Title: Diffuse idiopathic skeletal hyperostosis (DISH) is a risk factor for further surgery in short-segment lumbar interbody fusion

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This study was performed with the approval of the institutional ethics committee of Kyoto University.

Abstract

Purpose To elucidate the effect of diffuse idiopathic skeletal hyperostosis (DISH) on the clinical results of short-segment lumbar interbody fusion (LIF) for the treatment of degenerative lumbar spinal diseases.

Methods The 208 patients who underwent one- or two-level LIF were selected as the subjects of this study. Patients with prior lumbar fusion surgery or follow-up <1 year were excluded. Outcome measures were surgery-free survival or the need for further surgery for pseudoarthrosis and/or adjacent segment disease (ASD). The Cox proportional-hazards model were used to identify possible risk factors (DISH, age, sex, number of levels fused, level of lowest instrumented vertebra, and laminectomy adjacent to the index fused levels) for further surgery.

Results Among the 208 patients (39 with DISH), 21 patients required further surgery during follow-up. Cox analysis showed that DISH (hazard ratio = 5.46) and two-level fusion (hazard ratio = 2.83) were significant independent predictors of further surgery. Age, sex, level of lowest instrumented vertebra,

1

and laminectomy adjacent to the index fused levels were not significant predictors.

Conclusions DISH after short-segment LIF surgery is a significant risk factor for further surgery because of pseudoarthrosis or ASD.

Introduction

Lumbar interbody fusion (LIF) in conjunction with pedicle screw fixation has become a standard procedure for treating degenerative lumbar spinal diseases with satisfactory clinical results[1, 2]. However, numerous complications and problems have been reported. One major problem is pseudoarthrosis with persistent pain that requires further surgical intervention in some cases. Moreover, with successful fusion, there is also a risk of adjacent segment disease (ASD) and failure as a result of altered biomechanics, and several possible risk factors have been reported in association with ASD[1-3].

Diffuse idiopathic skeletal hyperostosis (DISH) is a skeletal disorder of unknown etiology described in the elderly especially older than 50 years and is characterized by abundant bone formation, ossification, and calcification of connective tissue, especially in the spinal region[4,5]. Bridging ossification occurs most often in the thoracic spine, and nonbridging ossification is characteristic of cervical and lumbar

involvement[4]. Although many reports have described the effect of DISH on dysphagia or spine trauma[6,7], little is known about the effect of DISH on the treatment of degenerative lumbar spinal diseases.

The thoracolumbar range of motion is restricted in patients with DISH[8]. Therefore, we presumed that the stress concentrated at the fused level or adjacent segment would be greater after fusion surgery in patients with DISH than in patients without DISH because of the longer lever arm, which is associated with a stiff spine. We hypothesized that the failure rate caused by pseudoarthrosis and/or ASD would be higher in patients with DISH than in patients without DISH even after short-segment LIF surgery. The aim of the present study was to determine the effect of DISH on the clinical results of short-segment LIF surgery.

Materials and Methods

Clinical study design

This study was performed with the approval of the institutional ethics committee of Kyoto University. The study was a retrospective chart review of 314 consecutive patients who had received one- or two-level LIF surgery for lumbar degenerative diseases performed at our institute from April 2003 through April 2012.

We excluded patients with previous lumbar fusion surgery, Parkinson disease, collagen disease, hemodialysis, active malignancy, lumbar scoliosis (Cobb angle >30 degrees), or age <50 years, or those with insufficient computed tomography (CT) data for the diagnosis of DISH. Two hundred thirty-one patients met the above criteria. Of these 231 patients, 208 patients were followed for >1 year with an average follow-up period of 49.6 months (range: 12–130 months). We analyzed their clinical charts. The clinical outcome was assessed according to the need for further surgery because of pseudoarthrosis and/or ASD in the follow-up period. The influence of possible risk factors on the need for further surgery was examined; these risk factors included sex, age (≥70 or <70 years), level of

5

the lowest instrumented vertebra (S1 or other levels), the number of the fused segments (one or two), laminectomy adjacent to the index fused levels (yes or no), and with or without DISH.

