

REVIEW

A review of the pathomechanism of forward slippage in pediatric spondylolysis : The Tokushima theory of growth plate slippage

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Abstract : Spondylolysis is a stress fracture of the pars interarticularis, which in some cases progresses to spondylolisthesis (forward slippage of the vertebral body). This slip progression is prevalent in children and occurs very rarely after spinal maturation. The pathomechanism and predilection for children remains controversial despite considerable clinical and basic research into the disorder over the last three decades. Here we review the pathomechanism of spondylolytic spondylolisthesis in children and adolescents, and specifically the Tokushima theory of growth plate slippage developed from our extensive research findings. Clinically, we have observed the slippage site near the growth plate on MRI ; then, using fresh cadaveric spines, we found the weakest link against forward shear loading was the growth plate. We subsequently developed an immature rat model showing forward slippage after growth plate injury. Moreover, finite element analysis of the pediatric spine clearly showed increased mechanical stress at the growth plate in the spondylolytic pediatric spine model compared with the intact pediatric spine. Thus, spondylolysis progresses to spondylolisthesis (forward slippage) in children and adolescents with the growth plate as the site of the slippage. Repetitive mechanical loading on to the growth plate may serve to separate the growth plate and subsequently progress to spondylolisthesis. *J. Med. Invest.* 62 : 11-18, February, 2015

Keywords : Spondylolysis, spondylolisthesis, growth plate, adolescents, children

INTRODUCTION

Lumbar spondylolysis, a stress fracture of the pars interarticularis, commonly occurs in children and adolescents (1-5). Few articles have described fresh stress fractures at the pars in adults over 20 years of age (6). Once pseudoarthrosis occurs, spondylolysis may progress to spondylolisthesis, involving forward slippage of the lytic spine. Similarly, the literature contains numerous reports of slippage in children and adolescents, but very few after spinal maturation in adults (7-12). It would seem reasonable then to assume that such slippage would occur at a specific anatomical location in pediatric patients ; however, the underlying pathomechanism is not yet completely understood. Over the last 30 years, the Department of Orthopedics at Tokushima University, Japan, has conducted various clinical and basic research into the slippage mechanism in children and adolescents. In this review article, we describe the pathomechanism of slippage in the spondylolytic spine and review the Tokushima theory of growth plate slippage that was developed over decades of research in our department.

SPONDYLOLYSIS : THE BASIC LESION IN SPONDYLOLISTHESIS

Figure 1 shows a three-dimensional posterior view and axial CT

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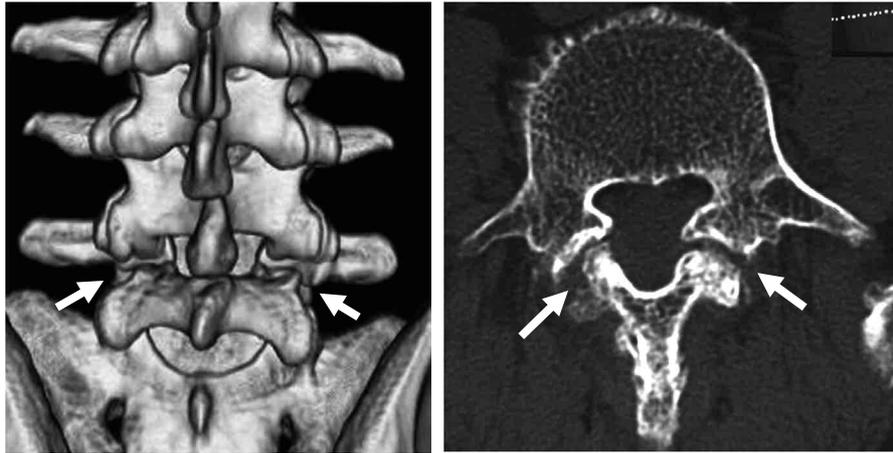
scan of lumbar spondylolysis, with arrows indicating the pars defects. Initially, spondylolysis was considered a congenital anomaly. However, current consensus is that the pathogenesis of spondylolysis involves a stress fracture at the pars interarticularis (3), based on the following evidence.

