

Frequency of Change in Assessment from Bony Union to Nonunion after Lumbar Interbody Fusion: A Multicenter Study

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Abstract:

Introduction: Assessments of early postoperative bony union after posterior lumbar interbody fusion via computed tomography (CT) have revealed cases in which interbody fixation by bony union resulted in nonfusion due to bone absorption. The apparent bone union state reverted to a nonunion state several months later, exhibiting a so-called “fake union” phenomenon. Additionally, few reports have evaluated the effect of teriparatide on bony union. The present study aimed to evaluate the frequency of change in assessment from fusion to nonfusion in the postoperative follow-up of lumbar interbody fusion, compare the late postoperative bony union rates in groups with or without early postoperative fusion, and examine the effect of postoperative teriparatide in those groups.

Methods: Sixty-nine subjects enrolled from multiple hospitals were prospectively evaluated following single-level lumbar interbody fusion. The patients were randomly allocated into treatment with or without weekly postoperative teriparatide. The subjects were then classified as having bony union or nonfusion at 2 months postoperatively, and fusion rates at 6 months were compared. For the evaluation of bony union, blinded radiological examinations were performed via CT. Additional comparisons were made according to teriparatide use.

Results: The rate of nonunion at 6 months postoperatively in patients with fusion at 2 months postoperatively was 27.8%. Among subjects with bony union at 2 months postoperatively, the fusion rate at 6 months in those who received teriparatide was 93.3% (p=0.027) versus 57.1% in those who did not.

Conclusions: The rate of nonunion at 6 months postoperatively in patients exhibiting union at 2 months after surgery was 27.8%. Postoperative weekly teriparatide treatment significantly reduced the rate of fake union.

Keywords:

posterior lumbar interbody fusion, transforaminal lumbar interbody fusion, bony union, delayed fusion, bone resorption, weekly teriparatide

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Introduction

The rapid progression of societal aging has been accom-

panied by an increase in lumbar degenerative disease¹⁾. Posterior (PLIF) or transforaminal lumbar interbody fusion (TLIF) is usually conducted to treat lumbar degenerative

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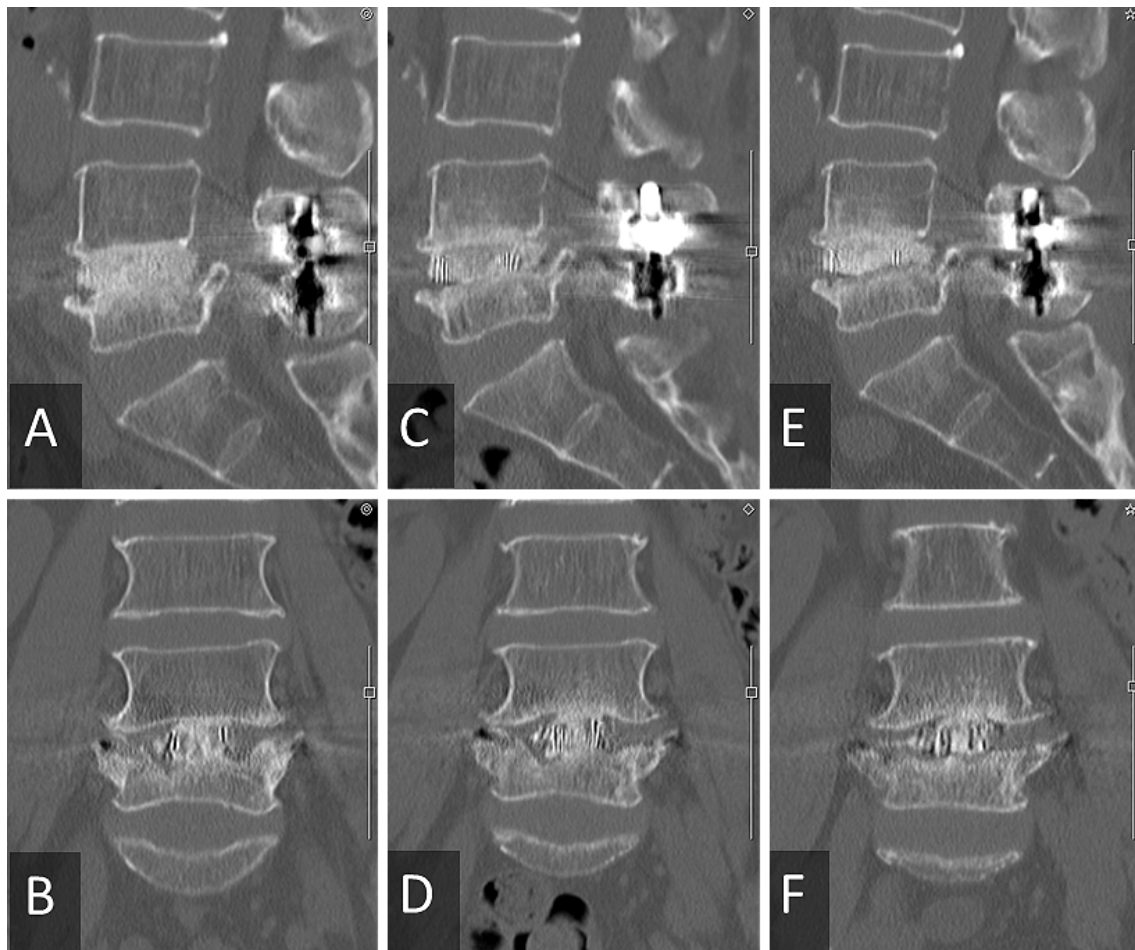