All surgical methods were performed under general anesthesia with a standard open midline approach or the Wiltse approach[9] using a pedicle screw system with one or two interbody cages using standard posterior LIF (PLIF) or transforaminal LIF (TLIF) methods.

Recombinant human bone morphometric protein 2 and other bone-stimulating agents were not used in this study. No patients developed infection in this series.

Definition of DISH

All patients underwent a CT scan from the lower thoracic area to the sacrum before surgery. Ossification of each disk space level from T10 to S1 was assessed by the lateral lumbar X-ray, reconstructed sagittal CT view,

and then graded according to the Mata scoring system[10]. Each vertebral level was scored as follows: 0) no ossification, 1) ossification without bridging, 2) ossification with incomplete bridging, and 3) ossification with complete bridging of the disk space. We defined DISH as the presence of ossification of grade 2 or 3 along the anterolateral aspect of three contiguous disk spaces with relative preservation of disk height according to the Resnick criteria[5].

Using these criteria, we classified the patients into two groups: DISH+ and DISH–. DISH was diagnosed by the senior author (BO). To evaluate interobserver reliability of the radiological assessments of DISH, another independent orthopedic surgeon (TS) also reviewed the last 70 consecutive cases blindly and independently, and these results were compared with those of the senior author.

Statistical analyses

Age and follow-up duration were compared between DISH+ and DISH– groups using a two-tailed t test and Mann–Whitney U test, respectively. Fisher's exact test was used to compare the rate of index pathology, the number of levels fused, and the rate of further surgery between the DISH+ and DISH– groups. Survival curves were produced using the Kaplan–Meier method. To evaluate the influence of possible risk factors on the need for further surgery, the log-rank test and proportional-hazards modeling were used in univariate and multivariate analysis, respectively. All factors in the univariate analysis were included in the multivariate analysis using backward stepwise selection of covariates. The proportional hazards assumption was checked for each explanatory factor by the method described previously[11], and a P value <0.05 was considered significant evidence that the assumption was violated by a given factor. All explanatory factors in our Cox model passed the test, suggesting that the proportional hazards assumption was reasonable. A P value <0.05

was considered significant in all analyses. All calculations were performed using R (R for 3.1.0 GUI 1.64).

Results

Patients' characteristics

A total of 208 patients (99 men and 109 women) underwent one- or two-level LIF surgery; their mean age was 67.7 years (range: 50–86). Among the 208 patients, 181 patients were treated with TLIF and 27 patients were treated with PLIF. In the follow-up period, 21 patients were treated with further surgery because of pseudoarthrosis and/or ASD. The results of the Kaplan–Meier analysis for all patients are shown in Fig. 1. The Kaplan–Meier survivorship analysis predicted 5- and 10-year prevalence rates of 12.1% (95% confidence interval [CI] = 7.4–19.5), and 24.6% (95% CI = 12.9–44.6), respectively.

Treatment and clinical results in the DISH+ and DISH– groups

Among the 208 patients, 39 patients were diagnosed with DISH (DISH+). In the test of interobserver reliability, the kappa coefficient was 0.89, which indicated significant high reliability for the two independent observers. Details of the baseline data are shown in Table 1. The mean age was significantly higher in the DISH+ than in the DISH– group, and the prevalence of DISH was significantly higher in men than in women. However, the index pathology, number of levels fused, rate of laminectomy adjacent to the index fused levels, and level of lowest instrumented vertebra did not differ significantly between the DISH+ and DISH– groups.

The rate of further surgery in the follow-up period was significantly higher in the DISH+ than in the DISH– group.

The effect of DISH and other possible risk factors on the need for further surgery

The univariate analysis using the log-rank test showed that DISH was a significant risk factor for further surgery ($P < 0.05$). Male sex, two-level fusion, and receiving a laminectomy adjacent to the index fused levels were borderline significant risk factors ($P < 0.15$) for further surgery (Table 2).