1 : Spondylolysis has never been observed in neonates (13).

2 : Rosenberg reported that spondylolysis does not occur in non-ambulatory patients (14), and Sakai *et al.* reported lumbar spondylolysis occurs only in patients with cerebral palsy who have involuntary repetitive movements of the trunk in daily life (15).

3 : The time course of lumbar spondylolysis from occurrence to progression to pseudoarthrosis is similar to that of stress fracture of the long bone. As shown in Figure 2, our group at Tokushima University have proposed classifying spondylolysis into three stages-early, progressive, and terminal (2, 5, 16-20). In the early stage, the defect is faint and seen only as bone absorption on CT ; in the progressive stage, the defect manifests as complete fracture of the pars interarticularis ; and in the terminal stage, the defect has the features of pseudoarthrosis.

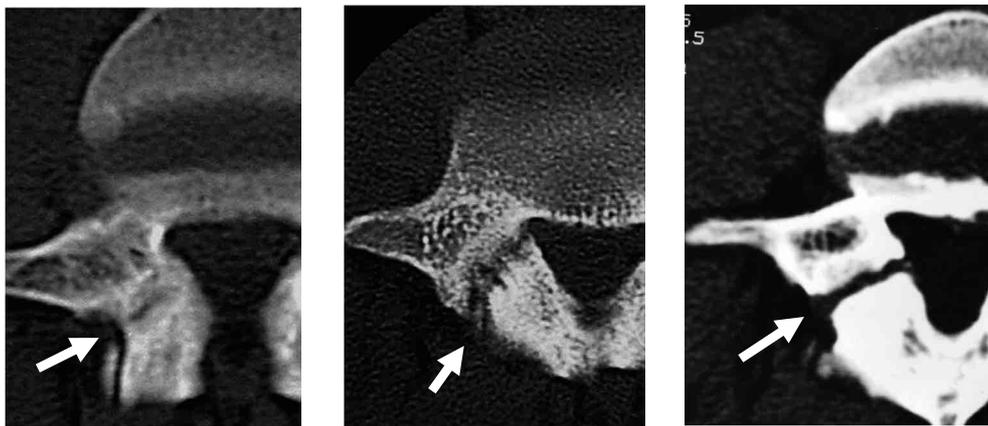
As the motions of extension and rotation may hold a clue to the pathomechanism of the pars stress fracture (21, 22), a brace is often recommended to immobilize the spine and thus restrict spinal rotation and extension (20). If spondylolysis is found in the early stage, the defect can heal osseously in about 90% of patients in around 3 months (20). However, the union rate decreases in the progressive stage, and when conservative treatment is not effective, the defect progresses to the terminal stage (pseudoarthrosis). The pediatric spine with terminal-stage spondylolysis could then progress to slippage.



(a) 3D-CT posterior view

(b) Axial CT

Figure 1 : Lumbar spondylolysis seen on (a)a three-dimensional CT and (b) axial CT. Arrows indicate the location of the pars defects.



(a) Early

(b) Progressive

(c) Terminal

Figure 2 : CT scans of the stages of lumbar spondylolysis proposed by Tokushima University research groups. (a) The early stage defect is faint and is only seen as bone absorption on CT. (b) The progressive stage defect involves a complete fracture of the pars interarticularis. (c) The terminal stage defect has features of pseudoarthrosis. Arrows indicate the location of the pars defects.

WHEN DOES SLIPPAGE OCCUR?

Once the pars defect is completed in the terminal stage of the spondylolysis, the vertebral body is no longer connected with the facet joint. Consequently, the vertebral body is likely to slip forward. Figure 3 shows plain radiographs and an MR image of isthmic spondylolysis, with the vertebral body showing forward slippage. Figure 3a shows moderate slippage, while Figure 3b,c shows severe slippage.

