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Single-Level Rigid Fixation Combined with Coflex: A Biomechanical Study

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Background: The purpose of this biomechanical *in vitro* study was to compare the kinematics and intradiscal pressure achieved with 2 methods: L4–L5 pedicle screw-rod fixation (PSRF) with an upper L3–L4 Coflex device and L4–L5 PSRF alone. The results were used to characterize the biomechanics of the topping-off operation with a Coflex device for the lumbar motion segment adjacent to single-level rigid fixation.

Material/Methods: Six human cadaveric spine specimens were biomechanically tested *in vitro* (6 males, 0 females). The 3-dimensional specimen motion in response to applied loads during flexibility tests was determined. Loads were applied along anatomic axes to induce flexion-extension, lateral bending, and axial rotation. All specimens were first studied with intact lumbar motion segments, then with L4–L5 PSRF alone, and finally with L4–L5 PSRF with an upper L3–L4 Coflex device. A non-paired comparison of the 3 configurations under 3 different conditions was made.

Results: PSRF, with or without a Coflex device, significantly increased the range of motion (ROM) in the upper adjacent motion segments in all directions of loading. The intradiscal pressure (IDP) changed slightly. A correlation analysis showed that the ROM and IDP are significantly positively correlated. The application of the upper motion segment of the Coflex device provided greater stability in all directions of motion than did PSRF alone, particularly for extension ($p<0.05$), while use of a Coflex device did not significantly decrease the IDP compared with PSRF alone ($p>0.05$).

Conclusions: These results suggest that L4–L5 PSRF with an L3–L4 Coflex device is more stable than L4–L5 PSRF alone. PSRF with an upper Coflex device is a promising alternative to PSRF alone. Based on these biomechanical tests, it might be considered a protective method to prevent adjacent segment degeneration (ASD), although some limitations with this *in vitro* study must be addressed in the future.

MeSH Keywords: **Biomechanical Phenomena • Spinal Diseases • Surgical Fixation Devices**

Abbreviations: **PSRF** – pedicle screw-rod fixation; **ROM** – range of motion; **IDP** – intradiscal pressure; **ASD** – adjacent segment degeneration

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Background

Adjacent segment degeneration (ASD) is a common complication of the adjacent motion segment after lumbar interbody fusion. It generally refers to the abnormal alteration that occurs in the segment adjacent to the fused segment. It has been reported that the incidences of ASD in radiography and symptomatology are 8–100% and 5.2%-18.5%, respectively [1]. Current risk factors for ASD include age, different fusion methods, physiological curvature of the spine, and anatomic abnormalities [2,3]. Some studies have suggested that lumbar instability, advanced age, spinal degeneration, and multisegment spinal fusion can increase the incidence of ASD to some extent [4,5]. From this viewpoint, degeneration is more likely to occur in upper adjacent segments than in lower ones, which is attributed to the compensatory increase of post-surgery adjacent motility and increased loading on the disc and facet joints [1,6].

Moreover, ASD causes long-term dissatisfaction after spine fusion in 20–40% of patients. It can be difficult to treat ASD with surgery due to previous lumbar fusion [1,4,7]; therefore, current research is focused on preventing the disease and delaying its progression [8,9]. Interspinous dynamic fixation provides a new method for preventing ASD after lumbar interbody fusion. Clinical applications, such as the 'topping-off operation' and filling the 'transition zone' (from the rigid segment to the non-fused area), are already in use. However, little attention has been focused on the lower motion segment adjacent to the fused spine, which is a clinical concern.

This study was conducted to determine the biomechanical changes in the adjacent segment by measuring the ROM and IDP of the human spine under PSRF combined with a Coflex device (Paradigm Spine, Wurmlingen, Germany). Previous studies have revealed that an increased ROM of the adjacent segment after PSRF is to some extent due to a compensatory mechanism [1,10]. It has been hypothesized that L4–L5 PSRF with an upper L3–L4 Coflex device is more stable than L4–L5 PSRF alone. The objective of this biomechanical *in vitro* study was to compare the segmental stability and intradiscal pressure achieved with 2 methods: PSRF with an upper Coflex device and PSRF alone. The results were used to characterize the biomechanics of the topping-off operation with a Coflex device for the lumbar motion segment adjacent to single-level rigid fixation.