Figure 1. Sagittal and coronal CT of L4/5 PLIF in a 70-year-old woman. Panels A and B: 2 months postoperatively; C and D: 4 months postoperatively; E and F: 6 months postoperatively. Bony union at 2 and 4 months was reassessed as nonfusion at 6 months.

disease in the elderly²⁻⁴), although these procedures sometimes fail to achieve bony union⁵. If bone union is not attained after the initial operation, failure rates as high as 40%-70% have been reported for repeat fusion surgery because of the development of pseudarthrosis⁶⁻¹⁰.

In some cases, patients assessed as having early postoperative bony union are subsequently diagnosed as having nonfusion, or a so-called “fake union,” several months later. We defined fake union as the phenomenon of bone continuity observed via computed tomography (CT) at 2 months after surgery but not at 6 months after surgery. This process is likely the result of bone absorption that is detectable on CT (Fig. 1). To the best of our knowledge, no reports have addressed the frequency or prevention of fake union.

The present study evaluated bony union at 2, 4, and 6 months after surgery in 69 subjects who underwent single-level interbody fusion to determine 1) the frequency of fake union; 2) the relationship between the presence/absence of bony union at 2 or 4 months postoperatively and fusion at 6 months postoperatively, as well as the effect of weekly teriparatide on the fake union in subjects assessed as having fusion at 2 or 4 months postoperatively; and 3) the factors associated with bony union at 2, 4, and 6 months after sur-

gery.

Materials and Methods

Patients and study measures

This was an additional analysis using data obtained by a prior² multicenter, prospective, randomized trial to investigate the impact of weekly teriparatide administration on bony union enhancement after PLIF or TLIF for osteoporosis-associated lumbar degenerative disease during the early postoperative period. Patient consent for additional research was obtained in the previous study². The subjects were enrolled from among three university hospitals and their affiliates. The patients were all women aged >50 years having a bone mineral density/young adult mean ratio of < 80% and/or previous spinal compression and/or hip fracture, as well as a lumbar degenerative disease. Single-level PLIF or TLIF was applied to treat lumbar spinal stenosis, degenerative spondylolisthesis, and isthmic spondylolisthesis. Multilevel decompression was performed when necessary, and these cases were included in the study. All subjects were treated using posterior instrumentation with pedicle screws.

Table 1. Characteristics of Patients at Baseline (N=69).