Multivariate analysis using the Cox proportional-hazards model revealed that DISH ($P = 0.00017$) and the number of levels fused ($P = 0.029$) were significant independent predictors of the need for further surgery, whereas other factors were rejected as independent contributors (Table 2). The hazard ratio for needing further surgery was 5.46 times higher in the DISH+ group compared with the DISH– group. The results of the Cox modeling of DISH and the number of levels fused on survival are shown in Fig. 2.

Discussion

DISH has been investigated in relation to dysphagia[6,12], dyspnea[13], spine trauma[7,14], and metabolic diseases[15], but little is known about the clinical effects of DISH on degenerative lumbar spine diseases. Although the intervertebral disk space is usually preserved in patients with DISH, the condition may coexist with degenerative disk disease[16]. Chi et al. [17] reported on the successful case report of L2/3 posterior fusion for degenerative change of L2/3, which was caudally adjacent level of contiguous ossification from C2 to L2. To our knowledge, no other report has described the treatment of lumbar degenerative disease complicated by DISH.

The current study is the first to focus on the relationship between DISH and the clinical outcomes of LIF surgery. In the analyses of 208 patients who received a short-segment LIF, the rate of further surgery was significantly higher in DISH+ group (25.6%) than in DISH- group (6.5%) during follow-up periods. Moreover, the univariate log-rank test also showed that DISH was a significant risk factor for the need for further

surgery (P = 0.00013). However, the baseline age and sex distribution differed between the DISH+ and DISH– groups (Table 1). Several factors, including age, sex, level of lowest instrumented vertebra, laminectomy adjacent to the index fused levels, and the number of levels fused, have been reported as risk factors for ASD[2,3,18]. Therefore, we selected these factors as potential confounding risk factors and included these factors together with DISH into the Cox proportional-hazards model. DISH and the number of levels fused were identified as independent risk factors, with hazard ratios for further surgical intervention of 5.46 and 2.83, respectively.

The reason for the worse clinical results in DISH+ patients is presumed as follows. The ossification in DISH is usually first seen in the thoracic region and extends to the lumbar region with age[10]. The average flexion-bending ranges of motion between T11 and L2 in healthy subjects has been reported as 18.7 degrees[19]. Patients with DISH lose the flexibility of the thoracolumbar junction[8], which may result in concentration of stress in the lumbar region. After a fusion surgery, the

length of the rigid sections increases further, so that the stress to the pedicle screw may be greater in patients with than in those without DISH. In some cases, severe instability of the index fusion levels leads to pseudoarthrosis at the index fusion levels. Even if a solid fusion can be acquired in the index fusion levels, the stress to the adjacent levels will be greater in patients with than in those without DISH, which may lead to severe ASD in patients with DISH.

As described previously, several risk factors have been reported to affect the clinical results of lumbar spine fusion surgery. Besides DISH, the number of levels fused was shown to be a risk factor for further surgery in this study. In a retrospective review of 106 lumbar fusions, Gillet et al. [20] noted that the rate of further surgery increased as the number of levels fused increased. The same trend was also confirmed by Sears[2] for 912 lumbar fusions. However, Ghiselli et al. [18] did not find a significant association between the number of levels fused and the subsequent development of ASD, and the issue remains controversial.

Increasing age is a risk factor for ASD[2,21]. However, age was not identified as an independent risk factor for further surgery in this study. The rates of comorbidity and surgical complications of spine surgery have been reported to increase with age[22]. We might hesitate to perform further surgery on older patients with several comorbidities even in those with clinically apparent ASD or pseudoarthrosis.

The issue of "floating" fusion remains controversial in the literature[2,23]. Although the present study did not find a significantly higher relative risk for fusion ending at L3, L4, or L5 compared with S1, the result might be different for longer-segment fusion surgery.

Apart from ASD and pseudoarthorosis, we also recorded the incidence rate of the vertebral fractures of the lower thoracic and lumbar spine after the surgery. In the follow-up period, ten out of 169 DISH– group and two out of 39 DISH+ group suffered from osteoporotic vertebral fracture. The incidence rate was not statistically different between two groups. One patient in DISH– group and one patient in DISH+ group

underwent vertebroplasty using polymethylmethacrylate cement.

