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Cervical Total Disc Replacement and Heterotopic Ossification: A Review of Literature Outcomes and Biomechanics

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Anterior cervical discectomy and fusion (ACDF) immobilizes surgical segments and can lead to the development of adjacent segment degeneration and adjacent segment disease. Thus, cervical total disc replacement (CTDR) has been developed with the aim to preserve the biomechanics of spine. However, heterotopic ossification (HO), a complication following CTDR, can reduce the segmental range of motion (ROM) and defects the motion-preservation benefit of CTDR. The pathological process of HO in CTDR remains unknown. HO has been suggested to be a self-defense mechanism in response to the non-physiological biomechanics of the cervical spine following CTDR. The current literature review is concerned with the association between the biomechanical factors and HO formation and the clinical significance of HO in CTDR. Endplate coverage, disc height, segmental angle, and center of rotation may be associated with the development of HO. The longer the follow-up, the higher the rate of ROM-limiting HO. Regardless of the loss of motion-preservation benefit of CTDR in patients with HO, CTDR confers patients with a motion-preservation period before the development of ROM-limiting HO. This may delay the development of adjacent segment degeneration compared with ACDF. Future clinical studies should explore the association between HO and changes in biomechanical factors of the cervical spine.

Keywords: Ossification; Heterotopic; Total disc replacement; Spine; Biomechanical phenomena

Introduction

Cervical total disc replacement (CTDR) has emerged as an alternative to anterior cervical discectomy and fusion (ACDF). In theory, the major advantage of CTDR over ACDF is the preservation of segmental range of motion (ROM) and function, thereby minimizing the risk of adjacent segment degeneration (ASD) [1]. ROM preservation can alleviate intradiscal pressure and stress at levels adjacent to the operated segments [2]. Compared with ACDF, CTDR demonstrates superiority in some aspects of clinical outcome, such as a higher rate of neurological success, while maintaining non-inferiority in the majority of other clinical and safety outcomes [3]. Unfortunately, heterotopic ossification (HO), which is consistently reported as a complication in clinical trials, may impact the long-term superiority of CTDR over ACDF.

The pathological process underlying the development

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of HO remains unclear. Although a number of modifiable and non-modifiable risk factors have been found to be associated with HO formation, the evidence is inconclusive [4,5]. Additionally, the postoperative use of non-steroidal anti-inflammatory drugs does not seem effective in reducing the rate of HO [6]. Three conditions have been postulated as essential for HO formation—osteogenic precursor cells, inducing agents, and a permissive environment [7]. The current literature review has the following objectives: (1) to discuss what biomechanical factors may act as an inducing agent of and create a permissive environment for HO formation in CTDR and (2) to discuss the clinical significance of HO.

Materials and Methods

A systematic review on the association between biomechanical factors of the cervical spine and HO in CTDR was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis protocols guideline and the guidelines for academic neurosurgeons [8-10]. We searched in the MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and PubMed databases for eligible studies published until April 2018. The following medical subject headings and text words were used: "heterotopic ossification," "heterotopic bone," "cervical," "arthroplasty," "total disc/disk replacement," "artificial disc/disk replacement," and "disc/disk prosthesis." A search in the reference lists of all the selected articles was manually performed to identify other potential studies.

After removal of duplicates and screening of title and abstract, full-text eligible studies were reviewed. The whole screening and reviewing process was conducted by two reviewers. Any disagreement in the reviewing process was first resolved by a discussion between the reviewers. If the reviewers could not reach a consensus, a senior author was consulted.

The inclusion criteria were as follows: (1) studies that reported the association between HO and ≥1 biomechanical factor(s); (2) subjects aged ≥18 years; and (3) there is no limitation on the number of doctors who diagnosed HO, the type of prosthesis, or the classification system used to grade HO. The exclusion criteria were as follows: (1) articles that did not provide original data, such as editorials; (2) studies written in languages other than English; (3) TDR in the lumbar spine; and (4) duplicated publications.