Slippage is rare after spinal maturation (7-12). Figure 4 shows the skeletal age of the lumbar spine through different stages. In the cartilaginous stage (Figure 4a), the secondary ossification center of the vertebral body is not seen radiographically. In this stage, the disc space looks wider than the vertebral body width, and the vertebral body has rounded corners of the vertebral body (arrows). In the apophyseal stage, the secondary ossification center is observed (arrows, Figure 4b). This stage typically involves the growth spurts

seen in adolescence. In the epiphyseal stage, the apophyseal ring fuses to the vertebral body, suggesting that the vertebra has reached maturation (Figure 4c). The edges of the vertebral body are now sharp and clearly different from those in the cartilaginous stage. Early studies reported that slippage is prevalent in children and adolescents but rare after spinal maturation (7-11), but there was little precise information on the relation between slippage and skeletal age at that time.

Our group were the first to report the relation between bony age on slippage based on data from 46 athletes aged under 18 in 2001 (12). The average follow-up period was 6.0 years. We found clear findings of slippage at certain bony ages (arrows, Figure 5) : first, from the cartilaginous stage to the apophyseal stage (80%, 16/20 cases ;) and second, from the cartilaginous stage to the epiphyseal stage(11.1%, 3/27 cases). Conversely, no slippage was seen after the epiphyseal stage in any of 22 patients with a mature spine. Thus, among pediatric patients with an immature spine

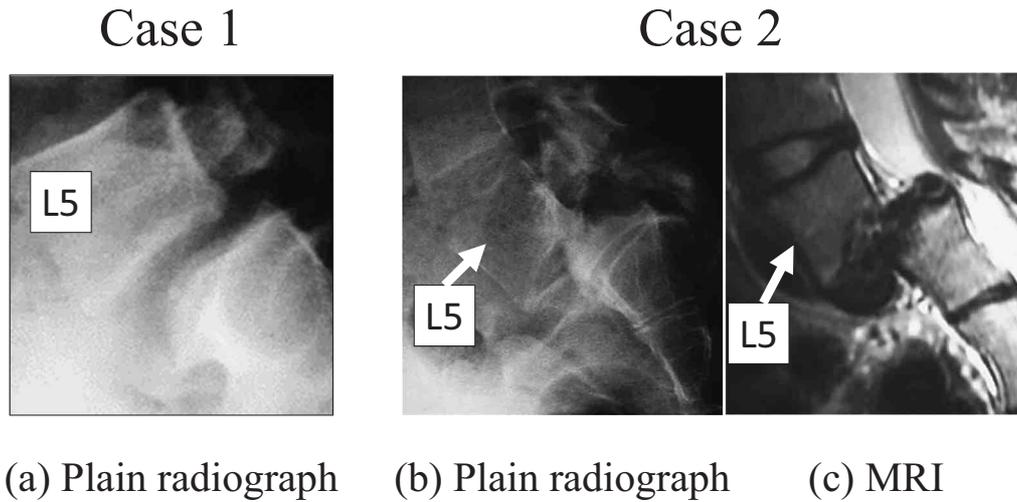


Figure 3 : Imaging of isthmic spondylolysis where the vertebral body has slipped forward. (a) Plain radiograph in Case1 shows a moderate slip. In Case 2, (b) a radiograph shows a high degree of slippage (arrow) and (b)MRI shows severe slippage (arrow).