Material and Methods

Specimen preparation

Six fresh human cadaveric lumbar spine specimens were provided by the Department of Anatomy of the Medical College at Fudan University. The exclusion criteria were spine deformity, tumor, or osteoporosis. The mean age was 39.0±5.3, and there were 6 males and 0 female cadavers. The specimens were kept in double-sealed plastic bags and stored at –20°C. Specimens were carefully cleaned of muscular tissue while keeping all ligaments, joint capsules, and discs intact. The implants were the pedicle screw fixation (Moss Miami System, DePuy Spine Inc, Raynham, Massachusetts, USA), the interbody fusion cage (PEEK, the Shanghai minimally invasive medical device company, Shanghai, China), and the interspinous dynamic device (Coflex, GE Medical Company, USA). The intact specimens were defined as group A.

The pedicle screw system was implanted in the L4–L5 segment in a conventional manner, and a complete discectomy was then performed using rongeurs and curettes with a transforaminal approach. The PEEK cages were sized to fit snugly within the disc space (group B).

The pedicle screw system was implanted in the same way as the L4–L5 segment, and the interspinous ligaments of the L3–L4 segment were then removed to insert the Coflex device. A trial inserter was used to determine the optimal size of the Coflex implant. The probe was used to measure the distance between the Coflex device and the ligamentum flavum, and the size of the implant was determined by the interspinous distance of each specimen. Finally, the Coflex wings were tightened with a clamp (group C). A total of 6 cases, distributed among the 3 groups, were studied.

Biomechanical testing

Specimens in all 3 groups were studied using standard pure moment flexibility tests (Figure 1). For these tests, an apparatus was used in which a system of cables and pulleys imparts nondestructive, nonconstraining torque in conjunction with a standard biomechanical test system (Zwick/Roell, Germany, provided by the Mechanics Laboratory of Shanghai University). An axial load of 500 N was applied to the specimen using a Zwick/Roell universal testing machine [11] in a rostral-to-caudal direction. A torque of ±8 Nm was applied in all directions (flexion-extension, lateral bending, and axial rotation) at a speed of 0.5°/s. Several studies have used different torques [12–18], ranging from 3.75 Nm to 10.6 Nm. Based on the literature, in our pre-experiment we used torque of 4 different values: 4 Nm, 6 Nm, 8 Nm, and 10 Nm. According to the preliminary results, we found that the torque of 8 Nm is the minimum value to exert the ability to the utmost extent in different motions, such as lateral bending and extension-flexion; therefore, we chose a torque of 8 Nm. A catheter was positioned to the left of the disc at both the L3–L4 and L5–S1 segments. The catheter was held in place during all tests. A pressure sensor (3200, SAMBA Sensors, Sweden [19]) was

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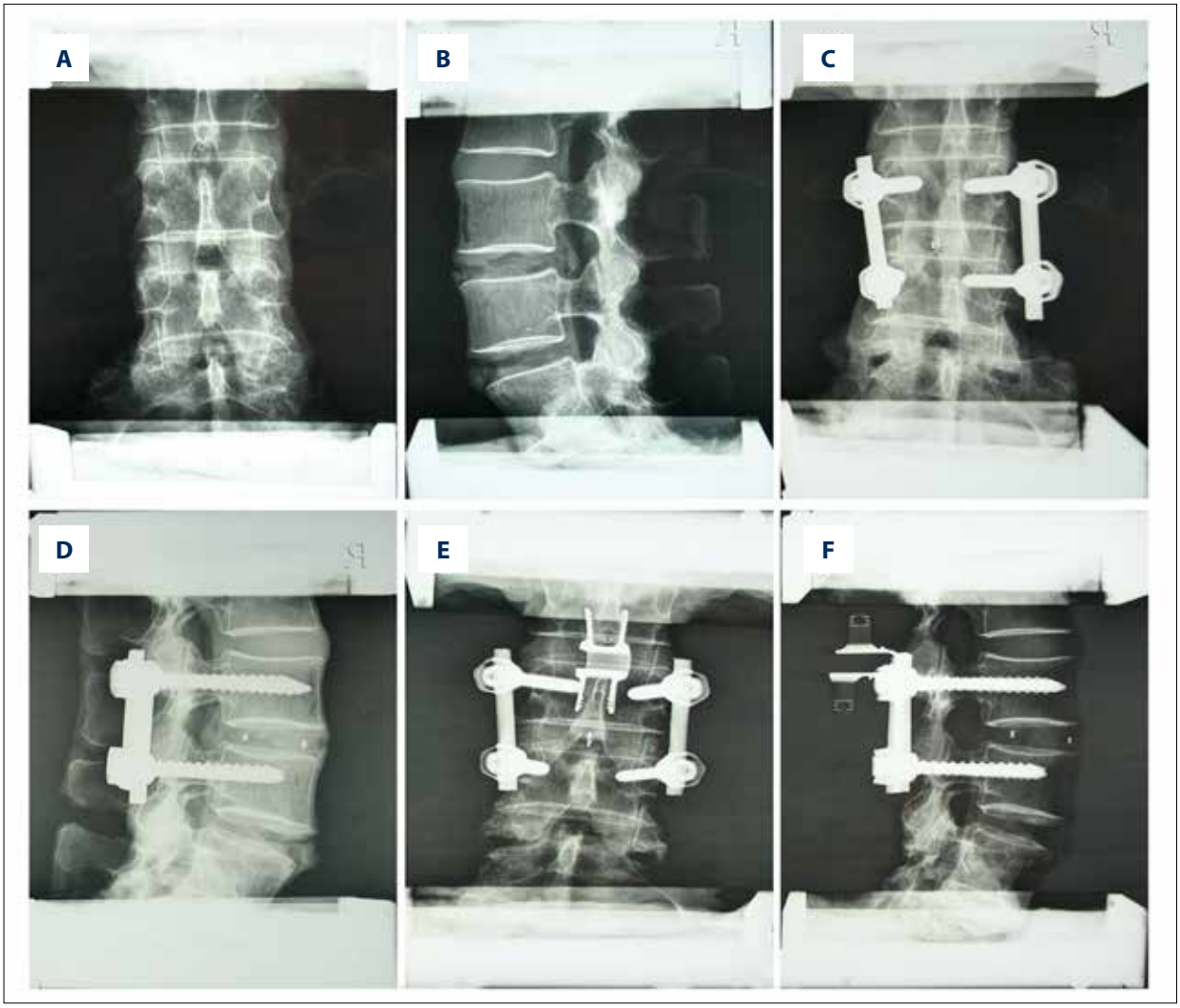