Biomechanical Factors

The human spine is a biomechanically complex structure.

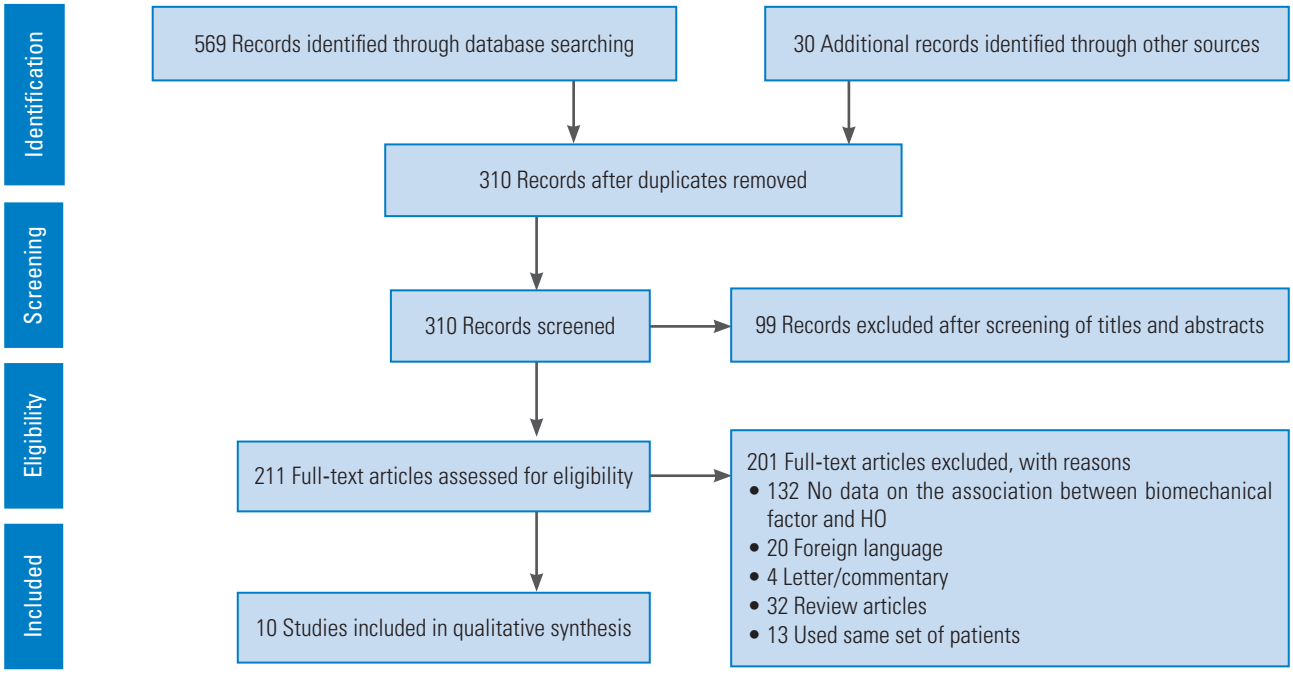

Fig. 1. PRISMA flow diagram. HO, heterotopic ossification; PRISMA, Preferred Reporting Items for Systematic Review and Meta-Analysis.

The replacement of cervical intervertebral discs with artificial implants designed to mimic natural motion is done in an attempt to preserve segmental- and adjacent-level motion [11]. However, there is potential for these devices to still result in non-physiological strain [12]. Cho et al. [13,14] reasoned that HO could actually be a self-defense mechanism in response to the non-physiological biomechanics of the cervical spine following CTDR. In order to investigate the association between biomechanical factors and HO, our initial search produced 310 articles after removal of duplicates, of which 10 studies were included in our review (Fig. 1) [5,12,15-22].

