

Table1. JOA score classifications for low-back pain

Parameter	JOA Score
subjective symptoms	9
low-back pain	
none	3
occasional mild pain	2
frequent mild or occasional severe pain	1
frequent or continuous severe pain	0
leg pain &/or tingling	
none	3
occasional slight symptoms	2
frequent slight or occasional severe symptoms	1
frequent or continuous severe symptoms	0
gait	
normal	3
able to walk >500m, although it causes pain, tingling, &/or muscle weakness	2
unable to walk >500m due to leg pain, tingling, &/or muscle weakness	1
unable to walk >100m due to leg pain, tingling, &/or muscle weakness	0
clinical signs	6
straight leg-raising test (including tight hamstrings)	
normal	2
30-70°	1
<30°	0
sensory disturbance	
none	2
slight disturbance (not subjective)	1
marked disturbance	0
motor disturbance	
normal (Grade 5/5)	2
slight weakness (Grade 4/5)	1
marked weakness (Grade 0-3/5)	0
restriction of ADL	14
ADL (restriction)	
turning over while lying down	
standing	
washing	
leaning forward	
sitting (~1 hr)	
lifting/holding heavy objects	
walking	
urinary bladder function	-6
normal	0
mild dysuria	-3
severe dysuria (incontinence, urinary retention)	-6

JOA: Japanese Orthopaedic Association

ADL = activities of daily living

For each activity of daily living category severe restriction was accorded a score of 0; moderate restriction, a score of 1; and no restriction, a score of 2.

Table2. Summary of preoperative patient's demographic data

Case	Age	Sex	Diagnosis	Level	Symptoms	Pre JOA	Pre VAS (LBP)	Pre VAS (LP)
1	54	F	DS	L4/5	LBP+LP	21	10	60
2	36	M	IS	L5/S	LBP+LPLP	12	80	50
3	51	F	DS	L4/5	LBP	19	80	0
4	61	F	DS	L4/5	LBP+LP	11	60	60
5	56	M	IS	L5/S	LBP+LP	16	50	20

DS: Degenerative Spondylolisthesis, IS: Isthmic Spondylolisthesis, LP: Leg pain, LBP: Low back pain, VAS: Visual Analogue Scale

Table3. Summary of postoperative patient's demographic data

Case	Op. Time (min.)	Blood loss (mL)	Post JOA score	JOA score recovery rate (%)	Post VAS (LBP)	Post VAS (LP)	Satisfaction score	ICBG	AEs	Bony union (month)
1	173	140	29	100	0	0	1	-	-	3
2	179	310	29	100	0	0	1	-	-	3
3	160	80	28	90	0	0	1	-	-	3
4	154	228	18	38.9	10	10	4	-	-	6
5	157	192	29	100	0	0	1	-	-	3

ICBG: Iliac crest bone graft, AEs: Adverse effects

Satisfaction score: 1; very satisfied, 2; satisfied, 3; somewhat satisfied, 4; somewhat dissatisfied, 5; dissatisfied

JOA score, VAS, and Satisfaction score are obtained at 12-month after the surgery.