Sociodemographic factor		
Age (y)		71.1±7.5 (56–88) ¹
Sex	Male	0
	Female	69
Height (cm)		149.3±6.5 (131.0–162.5) ¹
Weight (kg)		51.8±7.9 (37.7–70.6) ¹
Disease	Degenerative spondylolisthesis	54 (78%)
	Degenerative scoliosis	2 (3%)
	Spinal stenosis	10 (14%)
	Isthmic spondylolisthesis	3 (4%)
Pretreatment of osteoporosis	–	64 (93%)
	+	5 (7%)
Femoral BMD (%YAM)	Femoral neck	0.75±0.10 (0.47–0.93) ¹
	Total proximal	0.79±0.11 (0.51–1.07) ¹
Femoral BMD (T-score)	Femoral neck	–2.28±0.83 (–4.64–0.62) ¹
	Total proximal	–1.90±1.00 (–4.58–0.49) ¹
Serum PINP (µg/L)		45.1±18.8 (13.2–95.4) ¹
Serum TRACP-5b (mU/dL)		455±180 (128–1010) ¹

¹Numbers in parentheses are minimum–maximum values.

Plus-minus values represent the mean±standard deviation.

Abbreviations: BMD, bone mineral density; YAM, young adult mean; PINP, N-terminal cross-linking propeptide of type 1 procollagen; TRACP-5b, tartrate-resistant acid phosphatase-5b

Posterolateral fusion was not conducted. Interbody spaces were filled by a box cage of polyetheretherketone filled with local bone. Residual bone was discarded. After receiving informed patient consent, we registered each case with an independent central office, which randomly assigned the subjects into treatment groups of either teriparatide once weekly administered subcutaneously starting at week 1 for 6 months postoperatively or no teriparatide treatment. Postoperatively, all patients commenced 1.2 g/day calcium l-aspartate after 1 week as a basic treatment for osteoporosis, wore a soft lumbar corset for 3 months, and performed standardized physical training that included exercises to strengthen back muscles and improve walking.

Evaluation method for bony union

Bony union was assessed by CT and dynamic X-rays at 2, 4, and 6 months postoperatively by four physicians who were blinded to the results using a fusion grading system described by Bridwell¹¹. Two CT slices at the center of the cage in both the coronal and sagittal views were used to evaluate bone healing. Each evaluation was conducted by four clinicians (two clinicians each from two universities excluding the university at which the surgery was performed) using CT images. During the initial evaluation, a consensus was achieved after the agreement of ≥3 evaluators. If ≤2 evaluators agreed, further evaluation was performed until a unanimous decision.

Radiological assessment

Subjects were classified into either the fusion or nonfusion groups at 2 and 4 months postoperatively, and the fusion rate in each group was determined at 6 months postop-

eratively. Additional analyses were conducted according to the use/nonuse of postoperative weekly teriparatide. Baseline characteristics, surgical method and levels, and teriparatide administration after surgery were compared between the fusion and nonfusion groups at 2, 4, and 6 months postoperatively. We also examined for parameters related to bony union at those time points.

Statistical analysis

Analyses were conducted using Fisher's exact test for categorical data and Student's *t*-test for continuous data. Bony union scores were analyzed using analysis of covariance and adjusted for age as a covariate. For all analyses, the level of significance was set at $p < 0.05$. Statistical testing was conducted independently by three academic medical statisticians. All analyses were performed using SPSS Statistics 24 for Windows (SPSS Inc., Chicago, Illinois, USA).

Results

Overall data

A total of 69 subjects (all female, mean age at surgery: 71.5 years) who completed the evaluation of bony union using dynamic X-rays and three-dimensional CT at 2, 4, and 6 months postoperatively were enrolled. Surgery was performed for degenerative spondylolisthesis in 54 subjects, degenerative scoliosis in two subjects, spinal stenosis in 10 subjects, and isthmic spondylolisthesis in three subjects. Six subjects received osteoporosis treatment before surgery. Table 1 shows the baseline characteristics. PLIF was conducted in 65 patients and TLIF in four patients. No significant post-

Table 2. Surgical Techniques and Outcomes (N=69).