Endplate Coverage

Inappropriate endplate coverage may be associated with the development of HO. Pickett et al. [23] first proposed that the formation of grade IV HO at 17-month follow-up in a patient was due to undersizing of the prosthesis. This theory is corroborated in a retrospective study of the Bryan cervical disc, which classified "suboptimal carpentry group" as an uncovered vertebral endplate of >1 mm and/or kyphotic position of the implant [12]. They discovered that the suboptimal carpentry group was associated with a higher rate of grade II or more severe HO at 2-year follow-up [12]. In fact, the footprint mismatch between the endplates and prostheses was 43.7% in the Bryan and ProDisc-C, 60.4% in Discover, and 100% in Prestige implants in the anterior–posterior plane [24]. However, results are not unanimous, with vertebral endplate coverage not being significantly associated with a higher rate of ROM-limiting HO in patients undergoing CTDR with the ProDisc-C implant [16]. The use of different types of implant may explain the contradictory results in the studies. Additionally, Wenger et al. [25] postulated that complete endplate coverage could block osseous outgrowth of endplate, and, thus, minimize the risk of HO. As such, it has been recommended that CTDR prosthetics should be as large as possible to cover the whole endplate, dissipating loading force evenly across the endplate [24].

Disc Height

Disc height could potentially be another biomechanical factor contributing to HO formation. Although an increase in disc height is necessary in order to properly decompress the nerve roots, over-distraction of disc height is correlated with increased segmental ROM [16]. This result is in agreement with another study which found that approximately 30% of the inter-subject variability in C5/C6 and C6/C7 flexion–extension ROM could be attributed to the differences in disc height at these segments [26]. Given the changes in disc height and ROM after CTDR, HO has been theorized to stabilize the non-physiological movement of cervical spine [13,14]. However, the association between HO and disc height is yet to be proven.

Segmental Angle

Segmental angle is altered after CTDR with some types of prosthesis. Following CTDR using Bryan disc prosthesis, segmental angle became kyphotic relative to the preoperative segmental angle [27]. A prospective study quantified that only 36% of patients with segmental lordosis before CTDR had segmental lordosis preserved postoperation [28]. In spite of the loss of segmental lordosis in some subjects, the C2/C7 Cobb angle did not change significantly; as such, other cervical levels might have compensated for the loss of physiological alignment at surgical segment [27,29]. In contrast to the Bryan disc, ProDisc-C has been reported to result in significantly more lordosis at the surgical segment and across the global cervical spine [30,31].

The angle of the surgical spinal segment is associated with its ROM. An *in vivo* study demonstrated an inverse association between shell angle with segmental ROM in flexion and extension [32]. Also, an increase in flexion–extension ROM after CTDR with ProDisc-C prosthesis has been reported in both *in vitro* and *in vivo* studies [33,34]. Theoretically, increased segmental mobility can accentuate strain on the uncovertebral and facet joints [35]. Hence, Rabin et al. [32] recommended that upper and lower device endplates should be parallel to each other when inserted into the disc space to preserve segmental ROM. Although HO may develop in response to the non-physiological biomechanics of the cervical spine following CTDR [13,14], the effect of segmental hypermobility on HO development is unproven.

Center of Rotation

Center of rotation (COR) of the cervical spine is altered after CTDR. By adopting a finite element model of the C5/C6 cervical spine after CTDR, a biomechanical study found that the position of instantaneous COR of Bryan

