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# Progression of Adjacent-level Degeneration After Lumbar Total Disc Replacement

*Results of a Post-hoc Analysis of Patients With Available Radiographs From a Prospective Study With 5-year Follow-up*

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**Study Design.** Post-hoc analysis of 5-year follow-up data from a randomized, multicenter trial.

**Objective.** The aim of this study was to investigate the incidence of progression in radiographic adjacent-level degeneration (ΔALD) from preoperative assessment to 5 years after total disc replacement (TDR) and the relationship of these changes with range of motion and clinical adjacent-level disease. A secondary objective was to compare adjacent-level degeneration (ALD) outcomes between TDR and fusion.

**Summary of Background Data.** Fusion is associated with high rates of ALD in symptomatic lumbar disc degeneration. TDR may reduce this risk.

**Methods.** In total, 175 patients with single-level, symptomatic, lumbar disc degeneration who had received activL or ProDisc-L and had a preoperative and 5-year postoperative radiograph available were included. Over 5-year follow-up, ΔALD was defined as an increase in ALD of ≥1 grade and clinical ALD was defined as surgical treatment at the level adjacent to an index TDR. Matching-adjusted indirect comparisons were conducted to compare ALD outcomes after TDR (current trial) with those after fusion (published trial).

**Results.** At 5-year follow-up, 9.7% (17/175) of TDR patients had ΔALD at the superior level. In patients with preoperative ALD at the superior level, most (88% [23/26]) showed no radiographic progression over 5 years. The rate of clinical ALD was 2.3% (4/175) and none of these patients had ALD at baseline. For each degree of range of motion gained at the TDR level, there was a consistent decrease in the percentage of patients with ΔALD. After matching and adjustment of baseline characteristics, TDR had a significantly lower likelihood of ΔALD than fusion (odds ratio 0.32; 95% confidence interval 0.13, 0.76).

**Conclusion.** The rates of ΔALD and clinical ALD in this TDR population were similar to those previously reported in the literature for TDR at 5-year follow-up. TDR had a significantly lower rate of ΔALD than fusion.

**Key words:** adjacent-level degeneration, artificial disc, indirect treatment comparison, lumbar spine, matching adjusted indirect comparison, motion preservation, prospective study, range of motion, spinal fusion, total disc replacement.

**Level of Evidence:** 3

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A potential shortcoming of lumbar fusion is the development of accelerated disc degeneration at adjacent level(s). Interest in this area began in the 1980s, with a cadaver study describing the increased biomechanical stress at the adjacent level after fusion and a clinical series demonstrating the phenomenon.[1,2] Further biomechanical investigation confirmed this early work and found fusion to be associated with increased intradiscal pressure and facet joint strain at the adjacent level.[3,4] Clinically, fusion has been associated with adjacent-level degeneration (ALD) beyond what would be expected from natural processes alone.[5]

The concept of stabilizing one segment but creating additional stress that contributes to accelerated degeneration at an adjacent level was one factor that led to the development of a motion-preserving option to treat

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symptomatic disc degeneration. The motion allowed by lumbar total disc replacement (TDR) is thought to have a protective effect on the adjacent level. Biomechanical studies have compared the motion of the index and adjacent lumbar segments after TDR and fusion.[6,7] Unlike fusion, TDR maintained the kinematic properties at both the index and adjacent levels. Postoperative sagittal alignment has also been suggested as another biomechanical factor related to ALD in fusion patients.[8–10] One of the first studies investigating the possible relationship between motion and ALD found that at least 5° range of motion (ROM) was associated with significantly less ALD at 8.7-year follow-up.[11] Further research has also differentiated between radiographic findings of ALD and clinical ALD requiring treatment (*i.e.*, reoperation at adjacent level); however, data are limited.[12,13]

The purpose of this study was to investigate the progression of radiographic ALD 5 years after lumbar TDR with activL or ProDisc-L and the relationship of these changes with ROM and symptomatic, clinical ALD. Given the limited data comparing ALD outcomes between TDR and fusion, a secondary objective of this study was to conduct this comparison using a matching-adjusted indirect comparison (MAIC).