There are several limitations in the present study. The first is the definition of DISH. In the current study, the existence of DISH was diagnosed using lateral lumbar X-ray and a reconstructed sagittal CT view in which the lower thoracic spine to the sacrum was scanned. Therefore, we defined the criteria for DISH as an ossification of ≥ 4 contiguous vertebral levels from T10 to S1; that is, "thoracolumbar" or "lumbar" DISH[24]. Therefore, three lower contiguous levels of ossification entirely in the thoracic region, namely "thoracic" DISH[24], could not be diagnosed. Further study is needed to examine the effect of "thoracic" DISH on the outcomes of LIF surgery. The second limitation is that we chose the endpoint of further surgery for pseudoarthrosis and/or ASD rather than attempting to retrospectively identify and quantify clinically significant (symptomatic) ASD and/or pseudoarthrosis. Simplifying the methodology this way carries the risk of underestimating the rate of clinically significant pseudoarthrosis and/or ASD because some patients with symptomatic pseudoarthrosis and/or

ASD may be excluded for various reasons, such as intercurrent illness or patient preference. The small number of patients needing further surgery and the possible risk factors selected are other limitations. Only 21 of 208 patients were given further surgery, and we could select only five possible risk factors besides DISH. The patients' characteristics were heterogeneous in terms of implants type, size or material properties of the LIF cage, spinal balance before and after surgery, and bone mineral density. Further studies should include larger cohorts using various fusion techniques to gain a better understanding of various risk factors including DISH. Finally, the average follow-up period was about 50 months and was not enough for the precise evaluation of the clinical results after LIF surgery. We should evaluate the clinical data again several years later.

Although the detailed mechanism is unclear, DISH has been shown to be a significant risk factor for the need for further surgery after short-segment LIF. Surgeons should notice the existence of DISH when performing LIF surgery, even if ossification is seen only in the thoracic to

upper lumbar region.

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Figure legends

Fig. 1. Kaplan–Meyer analysis of further surgery in all patients. The dotted

lines show the 95% confidence interval.

