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Adjacent level disease-background and update based on disc replacement data

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Abstract
Purpose of review The precise etiology of adjacent segment disease following cervical spine surgery is controversial. Theories for development include inevitable changes secondary to the natural progression of the degenerative cascade and changes secondary to altered biomechanics of the fused cervical spine. Motion preserving techniques, such as cervical disc arthroplasties (CDA), have been introduced with the hopes of reducing the rates of adjacent segment pathology. Recently, 7-year data from the investigational device exemption (IDE) studies have been published. The purpose of this review is to provide an update on cervical adjacent segment disease incorporating this emerging data into the analysis.
Recent findings Although the 7-year data for CDA has confirmed continued success, specifically regarding improved neck pain and reduced re-operation rates, the influence of CDA on reducing rates of adjacent segment pathology remains questionable. Although some studies have found more radiographic adjacent segment disease after anterior cervical discectomy and fusion (ACDF) compared to CDA, an association between these findings and clinical symptoms has not been established.
Summary Cervical disc arthroplasty continues to outperform cervical disc fusion regarding some patient specific parameters, however, whether CDA reduces rates of radiographic and clinical adjacent segment pathology remains unknown. Without studies developed specifically to address this question, the answer remains elusive.

Keywords Adjacent segment disease · Cervical spine · Anterior cervical discectomy and fusion · Cervical disc arthroplasty · IDE studies

Introduction

Anterior cervical decompression and fusion (ACDF) has a long history of successfully treating radiculopathy or myelopathy [1–3]. One potential consequence of ACDF is adjacent segment disease, defined as the development of clinical symptoms of radiculopathy or myelopathy caused by radiographic degeneration (disc height loss, posterior osteophyte formation, all osteophyte formation, etc.) at motion segment(s) adjacent to the surgical levels. It has been reported to occur at a rate of 2.4–2.9% annually [4•, 5••]. Notably, about two thirds of these patients ultimately require an operation for symptomatic relief, suggesting that adjacent segment disease as a cause of radiculopathy may be more recalcitrant to nonoperative care, given this higher rate of intervention than typically observed for primary cervical radiculopathy [4•].

Many have debated the precise etiology of the radiographic findings of adjacent segment pathology. Some have suggested that these findings represent the natural history of degenerative cervical spine disease while others maintain that the altered biomechanics of the fused cervical spine may accelerate a degenerative cascade. In an effort to minimize these changes, motion preserving techniques, such as cervical disc arthroplasties (CDA), which better maintain normal kinematics, have been introduced with the hopes of reducing the rates of adjacent segment pathology. While early to mid-term

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patient-generated outcomes data has been promising, rates of adjacent segment disease have not been significantly affected [6–10]. Recently, 7-year data from the investigational device exemption (IDE) studies have been published [11••, 12••, 13, 14••]. The purpose of this review is to provide an update on cervical adjacent segment disease incorporating this emerging data into the analysis.

Clinical versus radiographic adjacent segment pathology

Adjacent segment pathology has been more precisely characterized as either radiographic adjacent segment pathology (RASP) or clinical adjacent segment pathology (CASP). RASP represents the development of new radiographic degenerative changes adjacent to a surgical fusion without any associated symptomatology while CASP refers to new degenerative changes adjacent to a fusion accompanied by symptoms referable to those levels. While neurocompressive pathology precipitating radiculopathy or myelopathy is included under the umbrella of CASP, neck pain referable to those levels is more controversial. Localization of pain to specific levels is more subjective, and characterization of those symptoms as CASP is more nuanced.

Natural history or iatrogenic?

Whether CASP is related to the natural history of age related changes of the cervical spine or whether it is a biomechanically induced phenomenon following fusion surgery is controversial. Several studies have documented progressive degenerative changes in the cervical spine with increasing age.

Boden et al. [15] prospectively studied the MRIs of 63 asymptomatic volunteers and found that 19% of the scans were abnormal. While 14% of the scans for those under 40 years old were abnormal, 28% were abnormal for those older than 40 years old. Moreover, degeneration of the cervical disc at one or more levels was identified in only 25% of those under 40 years old compared to 60% of those participants older than 40 years old.

Similarly, Matsumoto et al. [16] performed an MRI on 497 asymptomatic subjects and found a strong correlation between the occurrence of degenerative changes and age. Only 17% of men and 12% of women in their 20s had evidence of degenerative disease compared to 86 and 89% of men and women, respectively, over 60 years of age. In a follow-up study of that same cohort with 223 subjects available for a repeat MRI and examination, 81.1% of participants had progression of degenerative changes, and 34.1% of those patients had developed at least one clinical symptom related to those changes [17].