Table 1. A summary table of the association between biomechanical factors and HO

Article	Country	Study period	Sample size	Follow-up period (yr)	Prosthesis	Rate of HO (%)	Biomechanical factor	Association with HO
Zeng et al. [15] (2018)	China	January 2008 and July 2011	45	≥6	Prestige-LP	46.7	Segmental ROM	↓
Kim and Heo [16] (2016)	Korea	June 2005 and May 2006	23	5.1	ProDisc-C	69.6	Vertebral endplate coverage	↔ (≥grade III)
Lei et al. [17] (2016)	China	January 2005 and September 2007	31	8	Bryan Disc	51.4	C2–C7 ROM	↔
							Segmental ROM	↓ (≥grade III)
Tian et al. [18] (2016)	China	January 2004 and December 2009	71	6.6	Bryan Disc	-	Segmental ROM	↔ (grade I & II) ↓ (≥grade III)
Malham et al. [19] (2014)	Australia	March 2004 and December 2008	24	7.7	ProDisc-C	36.4	Segmental ROM	↔
Suchomel et al. [20] (2014)	Europe	January 2007 and December 2009	175	≥2	Activ-C standard version	-	More posterior implant-related centre of rotation	↑ (≥grade III)
Pimenta et al. [21] (2013)	Brazil	-	158	4.5	PCM	7.7	Segmental ROM	↓ (≥grade III)
Chung et al. [5] (2012)	Korea	January 2005 and September 2007	19	1.5	Bryan Disc	68.4	Decrease in segmental ROM	↑ (≥grade III)
Tu et al. [12] (2012)	Taiwan	-	75	≥2	Bryan Disc	56.1	An uncovered vertebral endplate of >1 mm and/or kyphotic position of the implant	↑ (≥grade II)
Huppert et al. [22] (2011)	France	November 2004 and August 2009	231	2	Mobi-C	62.0	Segmental ROM	↓ (≥grade II, except grade III HO in the single-level cervical total disc replacement group)

HO, heterotopic ossification; ROM, range of motion; ↓, inverse association; ↔, no significant association; ↑, positive association.

disc was less stable than that in intact cervical spine during flexion–extension movement [36]. Another radiological study examining Prestige LP and ProDisc-C prostheses showed that COR-Y (directed perpendicular to the endplate) was significantly different from the healthy controls while COR-X (directed along the x-axis of superior endplate of the lower vertebral body) was significantly more anterior to the control group [37]. Significant changes in postoperative COR-X and COR-Y have been reported in another study examining ProDisc-C and Synergy prostheses [35]. Indeed, a more posterior COR was correlated with a higher rate of HO [20]. Tu et al. [2] suggested that surgeons should place implants at the center of the disc space, with symmetrical disc space from the sides. However, such suggestion did not take the physiological COR in human spine into consideration. In general, finite axis of rotation is situated inferior to the intervertebral disc and posterior to the center of the endplate [38,39]. Moreover, from C1 to C7, axis of rotation gradually moves more superiorly and anteriorly [38,39]. Thus, COR of each cervical level is different from that of the other cervical levels.

To summarize, evidence on whether CTDR can restore cervical kinematics back to normal is lacking. While CTDR with Prestige prosthesis was found more compatible to physiological kinematics of spine than the Bryan disc, both types of prosthesis simulated significantly different spinal kinematics from the healthy population [40]. Incompatibility of spinal kinematics after CTDR with physiological kinematics may, therefore, be an inducing agent of HO [41]. Notably, some biomechanical factors are associated with the development of HO in CTDR (Table 1).

Does Heterotopic Ossification Really Matter to Patients in Cervical Total Disc Replacement?

Evidence about the association between follow-up period and HO is conflicting. A retrospective study with an average of 36.9-month follow-up period showed that over time patients were more likely to develop new and more severe HO [42]. Strikingly, in a meta-analysis of 38 studies, the prevalence of HO was comparable among studies with 1–2-year, 2–5-year, and 5–10-year follow-up [43]. Also, there was no significant association between HO and the duration of follow-up. The conflicting results can be attributed to the inclusion of studies with long follow-up period in the meta-analysis.