Fig. 2. Cox proportional-hazards regression survival curve for A, DISH

(stratified into DISH+ and DISH– groups) and B, the number of levels fused

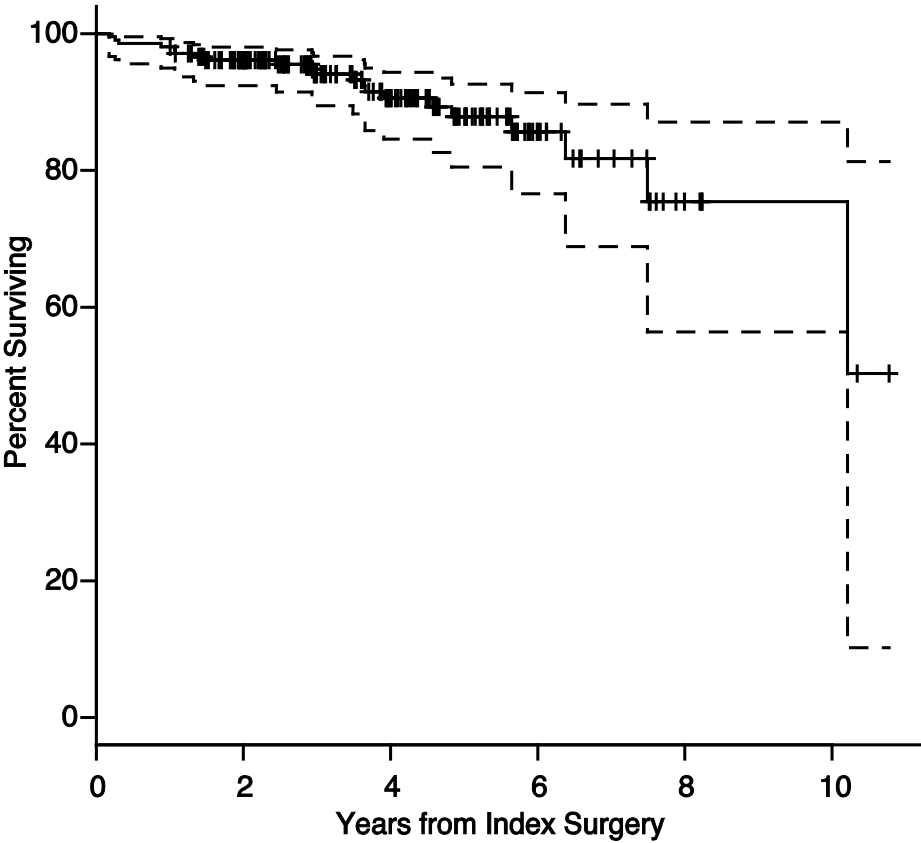(stratified into one-level fusion and two-level fusion).
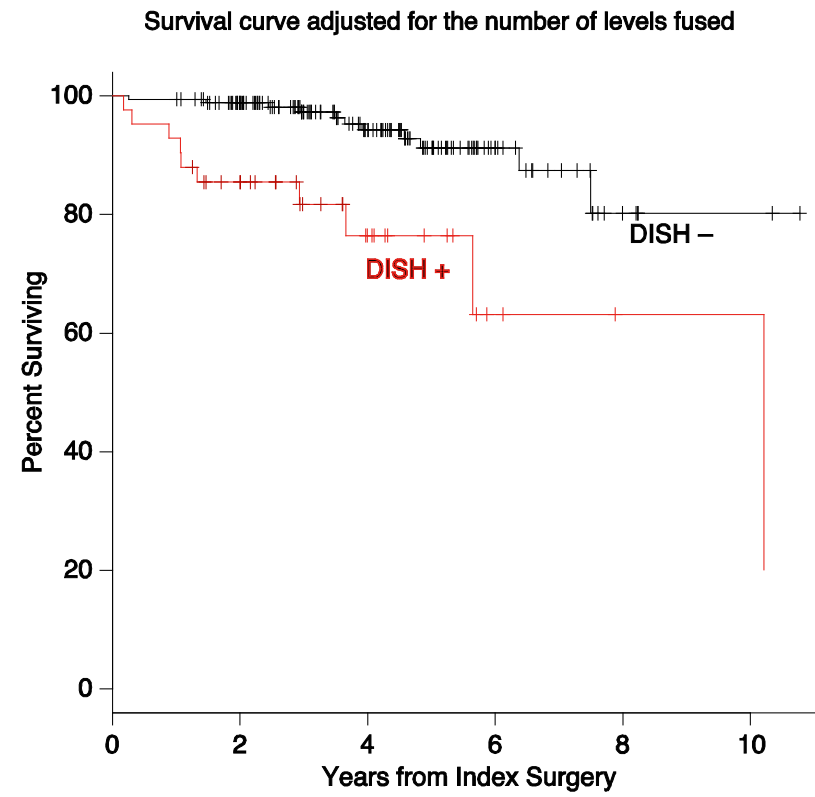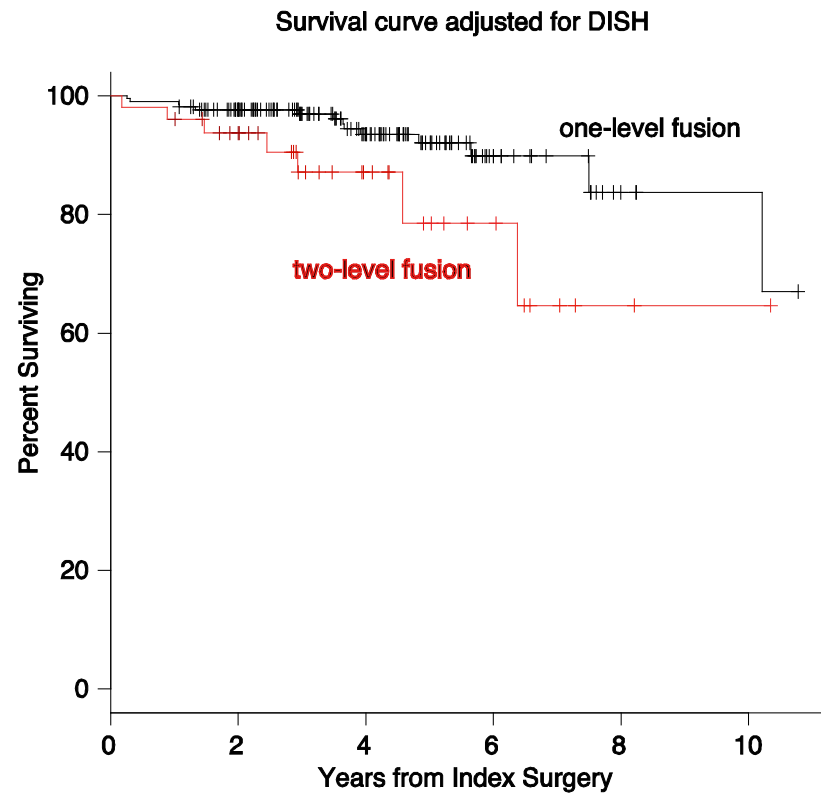
Fig. 1