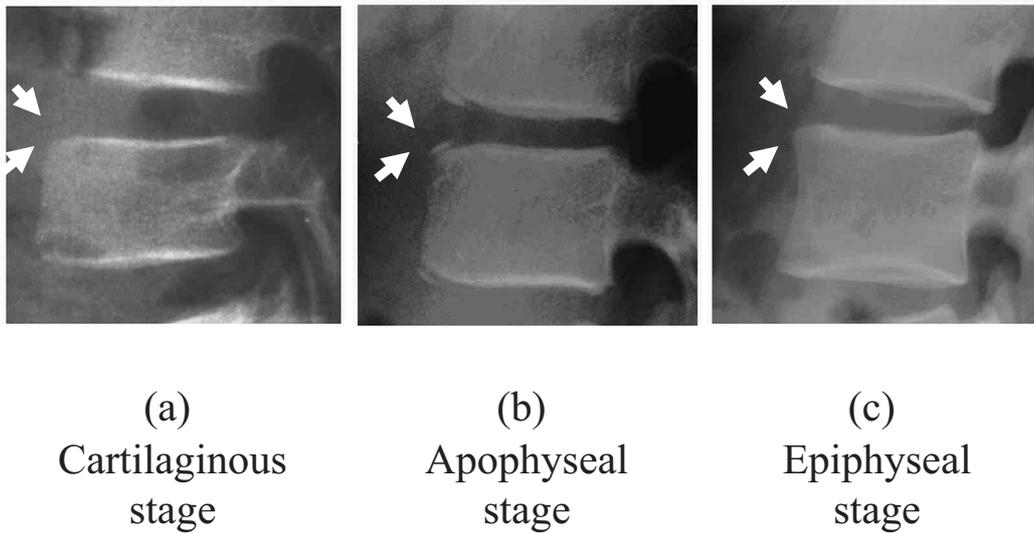


Figure 4 : Radiographs showing changes in the lumbar spine according to skeletal age. (a) In the cartilaginous stage, the secondary ossification center of the vertebral body is not evident, the disc space is wider than the vertebral body width, and the vertebral body has rounded edges (arrows). (b) The apophyseal stage shows the secondary ossification center (arrows). (c) In the epiphyseal stage, the apophyseal ring fuses to the vertebral body, suggesting that the vertebra has reached maturation and the vertebral body has sharp edges (arrows).

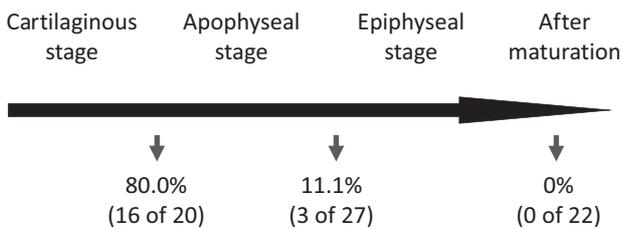


Figure 5 : Relation between bony age and slippage. Slippage was seen more frequently seen from the cartilaginous stage to the apophyseal stage (80.0%, 16/20 cases) and from the cartilaginous stage to the epiphyseal stage (11.1%, 3/27 cases). No slippage occurred after the epiphyseal stage (0/22 cases).

and terminal stage spondylolysis, maturation of the vertebral body appeared to be the most important factor for predicting consequent slippage. Clinically, this indicates that pediatric athletes with spondylolysis or slippage in whom spinal maturation has reached the epiphyseal stage can participate in sports activities without risk of further slippage. However, athletes with spinal maturation at the cartilaginous stage require special attention because they are at risk of further progression of the slippage. The results of a biomechanical study using fresh cadaveric calf spines that we published in the same year clearly supported our clinical findings (23). We found that the biomechanical strength of the growth plate against shear force is weak in the immature spine but increases with spinal maturation.

WHERE DOES SLIPPAGE OCCUR?

The location of slippage in pediatric patients with lumbar spondylolysis remains controversial. Radiologically, it is reasonable to consider that slippage occurs at the disc, as indicated by Saraste in 1993 (24). Seitsalo *et al.* (25) examined this theory by measuring disc degeneration on MR images in 227 patients with isthmic spondylolisthesis under 20 years of age. They found a significant association between degree of slippage and severity of disc degeneration. However, if this were actually the case, it would make it extremely difficult to explain why slippage is rare after spinal maturation.