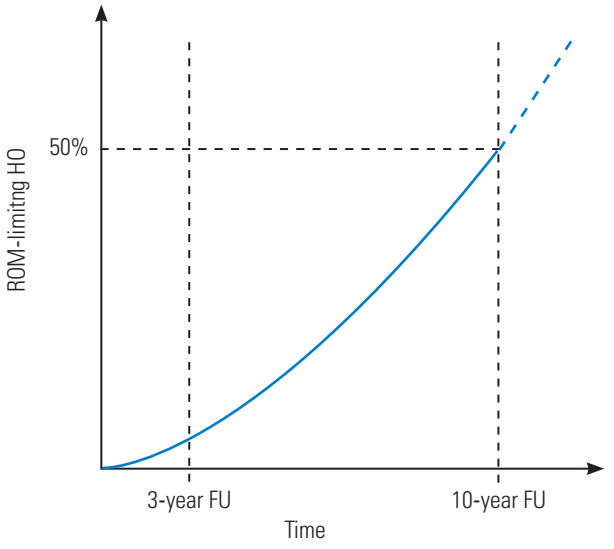

Fig. 2. The association between the rate of ROM-limiting HO and the duration of FU after CTDR. ROM, range of motion; HO, heterotopic ossification; CTDR, cervical total disc replacement; FU, follow-up.

In contrast to overall HO, the rate of ROM-limiting HO seemed to correlate with time [43]. A meta-analysis showed that the rates of ROM-limiting HO in studies with 2–5-year and 5–10-year follow-up were higher than those of studies with 1–2-year follow-up [43]. The positive association between ROM-limiting HO and follow-up duration is further supported by our meta-analysis of 94 clinical trials on CTDR [44]. There was 0.63% increase of ROM-limiting HO for every increase of one month in the follow-up time [43]. Given long enough follow-up time after CTDR, all prosthesis may eventually develop ROM-limiting HO (Fig. 2). However, patients are unlikely to develop ROM-limiting HO shortly after CTDR. In studies with an average or mean follow-up shorter than 3 years, most reported no cases of ROM-limiting HO [28,45-62]. The median HO-free period was 27.1 months [63].

Although CTDR was designed to preserve segmental ROM and prevent the development of ASD, deviation of postoperative ROM from the preoperative values has been reported in clinical trials. Segmental ROM has been reported to decrease shortly after surgery and could persist up to 6-month follow-up in some studies [30,58,64-67]. Factors that might have led to the decrease in segmental ROM reported in the studies include the following: (1) the cohort of subjects has greater impairment in ROM preoperatively [68]; (2) fear of moving the neck to the extremes

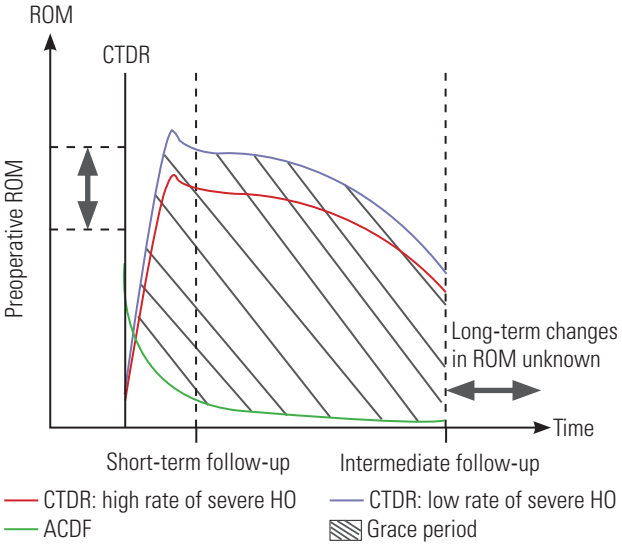

Fig. 3. Grace period of HO formation. ROM of the operated segment may be unchanged or more mobile in comparison with preoperative ROM in short-term follow-up. ROM tends to decrease as follow-up time increases. There is a "grace period" where operated segment remains mobile before ROM-limiting HO forms. HO, heterotopic ossification; ROM, range of motion; CTDR, cervical total disc replacement; ACDF, anterior cervical discectomy and fusion.