Figure 1. X-ray examinations of the different groups under the biomechanical test. (**A, B**) Intact lumbar motion segment (Group A) under the biomechanical test in the X-ray examination; (**C, D**) Pedicle screw-rod fixation in the L4–L5 segment (group B) under the biomechanical test in the X-ray examination; (**E, F**) Pedicle screw-rod fixation (PSRF) in the L4–L5 segment with a Coflex device in the L3–L4 segment (group C) under the biomechanical test in the X-ray examination.

inserted to the end of the catheter. Measurements of different motions were taken for each specimen.

Before the experiment, loading and unloading were carried out twice in all directions for each specimen. Cameras placed in appropriate positions were used to record the spatial position of the movement under the third loading to collect data, including the ROM and IDP, for analysis. All measurements were performed in the Mechanics Laboratory of Shanghai University on the same day.

Statistics analysis

The statistical analysis was performed with Statistical Product and Service Solutions (version 19.0 for Windows; SPSS, Chicago, IL, USA). The mean ± standard deviation (SD) is used to present measurement data when it satisfies the criteria for normality with $P>0.10$. Otherwise, data are expressed as the median (interquartile range, IQR). Statistical analyses between groups were performed using an independent samples t-test when data satisfied the criteria for normality and homogeneity of variance. The chi-square test was used for count data analysis. A value of $P<0.05$ was considered statistically significant.

Results

In the PSRF specimens (group B), the mobility of the upper adjacent segment (L3–L4) significantly increased compared to the intact specimen (group A) (Table 1, $P<0.05$). The lower

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Table 1. ROM of the L3–L4 segment under 8.0 Nm torque (mean ± standard deviation, n=6, unit: degree).

Motion	Group A	Group B	Group C
Flexion	2.93±0.26	3.47±0.42*	3.31±0.26*,##
Extension	2.41±0.23	2.75±0.30*	2.43±0.19**,#
Lateral bending	2.62±0.29	2.92±0.20*	2.90±0.17*,##
Axial rotation	2.15±0.24	2.34±0.14*	2.23±0.14#,##

ROM – range of motion; * Compared with Group A, P<0.05; ** Compared with Group B, P<0.05; # Compared with Group A, P>0.05; ## Compared with Group B, P>0.05.

Table 2. ROM of the L5–S1 segment under 8.0 Nm torque (mean ± standard deviation, n=6, Unit: degree).