In 1976, Farfan *et al.* (26) had suggested that slippage is prevalent in children mainly because of an epiphyseal separation following growth plate injury. Few other clinical and basic research studies were being conducted at that time to address where slippage was occurring. However, in the 1980s, a research group from Tokushima University (Chief researcher, Prof. Ikata, who is deceased in 2013) hypothesized that slippage in the pediatric spine with spondylolysis would not in fact be similar to that in the adult spine. Based on meticulous observations of MR images, they proposed that slippage in children might occur at a specific location between the cartilaginous and osseous endplates. In 1996, they reported, for the first time, this concept of endplate slippage as the Tokushima theory (27). Figure 6 shows the imaging findings of a pediatric patient with spondylolytic spondylolisthesis. Figure 6a is a plain radiograph indicating deformity after growth plate injury (arrows), and Figure 6b is an MR image of the slippage site in the endplate (arrows).

To prove this hypothesis, the Tokushima group started a collaborative biomechanical study with Prof. Vijay K. Goel of the University of Iowa in USA. Biomechanical investigations using fresh cadaveric calf spines (28) and baboon spines (29) confirmed in experimentally created spondylolysis that the weakest biomechanical link in the immature spine was the growth plate. Figure 7 shows radiographs and schematic explanations before and after slippage of the immature fresh calf spine (28). The data strongly indicated the growth plate as the location for forward slippage in pediatric patients with lumbar spondylolysis. These biomechanical results are in good agreement with the concept of endplate slippage put forward by the proposed Tokushima theory (27), since the growth plate of

the vertebral body is located between the cartilaginous and osseous endplates in children and adolescents. On the basis of this, the Tokushima theory of endplate slippage was modified to the Tokushima theory growth plate slippage. Now, with the inclusion of both clinical (27) and biomechanical (28, 29) findings, the Tokushima theory was seen to correspond to the hypothesis proposed by Farfan *et al.* two decades earlier (26).

As a next step, in 2000, Tokushima group attempted to create an animal model mimicking pediatric spondylolytic spondylolisthesis and used the model to conduct basic research (30-33). Using a 4-week-old rat, model because slippage is common at a youngest skeletal age (12), we performed posterior destabilization surgery, and evaluated slippage and subsequent spinal deformities on weekly radiographs until 3 weeks after the surgery. Spine samples were then evaluated histologically. The results are shown in Figure 8. Forward slippage was observed in 10% of the operated animals at 1 week after the surgery. At 3 weeks after the surgery, the spine showed a rounding and wedging deformity with a growth plate injury (Figure 8c, blue arrows in inset). Thus, after posterior destabilization, the immature rat model could mimic the spinal deformities in pediatric isthmic spondylolisthesis. The histological examination demonstrated growth plate separation. Thus, the model supported the Tokushima theory of growth plate slippage.

To further understand growth plate slippage, it was important to clarify the biomechanics of the growth plate during lumbar motion in the pediatric spine with or without spondylolysis. For this purpose, finite element (FE) analysis is most appropriate, since mechanical stress and its distribution can be understood clearly using this method. FE analyses have been widely conducted for a variety of surgical methods and spinal disorders in the adult spine (e.g., the pedicle screw system (34), artificial disc (35), pars screwing (22), decompression surgery (36), lumbar spondylolysis (2, 16, 21), spinal canal stenosis (37), and spina bifida occulta (38)). The FE model used in these studies was developed by Prof. Vijay K. Goel at the University of Toledo. The Tokushima group started developing an FE model of the pediatric spine in collaboration with the University of Toledo in 2005.