## METHODS

This is a post-hoc analysis of 5-year follow-up data from a large randomized, multicenter trial.[14] Briefly, the original trial enrolled patients from 14 sites; 218 were randomly assigned to the investigational group to receive an activL implant (Aesculap Implant Systems; Center Valley, PA) and 106 were randomly assigned to the control group to receive either ProDisc-L (n = 64) or Charité (n = 41) implants (both devices from Depuy Spine, Raynham, MA); one patient did not receive TDR because of an intraoperative posteroinferior rim fracture. The trial was registered on ClinicalTrials.gov, NCT00589797. The study was approved by each center's institutional review board. All patients were treated for single-level symptomatic disc degeneration unresponsive to at least 6 months of nonoperative care. Detailed study inclusion and exclusion criteria have been described previously.[14]

The current analysis included patients with single-level, symptomatic, lumbar disc degeneration who received activL or ProDisc-L and had a preoperative and 5-year postoperative radiograph available. Postoperative radiographic assessments were prespecified at all follow-up visits to evaluate the condition of the TDR device, identify device-related adverse events, and quantify disc height and ROM.

### Radiographic ALD Assessment

All radiographs were evaluated by an independent lab specializing in image assessment (Medical Metrics; Houston, TX). Measurements of ALD were evaluated using a modified version of the Kellgren-Lawrence scale,[15] as described in an earlier TDR study by Zigler *et al*.[16] Degeneration at adjacent levels was evaluated by examining disc height, endplate sclerosis, osteophytes, and spondylolisthesis. Each level assessed was scored for the severity of disc degeneration using a numerical grade scale that ranged from 0 to 3, where scores were defined as no, mild, moderate, or severe degeneration, respectively. Radiographic worsening of the ALD score (described as ALD progression or ΔALD) was defined as an increase of at least 1 grade at the superior adjacent level. For each level assessed, the ΔALD was calculated as the difference in the ALD grade at preoperative and postoperative assessment, where values 0 to 3 were defined as no, mild, moderate, or severe ΔALD, respectively. The ROM between flexion and extension radiographs of the index level was also assessed. For patients who received TDR at L4–5, changes in the inferior adjacent level were evaluated in a secondary analysis.

To investigate the possible relationship between segmental TDR, ROM, and ΔALD, the percentage of patients with ΔALD was calculated for each minimum degree of motion at the TDR level (*i.e.*, the percentage of patients with ΔALD among patients who had at least 1° of motion, at least 2° of motion, among others).

### Clinical ALD Assessment

Patients were classified as having clinical ALD if they underwent surgical treatment at a level adjacent to the index TDR during their 5-year follow-up. Surgical treatment included structure-modifying procedures such as fusion, TDR, or decompression. Interventions such as injections and rhizotomies were not included. Reoperation at an adjacent level was identified by an independent evaluator who reviewed the adverse events reported for the study.

### MAIC

To compare ALD outcomes between TDR and fusion, MAICs were conducted. Detailed methods are provided in the supplementary appendix, http://links.lww.com/BRS/B345. Briefly, individual patient-level data for TDR from the activL randomized trial[17] were matched and adjusted with summary data for the fusion arm from the Zigler *et al*,[16] study. After aligning inclusion/exclusion criteria between the two studies, baseline characteristics were compared and adjusted for any imbalances (*i.e.*, age, body mass index, sex, smoking status, index level, blood loss, and hospital stays; see Supplementary Tables, http://links.lww.com/BRS/B345). Results are presented as odds ratios (ORs) and 95% confidence intervals (CIs). Sensitivity analyses using an anchored MAIC approach were also performed to determine the benefit of activL compared with fusion on ALD and to validate the findings of the unanchored MAIC (detailed methods presented in Supplementary Appendix, http://links.lww.com/BRS/B345). Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC) and R version 3.3.1. (R Development Core Team, University of Auckland, New Zealand).