Surgical technique	N (%)
PLIF	65 (94%)
TLIF	4 (6%)
Level	
L3-4	4 (6%)
L4-5	58 (84%)
L5-S1	7 (10%)
Complications of surgery	
Dural tears	0
Epidural hematoma	0
Surgical site infection	0
Postoperative teriparatide	
Used	31 (45%)
Not used	38 (55%)
Bony union	
2 months postoperatively	36 (52%)
4 months postoperatively	37 (54%)
6 months postoperatively	34 (49%)
Screw loosening	
2 months postoperatively	0 (0%)
4 months postoperatively	2 (3%)
6 months postoperatively	3 (4%)

Abbreviations: PLIF, posterior lumbar interbody fusion; TLIF, transforaminal lumbar interbody fusion. Bony union was judged as achieved when the central slice in CT imaging of both coronal and sagittal sections revealed bony union. Bony union was judged as absent when either central slice showed nonfusion.

operative complications, such as epidural hematoma or surgical site infection, were recorded. Postoperative weekly teriparatide was administered to 36 subjects. The overall bony union rates at 2, 4, and 6 months postoperatively were 51%, 50%, and 46%, respectively (Table 2).

Rate of fake union

In patients with fusion at 2 and 4 months postoperatively, 72.2% and 73.0%, respectively, also achieved fusion at 6 months (Table 3). Accordingly, the respective rates of fake union in subjects with fusion at 2 and 4 months were 27.8% and 27.0%. Among the patients in the fusion (36 subjects) and nonfusion groups (33 subjects) at 2 months postoperatively, the fusion rates at 6 months were 72.2% and 24.2%, respectively. Therefore, subjects with fusion at 2 months postoperatively were more likely to achieve fusion at 6 months.

Impact of postoperative weekly teriparatide

Table 4 summarizes the additional analysis of fusion rates according to use/nonuse of postoperative weekly teriparatide. Patients receiving weekly teriparatide were more likely to maintain fusion. Of the 36 subjects who achieved fusion at 2 months after surgery, 15 subjects used teriparatide and 21 subjects did not. The numbers of patients

achieving bony union with and without teriparatide at 6 months postoperatively were 14 (93.3%) and 12 (57.1%), respectively. Accordingly, the respective rates of fake union in the teriparatide use and nonuse groups were 6.7% and 42.9%.

Predictors of bony union at 2, 4, and 6 months postoperatively

Table 5 shows the associations between predictive factors and bony union at 2, 4, and 6 months postoperatively. The procedure performed (TLIF or PLIF) was not a significant predictor of bony union. The bony union rates including and excluding L5/S were comparable at 57.1% and 48.4%, respectively. The use of weekly teriparatide was not remarkably associated with bony union at 2 or 4 months postoperatively but was significantly related to fusion at 6 months after surgery ($p=0.022$) (Fig. 2).

Discussion

This study made three important clinical observations regarding bony union after TLIF or PLIF. First, early (2 and 4 months) postoperative bony union was reassessed as nonfusion at 6 months, i.e., fake union, at an unexpectedly high frequency. Second, subjects judged as achieving early postoperative fusion showed higher bony union rates at the final evaluation than did those who did not attain early fusion. Third, although the use of weekly teriparatide was not notably related to bony union at 2 or 4 months postoperatively, it was significantly associated with bony union at 6 months ($p=0.022$).

Among the subjects assessed as having bony union at 2 months postoperatively, 27.8% were later reassessed as having nonfusion at the final evaluation. More alarmingly, 27.0% of subjects classified as having fusion at 4 months postoperatively were reclassified as having nonfusion at the final time point. We routinely perform follow-up to detect implant failure or screw back-out and determine the need for trunk orthosis until bony union. This study revealed that over a quarter of subjects with fusion at 4 months postoperatively might have had fake union. Hence, patients should be advised of a possibility of nonunion, and careful follow-up and lifestyle guidance should be continued.