The well-established adult FE model was modified to create the pediatric model (39-41). The model was of the pediatric spine in the apophyseal stage. In humans, apophyseal ring ossification

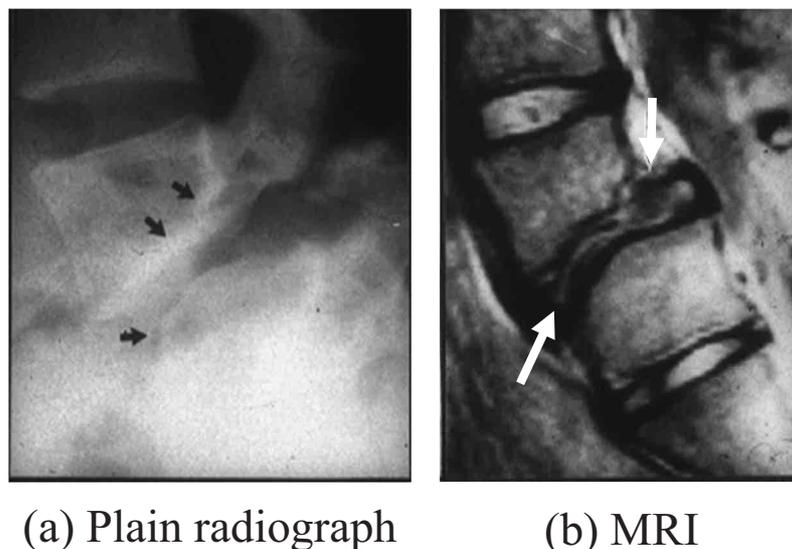


Figure 6 : Imaging of a pediatric patient with spondylolytic spondylolisthesis. (a) Black arrows on the plain radiograph indicate deformity after growth plate injury. (b) White arrows on MRI indicate the slippage site in the endplate.

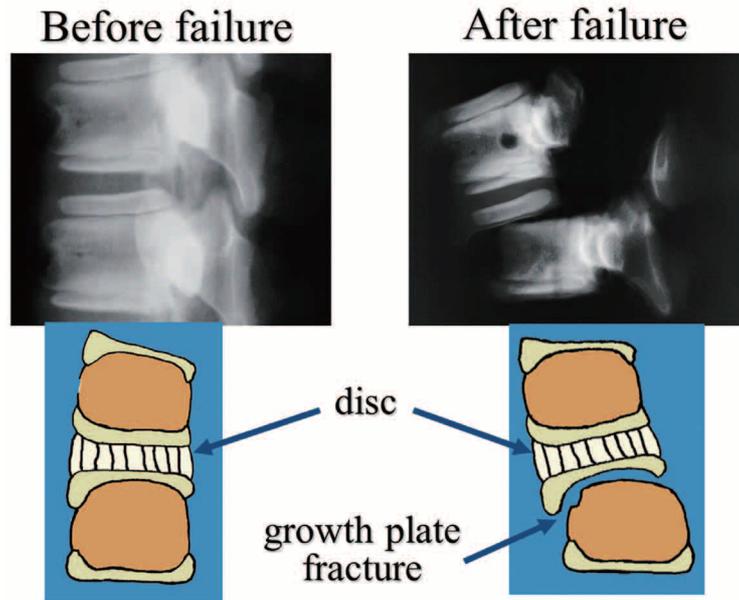


Figure 7 : Before and after failure against forward loading seen on radiographs and in schematics. The weakest link in the immature spine is the growth plate, and current data strongly support that the growth plate as the site of forward slippage in pediatric patients with lumbar spondylolysis.