**TABLE 1. Description of the Study Cohort of activL and ProDisc-L Patients With Radiographs at Preoperative Assessment and 5-year Follow-up**

| | N (%) or Mean (SD) (N = 175) |
|---|---|
| Age, y, mean (SD) | 39.54 (8.92) |
| BMI, kg/cm$^2$, mean (SD) | 26.67 (4.04) |
| Sex, N (%) | |
| Male | 96 (54.9) |
| Female | 79 (45.1) |
| Ethnicity, N (%) | |
| Non-hispanic or Latino | 167 (95.4) |
| Hispanic or Latino | 8 (4.6) |
| Race, N (%) | |
| White | 160 (91.4) |
| Non-white | 15 (8.6) |
| Smoking status, N (%) | |
| No | 107 (61.1) |
| Yes | 63 (38.9) |
| Index level operated, N (%) | |
| L4–5 | 51 (29.1) |
| L5–1 | 124 (70.9) |
| Blood loss, mL, mean (SD) | 137.40 (128.80) |
| Hospital stay, days, mean (SD) | 3.09 (1.10) |

*BMI indicates Body Mass Index; SD, standard deviation.*

## RESULTS

### Radiographic ALD With TDR

A total of 175 patients, 136 with activL and 39 with ProDisc-L, were included from the original trial. Table 1 provides details on this study cohort. Radiographs for all patients included were available for the superior adjacent level; radiographs at the inferior level were available for a subset of these patients with TDR at the L4–5 level (28%).

At 5-year follow-up, 90.3% (158/175) of all TDR patients showed no evidence of ΔALD at the superior adjacent level, whereas 9.7% (17/175) had ΔALD (Table 2). Among most patients with ALD at preoperative assessment, no progression was observed over 5 years; only three (11.5%) patients had mild, 1-grade ΔALD and no clinical ALD (Table 3). Of the TDR patients with no preoperative ALD at the superior adjacent level, 9.4% (14/149) showed ΔALD at 5 years (Table 3).

Figure 1 presents the percentage of patients with ΔALD for each minimal degree of ROM gained at the TDR level at 5 years. Improvements in ROM at the TDR level ranged from 0° to 16.1° at 5-year follow-up. For each additional degree of ROM gained at the TDR level, there was a consistent decrease in the percentage of patients with ΔALD, ranging from 10.6% among patients with any improvement in ROM at the TDR level to 0% for those with at least 16° of improvement in ROM at the TDR level.

Among patients who received TDR at the L4–5 level, 14.3% (7/49) of patients had ΔALD at the inferior adjacent L5-S1 level.

### Clinical ALD With TDR

At 5-year follow-up, 2.3% (4/175) of TDR patients had surgery at an adjacent level. These included one patient who underwent decompression, two who received fusions at adjacent levels, and one who underwent fusion at the index and adjacent segments to treat stenosis at both levels along with symptomatic disc degeneration at the adjacent level. No patients with clinical ALD had grade ≥1 radiographic ALD at preoperative assessment or ΔALD at 5 years (Table 4).

### Comparison of Radiographic ALD With TDR and Fusion

Results from the primary MAIC showed that after matching and adjustment of baseline characteristics (Supplementary Table 1, http://links.lww.com/BRS/B345), TDR had a statistically significantly lower likelihood of ΔALD than fusion (OR 0.32; 95% CI 0.13, 0.76) (Table 5). The likelihood of clinical ALD was also lower with TDR than with fusion, but was not statistically significant (OR 0.76; 95% CI 0.42, 1.36). Similarly, a sensitivity analysis that compared the