Motion	Group A	Group B	Group C
Flexion	3.34±0.40	3.72±0.30#	3.60±0.30#,##
Extension	2.62±0.35	2.84±0.25#	2.96±0.27#,##
Lateral bending	2.87±0.40	3.10±0.29#	3.13±0.30#,##
Axial rotation	2.32±0.23	2.46±0.20#	2.47±0.15#,##

ROM – range of motion; * Compared with Group A, P<0.05; ** Compared with Group B, P<0.05; # Compared with Group A, P>0.05; ## Compared with Group B, P>0.05.

Table 3. IDP of the L3–L4 segment under 8.0 Nm torque (mean ± standard deviation, n=6, Unit: kPa).

Motion	Group A	Group B	Group C
Flexion	10.20±1.22	12.02±1.69*	11.73±1.17*,##
Extension	8.94±0.98	10.82±1.51*	9.43±1.32**,#
Lateral bending	9.42±0.69	11.26±1.13*	11.13±1.00*,##
Axial rotation	9.56±0.91	11.01±0.86*	10.91±0.71*,##

IDP – intradiscal pressure; * Compared with Group A, P<0.05; ** Compared with Group B, P<0.05; # Compared with Group A, P>0.05; ## Compared with Group B, P>0.05.

adjacent segment (L5–S1) also increased in mobility, but the difference was not statistically significant (Table 2, P>0.05).

The PSRF with the upper segment Coflex device specimens (group C) had significantly reduced flexion and lateral bending mobility compared to group B in the upper adjacent segment (L3–L4) (Table 1, P <0.05), but comparison of the extension and axial rotation mobility between the 2 groups showed no significant difference (Table 1, P>0.05).

The increase of the IDP differed significantly between the 2 groups (group A and B) in both the upper and lower adjacent segments (L3–L4, L5–S1) (Table 3, P< 0.05). With the addition of the Coflex device (group C), the IDP in the upper adjacent segment (L3–L4) decreased significantly compared to group B (Table 3, P<0.05); however, the IDP in the lower adjacent segment (L5–S1) increased, but not significantly (Table 4, P>0.05).

Discussion

Topping-off and the optional dynamic fixation device

Many spinal nonfusion techniques are used to prevent the degeneration of the segment adjacent to the fused spine, which maintains the buffer zone. One such technique is the 'topping-off' technique, which include Dynesys, Isobar, Bioflex, Accuflex [20], and Coflex devices; the first 3 techniques are based on pedicle screw instrumentation. Considering that severe multifidus injury caused by the preparation for pedicle screws implantation or possibly a loosened pin tract may influence the surgical procedure, Bartagnoli et al. [21] graded this technique as the 6th level in escalation therapy for lumbar degeneration disease; in other words, it is close to the fusion technique. We believe that the Coflex technique has the following advantages: 1) It can avoid fusion of segments adjacent

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Table 4. IDP of the L5–S1 segment under 8.0 Nm torque (mean ± standard deviation, n=6, Unit: kPa).

Motion	Group A	Group B	Group C
Flexion	10.51±1.27	11.72±0.94*	11.33±0.96#,##
Extension	9.23±0.85	10.17±0.66*	10.07±0.17#,##
Lateral bending	9.52±0.88	10.22±0.71*	10.37±0.93#,##
Axial rotation	9.72±0.91	10.53±0.79*	10.71±0.88#,##

IDP – intradiscal pressure; * Compared with Group A, P<0.05; ** Compared with Group B, P<0.05; # Compared with Group A, P>0.05; ## Compared with Group B, P>0.05.

to the fused spine and therefore minimize fusion length and surgical trauma. 2) It can constrain lumbar hyper-flexion and hyper-extension and protect the adjacent segments. 3) It is easy to implant and can minimize the risk of a second surgery. The interspinous ligament is sectioned before the implantation of the Coflex device, which is implanted in a pre-compressed mode in the interspinous ligament, thereby maintaining the stability of internal fixation. This device can not only be subjected to the pressure of the upper and lower spinous process, which mainly manifests as dynamic changes according to the specific spine flexion and extension, but also promises other mobility improvements, such as rotation and lateral bending.

Biomechanics of Coflex with rigid fixation on upper adjacent segments

The results of this study indicate that the ROM and IDP in the upper adjacent segments (L3–L4) in the L4–L5 PSRF group (group B) significantly increased in all directions, showing that the upper adjacent segment after rigid fixation will suffer more from increased loading and show decreased flexibility under an identical load. William et al. [22] stated that the increase in hydrostatic pressure affects the synthesis of collagen and proteoglycan, resulting in disc degeneration. In this study, the upper adjacent segments of PSRF have a greater IDP, which could accelerate the degeneration of the intervertebral disc.