These studies imply a naturally progressive condition of cervical spine disease, but do not predict the outcome of future symptomatology once symptomatic levels are surgically addressed. Early studies of CASP following cervical spine surgery sought to characterize and predict the incidence of CASP among ACDF patients. Hilibrand et al. [4•] followed 374 patients undergoing 409 ACDF procedures for a maximum follow-up of 21 years and identified an incidence of CASP of 2.9% for the first 10 years following ACDF. A Kaplan-Meier survivorship analysis predicted a 25.6% prevalence of new disease within 10 years of the procedure. A subsequent literature review concluded that the prevalence of CASP is between 9%–17% with an annual incidence of reoperation for adjacent segment disease ranging from 1.5 to 4% [18]. Lee et al. [5••] confirmed these numbers in a retrospective review of 1038 consecutive patients who underwent anterior cervical spine arthrodesis for radiculopathy and/or myelopathy. The authors identified a 2.4% annual rate of re-operation (rather than adjacent segment disease not necessarily requiring surgical intervention) and a Kaplan-Meier analysis predicting a 22.6% re-operation rate by 10 years.

Although these studies describe the development of CASP following cervical spine surgery, they do not include a nonoperative cohort for comparison. Matsumoto et al. [19] performed an MRI follow-up of 64 patients who underwent uninstrumented ACDF and 201 asymptomatic controls to assess for the development of RASP. With greater than 10-year average follow-up, a significantly higher rate of RASP was identified in the ACDF cohort. However, the authors could not correlate these findings with symptomatology and did not report a similarly increased rate of CASP. In addition, although this study observed an increased rate of RASP after ACDF, the nonoperative group was not a matched cohort, and those undergoing ACDF may have been predisposed, both genetically and environmentally, to disc degeneration or to symptomatic pathology.

Some older studies examined the differences in rates of degeneration between fusion and non-fusion cervical spine surgery. Herkowitz et al. [20] prospectively compared 28 patients undergoing ACDF to 16 undergoing posterior foraminotomy without fusion for cases of cervical radiculopathy. At an average of 4.2 follow-up years, 40% of those in the ACDF group developed RASP while 50% in the fusion-less foraminotomy group developed RASP. Henderson et al. [21] followed 846 patients who underwent isolated posterior laminoforaminotomy and found the incidence of reoperation for CASP to be roughly 3% which is similar to accepted rates of CASP following ACDF. Lee et al. [22] reviewed 1358 patients who had undergone either arthrodesis (anterior, posterior, or both), posterior decompression, or arthroplasty and found no difference between the rates of reoperation for ACDF compared to posterior decompression alone. Collectively, these studies suggest that surgery itself

may be more of a risk factor in accelerating adjacent segment pathology rather than spinal fusion.

Risk factors for adjacent segment pathology after ACDF

Several studies have examined risk factors for adjacent segment disease that might be addressed through the surgical approach. Hilibrand et al. [4•] were the first to notice that patients with greater number of fused vertebrae had a decreased risk for CASP ($p < 0.001$). Moreover, they found that CASP was level dependent so that adjacent pathology developed most frequently when a fusion ended adjacent to C5–6 and C6–7 ($p < 0.001$). These levels also are those with the greatest motion and those most predisposed to arthritic change [3, 23]. The authors of that study theorized that longer fusion constructs likely incorporated more of the degenerated levels that would ultimately manifest as adjacent segment pathology, while those including fewer levels left those mobile levels "at risk." The longer fusions also tended to stop at levels that were less likely to develop adjacent segment pathology (C2–C5) as opposed to single and two level fusions which were more likely to end near "at risk" levels (C5–C7). These findings would support the theory that adjacent segment pathology is more likely a reflection of the natural history of cervical spine disease rather than the consequences of fusion. Another study specifically aimed at identifying risk factors for CASP could not identify any associated surgical parameters, and only associated osteopenia and lumbar degenerative disc disease with increased risk are bolstering the notion that adjacent segment pathology is the result of natural history rather than the sequela of ACDF [24].

Lee et al. [22] confirmed that surgery at 3 + levels decreased the re-operation rate for CASP in comparison with one or two-level fusions ($p = 0.045$). They also found that smoking ($p = 0.008$) and female sex ($p = 0.031$) were risk factors for re-operation. Song et al. [25] found the same risk factors as the Lee [22] study but added that plate augmentation for ACDF lowered the rate of RASP as well. While plate usage has decreased the risk of RASP, plate position may also play a role. Adjacent ossification has been found in cases where the plate is placed within 5 mm of the adjacent disc [26]. Nassr et al. [27] also stressed the role of soft tissue violation on the development of RASP by showing that incorrect needle localization was associated with a threefold increase in the rate of RASP at 2-year follow-up. However, the appearance of radiographic change has not been definitely associated with clinical disease.