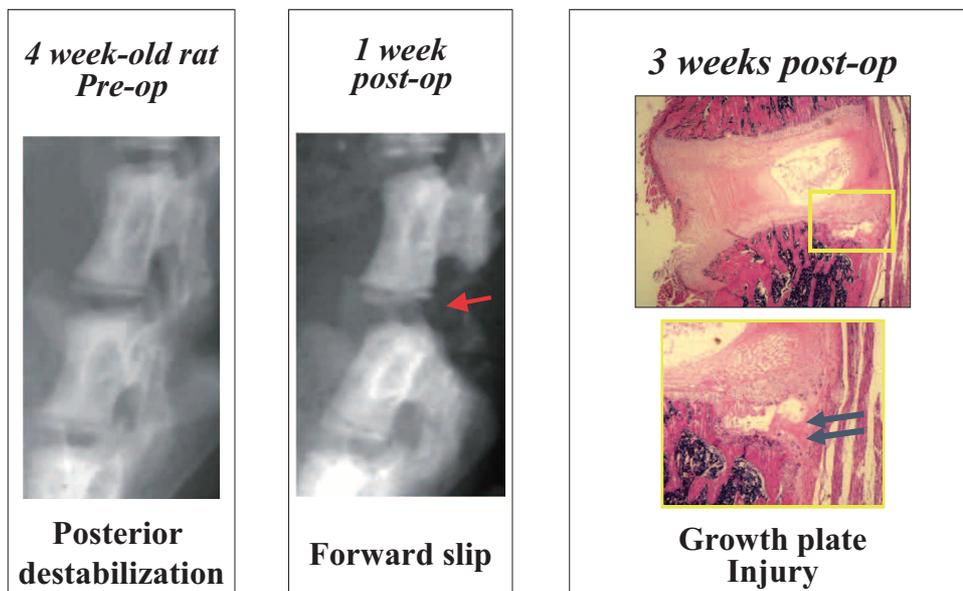


Figure 8 : Plain radiographs and histology in the immature spine slippage animal model. Slippage was observed in 10% of the animals at 1 week after posterior destabilization surgery. At 3 weeks after the surgery, the spine showed rounding and wedging deformity with growth plate injury histologically. Thus, posterior destabilization in the immature rat model could mimic the spinal deformities occurring in pediatric isthmic spondylolisthesis.

occurs around 10-15 years of age. Taking the ratio of mean sitting height in adults and 14-year-old children, we reduced the size of the adult spine model to 96% of its original size (39) and added growth plates and apophyseal bony rings. That characterize the pediatric spine. Figure 9 shows the pediatric FE model with the apophyseal ring and growth plate. A pars defect, representing lumbar spondylolysis, could be included in the model. Motion behavior was compared between the intact pediatric spine with and without a pars fracture and revealed that the stresses in all

structures, including the growth plate, apophyseal bony ring, and endplate, increased after spondylolysis in all loading modes. Extension showed the highest increase in stress with a pars fracture, around 6-fold at the growth plate when compared with the intact model (40). Based on these data, we concluded that the stress concentrations exerted on the growth plate during lumbar motion in the lytic spine could lead to physis stress fracture and eventually spondylolisthesis.

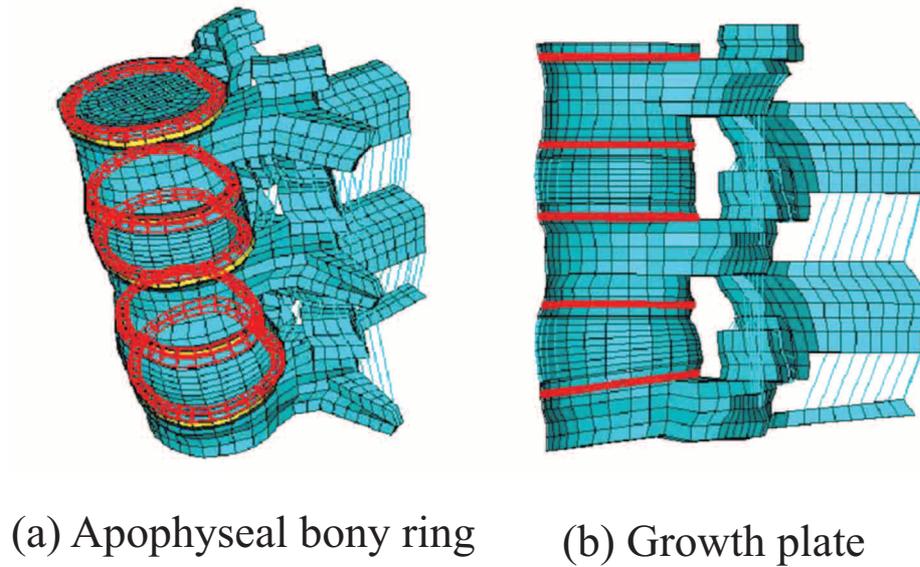


Figure 9 : The finite element model of the pediatric spine with (a) apophyseal rings and (b) growth plates shown in red.