**TABLE 2. Proportion of Patients With ALD at Baseline and 5-year Follow-up, and ΔALD at 5-year Follow-up based on Superior Adjacent Level**

| | Baseline ALD, % (n/N) | 5-y ALD, % (n/N) | ΔALD, % (n/N) |
|---|---|---|---|
| Radiographic ALD* | | | |
| None | 85.1 (149/175) | 77.7 (136/175) | 90.3 (158/175) |
| Present | 14.9 (26/175) | 22.3 (39/175) | 9.7 (17/175) |
| Zigler Scale Assessment | Grade of severity | Grade of severity | Degree of progression |
| Grade 1, mild | 88.5 (23/26) | 79.5 (31/39) | 76.5 (13/17) |
| Grade 2, moderate | 11.5 (3/26) | 12.8 (5/39) | 17.7 (3/17) |
| Grade 3, severe | 0 (0/26) | 7.7 (3/39) | 5.9 (1/17) |

*ΔALD indicates 5-year change in adjacent-level degeneration, where change is defined as a worsening; ALD, adjacent-level degeneration.*
**Analysis conducted for all patients. All patients had ALD at the level superior to the TDR level.*

**TABLE 3. Proportion of Patients With 5-year ΔALD in Those With and Without Radiographic ALD at Baseline**

| ΔALD at 5 y | Patients Without Preoperative ALD (*i.e.*, Grade 0) | Patients With Preoperative ALD (*i.e.*, ≥Grade 1) |
|---|---|---|
| None | 90.6% (135/149) | 88.5% (23/26) |
| Present | 9.4% (14/149) | 11.5% (3/26) |
| Grade 1, mild | 71.4% (10/14) | 100% (3/3) |
| Grade 2, moderate | 21.4% (3/14) | 0% |
| Grade 3, severe | 7.1% (1/14) | 0% |

*ΔALD indicates 5-year change in adjacent-level degeneration, where change is defined as a worsening; ALD, adjacent-level degeneration.*

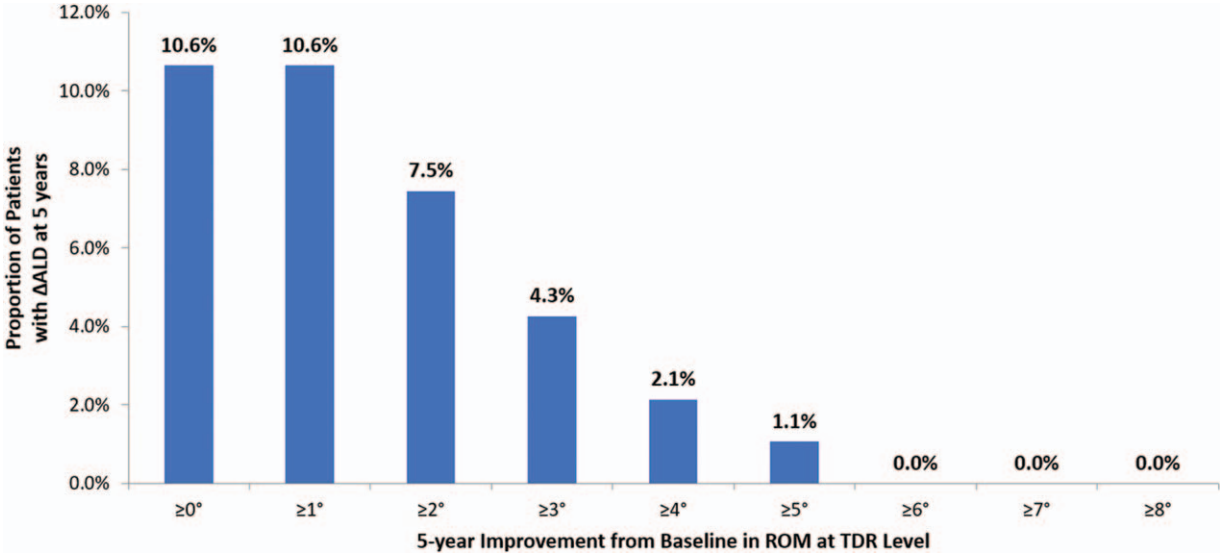


**Figure 1.** The percentage of patients with ΔALD at 5-year follow-up after TDR steadily decreased with improvement in ROM at the TDR level. Improvement in ROM from baseline to 5 years ranged from 0° to 16.1°. For each minimal degree of motion gained at the TDR level at 5-year follow-up, the percentage of patients with ΔALD steadily decreased from 10.6% to 0%. ΔALD indicates 5-year change in adjacent-level degeneration; ROM, range of motion; TDR, total disc replacement.