Combined with the Coflex device as group C, the ROM in the upper adjacent segments (L3–L4) had no significant difference in lateral bending compared with group B, but it was greater than in group A. Nevertheless, the ROM in flexion, extension, and rotation decreased significantly compared with group B. The ROM in group B in flexion and rotation, but not extension, was greater than that in group A. The ROM in flexion in the L3–4 segment was lower in group C than in group B. This could be explained in 2 ways. First, the Coflex device in the interspinous space exerts distraction in the corresponding space, thereby manifesting the tendency of anteflexion and reducing the ability of flexion. Second, the crimping of the wings to the spinous process creates an extra restriction to flexion. All of the above results showed that the Coflex device could effectively restrict extension movement and moderately restrict flexion and rotation movements, but plays no role in lateral bending movement. This is consistent with the findings of other studies [17]. In the present study, the data also showed that the restriction abilities of the Coflex device for different extension movements may be stronger than they are for flexion movements.

The posterior column of the spine, and particularly the interspinous ligament, plays a crucial role in maintaining stability and restricting hyper-flexion. Ligament injuries during the Coflex implant procedure have unavoidably negative effects on function, particularly in restricting extension. The IDP in group C was nearly identical to that in group B in flexion and lateral bending. In terms of extension movement, the IDP was slightly different between groups B and C.

Biomechanics of Coflex with rigid fixation on lower adjacent segments

Some scholars [23,24] believe that the upper segments adjacent to the fused spine are more prone to stress than the lower ones. However, Sheno et al. [25] performed a biomechanical comparison of the upper and lower segments adjacent to the fused spine and found that lower segments suffered greater stress than upper ones in bovine lumbar functional spinal units *in vitro*. However, there is no consensus on this issue. In this study, in PSRF combined with an upper Coflex device specimens (group C), the IDP exhibited lateral bending and axial rotation, and the ROM in terms of extension, lateral bending and axial rotation on the lower adjacent segment increased to some extent compared to group B, although the difference was not significant (P>0.05). We hypothesize that our results are related to increased stiffness of the spine due to the interspinous device. This phenomenon may accelerate the long-term degeneration of the lower adjacent segment. Considering our limited sample size, more studies are required to support our conclusion.

Limitations of the study

This study has several limitations. First, the use of cadaveric spine *in vitro* study itself brings about inevitable bias, because

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it is impossible to determine the effect of paravertebral muscles and intra-abdominal pressure on this experiment. An advanced sensor apparatus might be applied to patients who undergo spinal fusion, and therefore we should monitor meaningful parameters in a follow-up study to obtain data that are closest to the actual values. Second, the sample size in the current study limits the value of the results. A study with a larger sample size is necessary. Third, our study focused only on IDP in the adjacent segment. The facet joints, which are a crucial component of the 'triple joint complex', should be evaluated in future research. Finally, our study did not focus on the degeneration of intervertebral disc, which also requires future study.

Conclusions

In summary, this study suggests that PSRF with an upper Coflex device is a promising alternative to PSRF alone. A Coflex device is more stable than PSRF alone. Although it increased stress on the lower adjacent segment, which might potentially accelerate the long-term degeneration of the lower segment, it might be considered a protective method to prevent ASD, although some limitations with the biomechanical *in vitro* study must be addressed in the future.

Conflict of interest

None of the authors of this paper have any financial or personal relationships with other people or organizations that could inappropriately influence or bias the content of the paper. The authors indicate no potential conflicts of interest. The authors alone are responsible for the content and writing of this paper.

References:

1. Park P, Garton HJ, Gala VC et al: Adjacent segment disease after lumbar or lumbosacral fusion: review of the literature. Spine, 2004; 29(17): 1938–44
2. Okuda S, Iwasaki M, Miyauchi A et al: Risk factors for adjacent segment degeneration after PLIF. Spine, 2004; 29(14): 1535–40
3. Lee CS, Hwang CJ, Lee SW et al: Risk factors for adjacent segment disease after lumbar fusion. Eur Spine J, 2009; 18(11): 1637–43
4. Yang JY, Lee JK, Song HS: The impact of adjacent segment degeneration on the clinical outcome after lumbar spinal fusion. Spine, 2008; 33(5): 503–7
5. Videbaek TS, Egund N, Christensen FB et al: Adjacent segment degeneration after lumbar spinal fusion: the impact of anterior column support: A randomized clinical trial with an eight- to thirteen-year magnetic resonance imaging follow-up. Spine, 2010; 35(22): 1955–64
6. Chen CS, Cheng CK, Liu CL, Lo WH: Stress analysis of the disc adjacent to interbody fusion in lumbar spine. Med Eng Phys, 2001; 23(7): 483–91
7. Phillips FM, Carlson GD, Bohlman HH, Hughes SS: Results of surgery for spinal stenosis adjacent to previous lumbar fusion. J Spinal Disord, 2000; 13(5): 432–37
8. Fu L, France A, Xie Y et al: Functional and radiological outcomes of semi-rigid dynamic lumbar stabilization adjacent to single-level fusion after 2 years. Arch Orthop Trauma Surg, 2014; 134(5): 605–10
9. Grasso G, Giambartino F, Iacopino DG: Clinical analysis following lumbar interspinous devices implant: Where we are and where we go. Spinal Cord, 2014; 52(10): 740–43
10. Zhu Z, Liu C, Wang K et al: Topping-off technique prevents aggravation of degeneration of adjacent segment fusion revealed by retrospective and finite element biomechanical analysis. J Orthop Surg Res, 2015; 28; 10: 10
11. Tremblay J, Brailovski V, Mac-Thiong JM, Petit Y: Factors affecting intradiscal pressure measurement during *in vitro* biomechanical tests. Scoliosis, 2015; 11(2): 10(Suppl 2): S1
12. Nachemson AL, Schulz AB, Berkson MH: Mechanical properties of human lumbar spine motion segments. Part III: Influence of age, sex, disc level and degeneration. Spine, 1979; 4(1): 1–8
13. Rohlmann A, Neller S, Claes L et al: Influence of a follower load on intradiscal pressure and intersegmental rotation of the lumbar spine. Spine, 2001; 26: E557–61
14. White AA, Panjabi MM: Clinical biomechanics of the spine, Second Edition, Philadelphia, 1990
15. Dahl MC, Freeman AL: Kinematic and fatigue biomechanics of an interpositional facet arthroplasty device. Spine J, 2015; 11: 24
16. Bartanusz V, Harris J, Moldavsky M et al: Short segment spinal instrumentation with index vertebra pedicle screw placement for pathologies involving the anterior and middle vertebral column is as effective as long segment stabilization with cage reconstruction: A biomechanical study. Spine, 2015; 40(22): 1729-36
17. Wilke HJ, Drumm J, Haussler K, Mack C, Steudel WI, Kettler A: Biomechanical effect of different lumbar interspinous implants on flexibility and intradiscal pressure. Eur Spine J, 2008; 17(8): 1049–56
18. Schmoelz W, Huber JF, Nydegger T et al: Dynamic stabilization of the lumbar spine and its effects on adjacent segments. J Spin Disord Tech, 2003; 16(4): 418–23
19. Mahmoud AS, Nick S, David W: Effects of procedures of remineralization around orthodontics bracket bonded by self-etching primer on its shear bond strength. J Orthod Sci, 2012; 1(3): 63–68
20. Reyes-Sanchez A, Zarate-Kalfopulos B, Ramirez-Mora I et al: Posterior dynamic stabilization of the lumbar spine with the Accuflex rod system as a stand-alone device: Experience in 20 patients with 2-year follow-up. Eur Spine J, 2010; 19(12): 2164–70
21. Bertagnoli R, Yue JJ, Shah RV et al: The treatment of disabling multilevel lumbar discogenic low back pain with total disc arthroplasty utilizing the ProDisc prosthesis: A prospective study with 2-year minimum follow-up. Spine, 2005; 30(19): 2192–99
22. Williams FM, Bansal AT, van Meurs JB et al: Novel genetic variants associated with lumbar disc degeneration in northern Europeans: A meta-analysis of 4600 subjects. Ann Rheum Dis, 2013; 72(7): 1141–48
23. Dennison CR, Wild PM, Byrnes PW et al: *Ex vivo* measurement of lumbar intervertebral disc pressure using fibre-Bragg gratings. J Biomech, 2008; 41(1): 221–25
24. Hasegawa K, Kitahara K, Hara T et al: Evaluation of lumbar segmental instability in degenerative diseases by using a new intraoperative measurement system. J Neurosurg Spine, 2008; 8(3): 255–62
25. Shono Y, Kaneda K, Abumi K et al: Stability of posterior spinal instrumentation and its effects on adjacent motion segments in the lumbosacral spine. Spine, 1998; 23(14): 1550–58

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