of flexion and extension during dynamic X-ray; (3) and postoperative neck pain [30]. However, in longer term follow-up, ROM became comparable to preoperative values [30,58,64-67]. Other studies have reported preserved segmental ROM compared with preoperative ROM at 1–2-year [14,20,55,69-72], 3–5-year [73-80], 7-year [81], and 8-year follow-up [82]. Interestingly, some studies even reported significantly more mobile segments over 1-year follow-up [48] than at 5-year follow-up [83]. Of note, the rate of grade IV HO reported ranges from 0% to 2.9% in these studies [48,83], which are lower than those reported in meta-analyses of CTDR [43,84]. Since grade IV HO is known to bridge across the disc space and significantly restricts the segmental ROM, the low prevalence of grade IV HO in these trials may explain the increased segmental ROM (Fig. 3).

On the contrary, in studies with intermediate or long-term follow-up, ROM tends to significantly decrease in relation to preoperative ROM. Segmental ROM significantly decreased at 2-year [52,68], 4-year [85], >6-year [15], average 8-year [17], and average 10-year follow-up [86]. As the severity of HO and the incidence of ROM-limiting HO correlated with the length of the follow-up period [42,43], the formation of ROM-limiting HO may be accounted for the reduced ROM reported in clinical trials with intermediate to long-term follow-up. Indeed, the segmental ROM was reduced in patients with HO [5,17,18] and those with grade II or higher HO [22]. The decrease in segmental ROM was significantly higher in patients who developed ROM-limiting HO, compared to patients with ROM-preserving HO and those without HO [5]. Also, HO formation was correlated with reduced ROM in a study with over 6-year follow-up [15], but not over 5-year follow-up [19]. Similarly, ROM-limiting HO was inversely associated with segmental ROM [21].

Overall, the segmental ROM shortly after CTDR is comparable or even higher than that before surgery. As shown in Fig. 3, segmental ROM tends to be preserved in short- to intermediate-term follow-up [14,20,30,55,58,64-67,69-82], and the prosthesis continues to exercise its biomechanical functions. As the follow-up time increases, there will be an increased rate of ROM-limiting HO, which is functionally similar, if not identical, to the fused segments in ACDF [43]. While HO is gradually fusing the spinal segments, the formation of ROM-limiting HO is preceded by years of preservation of segmental mobility [14,20,30,55,58,64-67,69-82]. The years of preserved segmental mobility may serve, in theory, as a "grace period" to delay the formation of ASD in CTDR, compared with ACDF (Fig. 3). Although a meta-analysis showed that the rate of adjacent segment disease is significantly lower in CTDR than ACDF at 2-year follow-up, intermediate- to long-term data are lacking [87]. In addition, HO formation does not seem to significantly jeopardize clinical outcomes of patients in short- to intermediate-term follow-up [88]. Therefore, CTDR may confer patients, at least, non-inferior clinical outcomes in short- to intermediate-term follow-up, in comparison with ACDF. Long-term data on the clinical and radiological outcomes are warranted to ascertain the safety profile of CTDR.

Conclusions

The biomechanical parameters of the operative segment and cervical spine are altered following CTDR. Some studies demonstrated that the changes in biomechanical factors were associated with the prevalence and/or severity of HO; however, a causal relationship between these factors remains unproven. Regardless, HO formation has not been shown to correlate with clinical outcomes in meta-analyses of short- to intermediate-term follow-up studies. CTDR preserves segmental mobility for years and

confers patients a grace period to delay the formation of ASD, compared with ACDF. Clinical trials with long-term follow-up are warranted to confirm the extended efficacy of CTDR in light of increased rates of ROM-limiting HO.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Author Contributions

All authors participated in the conception of the manuscript. N.H. led the drafting under the supervision of K.P. and R.J.M. All authors revised the manuscript critically for important intellectual content.

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