Biomechanics

Perhaps the most controversial risk factor is the presence of fused vertebrae. Numerous biomechanical studies have found that fusion leads to altered biomechanics of the native spine with diminished motion at the incident level and increased compensatory motion at the levels above and below [28, 29]. After fusion, adjacent levels experience increased intradiscal pressure [28, 30, 31] and facet loads [31].

However, Hilibrand et al. [4•] had found that longer fusions actually were less likely to lead to symptomatic adjacent segment disease even though the longer lever arms would have increased the stress at adjacent levels. This led the authors to question whether CASP was a product of fusion or a consequence of the natural history of the disease.

Contrary to Hilibrand et al.'s clinical experience, Matsunaga et al. [32] evaluated the pre-operative and post-operative radiographs of 96 patients who had undergone ACDF at an average of 6.5 years of follow-up and found that by 1 year-post-operatively, for two and three level cervical fusions, strain in the disks at adjacent intervertebral levels increased by 20%, while one level fusion patients maintained normal strain. For multi-level cases, that increased strain led to disc herniation in 85% of patients at last follow-up.

Cervical disc arthroplasty

Cervical disc arthroplasty was developed to address biomechanical concerns following fusion surgery. In vitro studies have found that adjacent segment motion, intradiscal pressure, and facet joint loading are unchanged following cervical disc arthroplasty [29, 30]. Several prospective clinical studies using plain films and MRI have similarly demonstrated preserved physiologic range of motion at the operated segment and the cervical spine as a whole after cervical disc arthroplasty [33–35].Cervical disc arthroplasty has shown early promise at mid-term follow-up [6–9]. Recently, 7-year follow up data from the original IDE studies have emerged confirming the continued success of the CDA cohorts [11••, 12••, 13, 14••]. The four studies with the longest follow-up published to date have all shown that the CDA cohort performed significantly better in terms of neck pain (and the neck disability index (NDI)) and experienced a lower re-operation rate than the control groups which underwent ACDF [11••, 12••, 13]. One study found that the CDA cohort benefited from improved rates of neurological recovery [12••], and another found that they enjoyed improved patient satisfaction [11••].

While clinical results have been excellent following CDA, the influence of CDA on reducing rates of adjacent segment pathology has been more questionable. Coric et al. [6] compared the outcomes of 136 patients undergoing Kineflex C (metal on metal cervical disc replacement) to 133 undergoing ACDF in a RCT with minimum of 2 years of follow-up. RASP was graded in severity (none, mild, moderate, or severe), and significantly more severe RASP was identified after ACDF

than after CDA ($p < 0.0001$), but no significant differences in terms of reoperation rates for that degeneration was identified (7.6% ADR versus 6.1% ACDF). Maldonado et al. [36] reviewed minimum 3-year follow-up data for 105 patients undergoing ACDF and 85 undergoing CDA (Discover-Depuy) to determine the incidence of RASP and could only find a non-significant increase in RASP in the ACDF (10.5%) cohort compared to CDA (8.8%) ($p = 0.72$). Nunley et al. [24] analyzed the 2–4 year follow-up data from three RCTs and found that at an average of 42 months, more patients in the CDA group actually required surgery for CASP compared to the ACDF cohort (14.3% ACDF versus 16.8% CDA).

More recently, 7-year data from the IDE studies have emerged which paint a more favorable picture for adjacent segment degeneration after CDA. Janssen et al. [14••] presented data from the ProDisc-C trial which compared 103 patients undergoing CDA to 106 patients undergoing ACDF. At 7 years, the follow-up was 92%, and both cohorts had performed well clinically with no significant differences in clinical outcomes such as neck and arm pain, SF-36 scores, or neurological status. While the shorter term data from this study found no difference in the rate of re-operation at adjacent segments, the 7-year data found that 22 procedures in 13 patients were performed for adjacent segments in the ACDF cohort compared to only six procedures in six patients in the ProDisc-C cohort ($p = 0.01$).

Phillips et al. [11••] recently published 7-year data from the PCM Cervical Disc trial. The authors identified more RASP (particularly, at superior levels) after ACDF compared to CDA (33.1% PCM, 50.9% ACDF; $p = 0.006$), but an association between these findings and clinical symptoms was not established. The authors note that between years 2 to 7, 13/14 re-operations for the ACDF group were for adjacent segment pathology as opposed to the PCM group which only had 1/7 patients treated for ASD. However, the trend toward fewer re-operations in the PCM cohort overall was not statistically significant (18/211, 8.5% PCM; 24/184, 13.0% ACDF, $p = 0.190$).