Fig. 2

Survival curve adjusted for DISH

Survival curve adjusted for the number of levels fused

TABLE 1 Demographic data and clinical results in the DISH+ and DISH– Groups

	DISH+	DISH–	*P*
No. of patients	39	169	
Mean age ± SD (years)	71.4 ± 6.82	66.9 ± 8.36	0.0021 [a]
Sex			
Male	29	70	0.00030 [a]
Female	10	99	
Follow-up period ± SD (months)	46.6 ± 25.5	50.3 ± 22.8	0.37
Index pathology	*(Not mutually exclusive)*		
Lumbar spinal canal stenosis	20	60	0.10
Degenerative spondylolisthesis	14	82	0.21
Lytic spondylolisthesis	4	19	1.00
Degenerative disk disease	2	14	0.74
Degenerative scoliosis	1	9	0.69
Disk hernia	6	17	0.39
One-level fusion	31 (79.5%)	139 (82.2%)	
L2/3	1	4	
L3/4	4	10	
L4/5	19	92	
L5/S	7	27	0.65
Two-level fusion	8 (20.5%)	30 (17.8%)	
L2/3/4	1	0	
L3/4/5	3	26	
L4/5/S	4	10	
Laminectomy adjacent to the index fused levels	15 (38.5%)	42 (24.9%)	0.11
Level of lowest instrumented vertebra			
S1	11	37	0.40
L3, L4, or L5	28	132	
Further surgery	10 (25.6%)	11 (6.5%)	0.0014[a]
ASD	7	7	
Pseudoarthrosis	2	2	1.0
ASD + pseudoarthrosis	1	2	

DISH, diffuse idiopathic skeletal hyperostosis; ASD, adjacent segment disease; SD, standard deviation
[a], $P < 0.05$

TABLE 2 Relationships between potential risk factors and survival

	Univariate analysis		
Factors	Variables (number)	Further surgery (%)	P
Sex	Male (99)	15 (15.2)	0.10 [b]
	Female (109)	6 (5.5)	
Age	<70 (113)	12 (10.6)	0.90
	≥70 (95)	9 (9.5)	
Level of lowest instrumented vertebra	S1 (48)	6 (12.5)	0.20
	L3, L4, or L5 (160)	15 (9.3)	
Number of levels fused	One (170)	14 (8.2)	0.09 [b]
	Two (38)	7 (18.4)	
Laminectomy adjacent to the index fused levels	Yes (57)	7 (12.0)	0.13 [b]
	No (151)	14 (9.3)	
DISH	DISH+ (39)	10 (25.6)	0.00013 [a]
	DISH– (169)	11 (6.5)	
	Multivariate analysis		
Factors	Hazard ratio	95% CI	P
DISH	5.46 (DISH+ vs DISH–)	2.25–13.3	0.00017 [a]
Number of levels fused	2.83 (two-level vs one-level)	1.11–7.20	0.029 [a]

DISH, diffuse idiopathic skeletal hyperostosis; CI, confidence interval; a, P < 0.05; b, P < 0.15