In subjects with bony union at 2 months postoperatively, 72.2% maintained fusion at the final evaluation, whereas only 24.2% of patients with nonfusion at 2 months could achieve fusion at 6 months. Early postoperative CT can predict the likelihood of bony union at the final evaluation and provide the meaningful information needed to establish a treatment plan. However, early postoperative CT images appearing to show bony union may be misread, which instead represents curettage of endplate cartilage or dense bone grafting with the actual bony union not yet present. Fake union is presumed to be a failure of a biological bony union as a result of the reabsorption of the impacted bone graft. Cho et al. performed PLIF on 47 patients with osteoporosis

Table 3. Relationship Between Bony Union at 2 and 4 Months Postoperatively and Bony Union at 6 Months Postoperatively.

		2 months				4 months					
		Fusion		Nonfusion		p	Fusion		Nonfusion		p
6 months	Fusion	26	72.2%	8	24.2%	<0.001	27	73.0%	7	21.9%	<0.001
	Nonfusion	10	27.8%	25	75.8%		10	27.0%	25	78.1%	
Total		36	100.0%	33	100.0%		37	100.0%	32	100.0%	

A p-value of <0.05 was defined as statistically significant.

Table 4. Relationship Between Bony Union at 2 Months Postoperatively and Bony Union at 4 or 6 Months Postoperatively According to Weekly Teriparatide Use.

2 months fusion group (n=36)

	4 months				p	6 months				
	Teriparatide (-)		Teriparatide (+)			Teriparatide (-)		Teriparatide (+)		p
Fusion	14	66.7%	14	93.3%	0.104	12	57.1%	14	93.3%	0.024 ¹
Nonfusion	7	33.3%	1	6.7%		9	42.9%	1	6.7%	
Total	21	100.0%	15	100.0%		21	100.0%	15	100.0%	

2 months nonfusion group (n=33)

	4 months				p	6 months				
	Teriparatide (-)		Teriparatide (+)			Teriparatide (-)		Teriparatide (+)		p
Fusion	3	17.6%	6	37.5%	0.259	2	11.8%	6	37.5%	0.118
Nonfusion	14	82.4%	10	62.5%		15	88.2%	10	62.5%	
Total	17	100.0%	16	100.0%		17	100.0%	16	100.0%	

Teriparatide (-) represents the nonuse of weekly teriparatide.

Teriparatide (+) represents the use of weekly teriparatide.

A p-value of <0.05 was defined as statistically significant.

¹Indicates statistical significance.

and evaluated bony union with or without weekly teriparatide use at 24 months postoperatively using Ito's classification¹². The 6 month postoperative fusion rates with and without teriparatide were 77.8% and 53.6%, respectively. In our cohort, the fusion rates at 6 months postoperatively with and without weekly teriparatide use were lower at 58.8% and 41.2%, respectively. This finding might be attributed to a different evaluation method used in our study, with the fusion grading system by Bridwell¹¹ being stricter than that of Ito. The overall fusion rate in our study was also lower than that in previous studies, possibly because of the involvement of four evaluators, as described previously¹³. Moreover, the inclusion of women aged ≥50 years in our study population might have decreased the bony union rate¹³.

Teriparatide use was not related to bony union at 2 or 4 months postoperatively but was significantly related to fusion at 6 months (p=0.022). Among the subjects assessed as having bony union at 2 months postoperatively, 6.7% who received weekly teriparatide in fact had fake union, whereas 42.9% of those who did not take the drug had fake union. Hence, teriparatide use was associated with a significantly lower fake union rate (p=0.024). No other factors were

found to be related to bony union at 2 months postoperatively, suggesting that the occurrence of fusion at that time was related more to the quality of bone graft surgery and less to patient status. Weekly teriparatide administration may promote osteogenesis and increase fusion rates at 6 months². Bone absorption leading to fake union in the early stages (approximately 2-6 months) is typically followed by bone union; teriparatide may help mitigate these initial symptoms. Accordingly, we recommend at least 6 months of continuous weekly teriparatide in women with lower bone density.

Several studies have examined pseudarthrosis and methods to reduce its incidence^{12,14}, one of which is the use of teriparatide. Ohtori et al. prospectively analyzed bony union rates after posterolateral lumbar fusion with local bone grafting in patients postoperatively treated with daily subcutaneous injections of 20 µg of teriparatide and revealed a fusion rate of 82% in the teriparatide group and 68% in the oral bisphosphonate group¹³. Similarly, in 2016, our team described that combined lumbar interbody fusion and weekly teriparatide administration could be an option for the management of lumbar degenerative disease in the elderly² since the drug was effective in reducing pseudarthrosis.