activL TDR with fusion after matching and adjustment (Supplementary Table 2, http://links.lww.com/BRS/B345) showed a statistically significantly lower likelihood of ΔALD with activL than with fusion (OR 0.13; 95% CI 0.03, 0.61) (Table 5), but results were not statistically significant for clinical ALD (OR 0.42; 95% CI 0.15, 1.19).

**TABLE 4. Proportion of Patients With Clinical Adjacent-level Disease, by Radiographic ALD Assessment at Baseline**

| | Clinical ALD, % (n) |
|---|---|
| All patients | 2.3% (4/175) |
| No ALD at baseline (*i.e.*, Grade 0) | 2.7% (4/149) |
| ALD grade ≥1 at baseline | 0% (0/26) |
| ΔALD | 0% (0/17) |

*ΔALD indicates 5-year worsening in adjacent-level degeneration; ALD, adjacent-level degeneration.*

## DISCUSSION

The results of this post-hoc analysis of prospectively collected TDR data at 5 years showed that radiographic ΔALD and clinical ALD (*i.e.*, surgical treatment at the level adjacent to the index TDR), were both reasonably low in this study. Along with ProDisc-L, this analysis included the newly marketed, activL artificial disc, which was designed to incorporate advancements in motion-preserving technology and has never been evaluated for long-term ALD outcomes. Importantly, this study showed that the implantation of a lumbar TDR in patients with preoperative ALD did not lead to clinical ALD, nor did it lead to substantial progression of additional radiographic degeneration at that adjacent level (ΔALD) at 5 years. This finding suggests that implantation of a lumbar TDR in the presence of asymptomatic adjacent-level degenerative disc disease is entirely appropriate.

**TABLE 5. Summary of MAIC Results Comparing TDR or activL With Fusion for ΔALD and Clinical Adjacent-level Disease Before and After Matching/Adjustment**

| | Before Matching/Adjustment | After Matching/Adjustment |
|---|---|---|
| Primary analysis: TDR *vs.* fusion | | |
| ΔALD, OR (95% CI) | 0.28 (0.12, 0.63) | 0.32 (0.13, 0.76) |
| Clinical ALD, OR (95% CI) | 0.56 (0.12, 2.54) | 0.76 (0.42, 1.36) |
| Sensitivity analysis: activL *vs.* fusion | | |
| ΔALD, OR (95% CI) | 0.17 (0.04, 0.71) | 0.13 (0.03, 0.61) |
| Clinical ALD, OR (95% CI) | 0.39 (0.02, 6.43) | 0.42 (0.15, 1.19) |

*ΔALD indicates 5-year worsening in adjacent-level degeneration; ALD, adjacent-level degeneration; CI, confidence interval; MAIC, matching-adjusted indirect comparison; OR, odds ratio; TDR, total disc replacement.*

Specifically, the ΔALD at 5 years was demonstrated to be 9.7% for TDR devices. These results are similar to those reported by Zigler *et al*[16] (9.2%) and those reported by a European registry-based study[18] (10.7%) for TDR devices. Furthermore, in a meta-analysis comparing TDR with fusion, ΔALD was similar to our results, at 9% for TDR, and was significantly less than that for lumbar fusion (34%; $P < 0.0001$).[13] The meta-analytic evidence is supportive of our MAIC findings that significantly favor TDR over fusion for ΔALD. In a sensitivity analysis further investigating ΔALD, activL was also shown to have a significantly lower likelihood of ΔALD than fusion.