Burkus et al. [12••] compared the Prestige (Medtronic) CDA (212 patients) to ACDF (182 patients) and reported that at 7-year follow-up, there was a nonsignificant decrease in the rate of re-operation at adjacent segments for the CDA cohort (3.9%) compared to the ACDF group (5.4%) ($p = 0.451$) Moreover, from a biomechanical perspective, from 6 weeks on, there was no difference in ROM of adjacent segments when comparing the CDA and ACDF groups ($p > 0.097$), making the case for reduced rates of adjacent segment pathology after CDA more tenuous.

Another group studying the Prestige LP cervical disc found that at 84 months, the percentage of patients undergoing secondary surgeries at the adjacent level alone or in conjunction with the index level was similar when comparing TDA (9.6%) and ACDF (8.3%) [13].

A meta-analysis from 2013 examining the differences in rates of adjacent segment disease between cervical arthrodesis and arthroplasty concluded, based on a pooled analysis of studies with 2–5 year-follow-up, that no statistically significant difference in the incidence of CASP existed (2.4% ± 1.7% for ACDF versus 1.1 ± 1.5% for CDA, $p = 0.44$) [10]. However, a more recent meta-analysis including studies through November 2015 concluded that as data from newer RCTs were published and as longer-term follow-up of the original studies were made available, the rate of CASP following CDA was in fact lower than that after ACDF (RR, 0.57; 95% CI, 0.37 to 0.87; $p = 0.009$) [37•]. Interestingly, this meta-analysis performed a subgroup analysis stratifying rates based on total disc replacement type. Only the Prestige Disc displayed a significantly lower rate of ASD compared to ACDF (as opposed to Bryan and ProDisc-C) (RR, 0.42; CI, 0.21 to 0.82; $p = 0.01$). Regarding adjacent segment reoperations, there were fewer in the CDA group compared with the ACDF group (RR, 0.47; CI, 0.32 to 0.70; $p = 0.0002$).

Rather than comparing rates of adjacent segment pathology only in head to head comparisons, Shriver et al. [38] recently completed a meta-analysis of rates of CASP and RASP among all studies of patients treated with CDA. Although the studies comprise a heterogeneous group of patients, implants, and techniques, the annual incidence of RASP and CASP were 8.3 and 0.9%, respectively. This rate of 0.9% is much lower than the commonly accepted rate of CASP after ACDF of ~3%. However, only 0.2% of patients developed symptoms of ASD in the early post-operative period, while 2.6% of patients developed CASP with greater than 2-year-follow-up, and among those studies, only four of them had greater than 4-year-follow-up. This study highlights the importance of measuring the rates of CASP for CDA alongside those of ACDF in matched prospective studies.

Conclusion

Clinical adjacent segment disease is likely a multifactorial process that is driven by natural history, but also affected by increased adjacent segment mobility and disruption of normal anatomy. A recent meta-analysis found that the incidences of RASP, CASP, and those requiring additional surgery were 2.79, 1.43, and 0.24%, respectively [39]. According to this analysis, although almost half of patients with RASP ultimately develop CASP, whereas less than half of those patients go on to require further surgery.

Over the past decade, motion sparing technology (i.e., CDA) has been developed to mitigate the risk of adjacent segment pathology, yet at mid-term follow-up, no clear benefit had been demonstrated. As 7-year data emerges, a trend toward decreased reoperation for CASP is evolving. The

weakness of these studies is that they are largely based on the original IDE studies which were designed as non-inferiority trials rather than as studies intended to discern rates of ASD.

A review of a single surgeon's experience with 1358 patients undergoing all types of cervical spine surgery found an overall rate of reoperation for ASD of 2.3%, with no significant difference in the rates of ASD between CDA and ACDF [22].

The question of whether adjacent segment disease is influenced by fusion, and the degree to which fusion influences long-term degenerative change at adjacent levels rather than the natural course of degenerative disease itself, remains unanswered. The addition of 7-year data to the CDA literature has confirmed maintenance of clinical improvement, preserved range of motion, and decreased rates of re-operation, but a definitive association between rates of re-operation and clinical adjacent segment pathology remains elusive.

Compliance with ethical standards

Conflict of interest Alan S. Hilibrand is a board member for AAOS, the Cervical Spine Research Society, and the North American Spine Society. He reports stock options for Amedica, Benvenue Medical, Lifespine, Nexgen, Paradigm Spine, PSD, Spinal Ventures, and Vertiflex. He also reports personal fees from Aesculap/B.Braun and Biomet.

I. David Kaye declares that he has no conflict of interest.

Human and animal rights and informed consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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