Table 5. Predictors of Bony Union at 2, 4, and 6 Months Postoperatively.

		Bony union at 2 months					Bony union at 4 months					Bony union at 6 months				
		Nonfusion		Fusion		P	Nonfusion		Fusion		P	Nonfusion		Fusion		P
		n	%	n	%		n	%	n	%		n	%			
Fragility fracture	(-)	28	84.8%	31	86.1%	0.999	28	87.5%	31	83.8%	0.742	30	85.7%	29	85.3%	1.000
	(+)	5	15.2%	5	13.9%		4	12.5%	6	16.2%		5	14.3%	5	14.7%	
Level	L3-4	1	3.0%	3	8.3%	0.246	1	3.1%	3	8.1%	0.652	1	2.9%	3	8.8%	0.495
	L4-5	27	81.2%	31	86.1%		28	87.5%	30	81.1%		31	88.6%	27	79.4%	
	L5-S1	5	15.2%	2	5.6%		3	9.4%	4	10.8%		3	8.6%	4	11.8%	
Surgical treatment	PLIF	30	90.9%	35	97.2%	0.343	30	93.8%	35	94.6%	1.000	32	91.4%	33	97.1%	0.614
	TLIF	3	9.1%	1	2.8%		2	6.3%	2	5.4%		3	8.6%	1	2.9%	
Weekly teriparatide	(-)	17	51.5%	21	58.3%	0.633	21	65.6%	17	45.9%	0.101	24	68.6%	14	41.2%	0.022 ¹
	(+)	16	48.5%	15	41.7%		11	34.4%	20	54.1%		11	31.4%	20	58.8%	
Pretreatment of osteoporosis	(-)	29	87.9%	35	97.2%	0.186	30	93.8%	34	91.9%	1.000	32	91.4%	32	94.1%	1.000
	(+)	4	12.1%	1	2.8%		2	6.3%	3	8.1%		3	8.6%	2	5.9%	
		33		36												
Hypertension	(-)	23	69.7%	23	63.9%	0.799	21	67.7%	24	64.9%	0.803	22	64.7%	23	67.6%	0.798
	(+)	10	30.3%	13	36.1%		10	32.3%	13	35.1%		12	35.3%	11	32.4%	
Diabetes	(-)	30	90.9%	32	88.9%	0.999	27	87.1%	34	91.9%	0.694	31	91.2%	30	88.2%	1.000
	(+)	3	9.1%	4	11.1%		4	12.9%	3	8.1%		3	8.8%	4	11.8%	
Malignant neoplasm	(-)	33	100.0%	33	91.7%	0.240	30	96.8%	35	94.6%	1.000	33	97.1%	32	94.1%	1.000
	(+)	0	0.0%	3	8.3%		1	3.2%	2	5.4%		1	2.9%	2	5.9%	

Abbreviations: (-), absence of symptom; (+), presence of symptom; PLIF, posterior lumbar interbody fusion; TLIF, transforaminal lumbar interbody fusion
 A p-value of <0.05 was defined as statistically significant.

¹Indicates statistical significance.

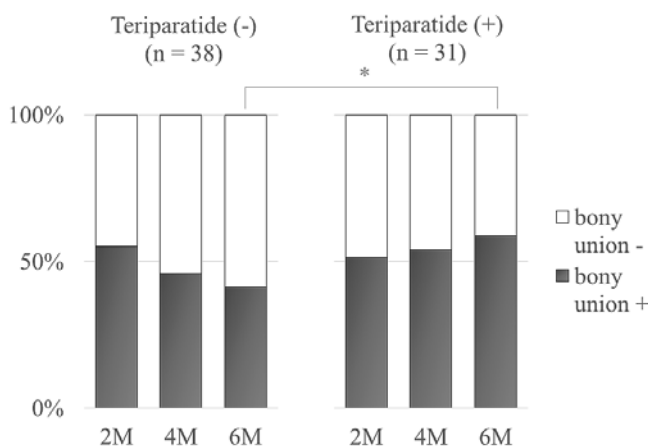


Figure 2. Differences in bony union rates with postoperative teriparatide.