The rationale for the reduced rate of ΔALD associated with TDR compared with fusion is that the motion preservation provided by the implant produces low levels of stress on adjacent segments, in contrast to the increased stresses on adjacent levels created by rigid fusion. This concept has been supported by findings from biomechanical studies, wherein TDR resulted in motion and stresses in the adjacent-level disc similar to the intact spine and that were significantly less than fusion.[19,20] Clinically, Huang *et al*[11] reported an association between TDR motion and ΔALD, with increased motion associated with less progression of ALD. In the present study, a steady decline in ΔALD was identified with increasing ROM at the TDR level. This supports the idea that, for symptomatic degenerative disc disease, motion at the index surgical level has a protective effect against change in ALD at an adjacent level.

In the present study, clinical ALD occurred in only 2.3% of patients during 5-year follow-up. This low rate is similar to that reported in other TDR studies with 5-year follow-up.[13,16,18] Our comparative results from the MAIC, showing a numerically lower likelihood of clinical ALD with TDR than with fusion, are similar to those reported in published studies.[13,16] Strong evidence for an increased rate of surgical intervention at the adjacent level related to fusion *versus* TDR comes from a meta-analysis reporting an OR of 13.93 (95% CI 7.01, 32.96).[13]

This study has limitations. First, this study is a post-hoc analysis of a subset of patients from the original randomized trial. Therefore, it does not represent all patients originally evaluated because not all preoperative and 5-year radiographs were available, primarily because of loss to follow-up. Nevertheless, our sample size of 175 patients is relatively comparable to a recent study that included 161 patients with ProDisc-L and evaluated ALD outcomes.[16] Second, caution should be exercised when comparing results of various studies because of the potential for variations in scoring methods and follow-up duration. Our study was aligned with the methods published in the 2012 study conducted Zigler *et al*,[16] which comprehensively considered several parameters, including disc height, endplate sclerosis, osteophytes, and spondylolisthesis, in the grading scheme. Furthermore, although the indications for TDR have generally been consistently applied in randomized controlled trials, fusion data may come from less homogeneous patient cohorts, particularly in studies not involving randomized comparison to TDR. Third, an MAIC was conducted because of the absence of randomized data directly comparing currently marketed TDR devices (*i.e.*, activL and ProDisc-L) with fusion for the ALD outcomes of interest. Although MAICs involve consideration and adjustment for treatment-effect modifiers and/or prognostic factors, there is risk that treatment groups are not perfectly balanced. In the comparison of TDR with fusion, unanchored methods were used that involved more methodological assumptions. In the comparison of activL with fusion, anchored methods were used, wherein the ProDisc-L arm from each trial acted as an anchor treatment. Results for ALD outcomes were comparable using both anchored and unanchored methods, illustrating the robustness of the methods.

In conclusion, the results of this study show that rates of ΔALD and clinical ALD are low and consistent with those reported in other TDR studies with 5-year follow-up. The significantly lower prevalence of ΔALD with TDR than with fusion was also consistent with other comparative studies. The finding that there was a steady decline in ΔALD for each degree of motion at the TDR level suggests that motion preservation at a treated segment has a protective effect on adjacent levels. This analysis of prospective study data with 5-year follow-up adds further support that, by providing mobility at the operated segment, lumbar TDR has a protective effect on radiographic degeneration at the adjacent level.

## ➢ Key Points

- ❑ This post-hoc analysis of long-term follow-up data from a large randomized trial found that the rate of progression in ΔALD was 9.7% 5 years after lumbar TDR.
- ❑ Most patients (88%) with preoperative ALD did not progress radiographically over 5 years.
- ❑ The rate of ΔALD declined with improved ROM at the TDR level, suggesting that motion has a protective effect on adjacent levels.
- ❑ Results from an MAIC showed that TDR was associated with a statistically significantly lower likelihood of ΔALD than fusion.

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