Teriparatide use was not remarkably related to fusion at 2 or 4 months but was significantly associated with fusion at 6 months (p=0.022).

Abbreviation: M: months

A p-value of <0.05 was defined as statistically significant.

*Statistically significant.

Lastly, pseudarthrosis may still occur despite various preventive measures, including those discussed above. The failure rate of repeat surgery for pseudarthrosis correction is 40%-70%⁶⁻¹⁰. CT is mandatory to evaluate bony union¹⁵. However, some reports have suggested a relationship between increased X-ray exposure and cancer development

and recommended less frequent CT imaging^{13,16-18}. We propose performing CT at two time points: once in the early postoperative period to assess implant position, bony decompression, and early fusion and a second time at 6 months after surgery to evaluate bony union.

This study has several limitations. First, the follow-up period was relatively short. Although the natural course of this type of treatment includes initial absorption of implanted bone, teriparatide may prevent absorption and promote earlier bony union. In previous reports on bony union rate after intervertebral fusion, Cho et al. reported fusion within 6.0 months¹², and Ebata et al. performed their final evaluation for bony union at 6 months after surgery². However, the definitive diagnosis of pseudarthrosis requires at least 12 months of follow-up. Second, this study assessed bony union with CT, which might have misinterpreted bone surfaces in contact with each other as bony union. Since a conclusive assessment of bony union cannot be performed solely using CT, other modalities, including dynamic CT, magnetic resonance imaging, positron emission tomography, contrast radiography, and bone scintigraphy, should be considered to improve diagnostic precision. Third, the subjects in this study were limited to women aged ≥50 years with osteoporosis who underwent single-vertebral PLIF or TLIF (Table 6). The same results may also be expected for multilevel fusion, oblique lumbar interbody fusion, and extreme lateral interbody fusion; additional research of those groups is necessary. Fourth, this study did not analyze the effects of cage type or smoking, both of which could have affected nonun-

Table 6. Comparison of Preoperative Bone Metabolism Markers in the Bony Union Group and Non-bony Union Group.

	Bony union at 6 months postoperatively		P
	Nonfusion (n=35)	Fusion (n=34)	
BMD of femoral neck (%YAM)	0.73±0.10	0.74±0.10	0.810
BMD of total proximal femur (%YAM)	0.79±0.10	0.79±0.12	0.953
P1NP (µg/L)	48.2±19.7	41.9±17.7	0.195
TRACP-5b (mU/dL)	493±212	415±134	0.088

Abbreviations: BMD, bone mineral density; P1NP, N-terminal cross-linking propeptide of type 1 procollagen; TRACP-5b, tartrate-resistant acid phosphatase-5b
 Plus-minus values represent the mean±standard deviation.
 A p-value of <0.05 was defined as statistically significant.

ion rates. Lastly, the number of subjects in this study was relatively small.

Conclusion

Subjects assessed as having an early postoperative bony union at 2 months tended to achieve fusion at the final evaluation at 6 months more frequently than those without bony union at an early stage. However, 27.8% of patients with fusion at 2 months postoperatively were reassessed as having nonfusion at 6 months after surgery, a condition considered to be fake union. Hence, careful follow-up remains necessary even with apparent early postoperative bony union. Since postoperative weekly teriparatide significantly reduced the rate of fake union and was significantly associated with bony union at 6 months, the drug may be advisable for improving surgical outcomes.

Conflicts of Interest: The authors declare that there are no relevant conflicts of interest.

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Author Contributions: Hiroki Oba wrote and prepared the manuscript, and all of the authors participated in the study design. All authors have read, reviewed, and approved the article.

Ethical Approval: This multicenter study was approved by our institutional review board and registered with the University Hospital Medical Information Network (UMIN) clinical trials registry (UMIN000007151).

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