PEDIATRIC SLIP OR ADULT SLIP?

While the occurrence of slippage is very frequent in childhood and adolescence but very rare in the mature spine, isthmic spondylolisthesis can occur after maturation (42-44). In adults, there is no growth plate, which is the location of slippage in the pediatric population, so the slippage occurs at the intervertebral disc due to degeneration and dysfunction of the disc. Thus, the slippage site differs between pediatric and adult patients with a spondylolytic spine. Figure 10 shows the typical lateral view of plain radiographs for slippage in children and adults. Figure 10a shows pediatric slippage, where the growth plate is involved in the slippage ; as a

result, spinal deformity is frequently associated with this condition. The black arrows indicate deformity of the L5 vertebral body, and the body has a wedge-like shape. The white arrow indicates poor development of the anterior edge of the S1 vertebral body, a malformation known as a dome-like deformity of the sacrum. For comparison, Figure 10b shows adult slippage. The vertebral body is almost square, the anterior edge of the sacrum is sharp as is normal (arrow), and there is no deformity in the sacrum. These characteristics can be used to distinguish between pediatric and adult slippage.

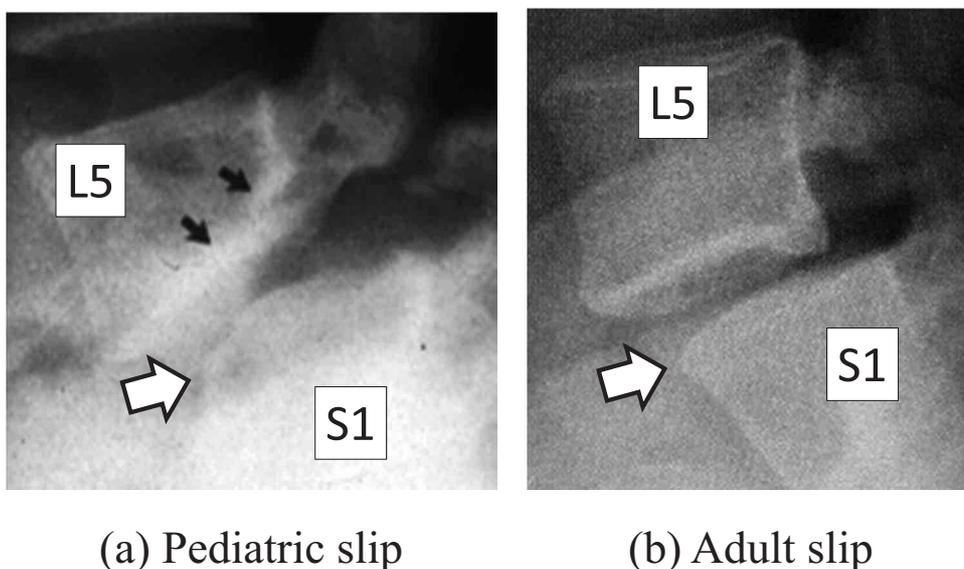


Figure 10 : Plain radiographs of pediatric and adult slippage of the spondylolytic spine. (a) Pediatric slippage : Black arrows indicate a deformity in the L5 vertebral body and the vertebral body is wedge-shaped. The white arrow indicates poor development of the anterior edge of the S1 vertebral body. (b) Adult slippage : no deformity in the sacrum is evident and the anterior edge of the sacrum is sharp as normal (arrow).

CONCLUSION

Figure 11 illustrates the Tokushima theory of growth plate slippage in pediatric spondylolisthesis. First, the pars stress fracture progresses to pseudoarthrosis, and these defects may alter the biomechanics affecting the growth plate. In the pediatric spine with pars defects, the mechanical stress in the growth plate increases, which through repetitive lumbar motions creates a stress fracture of the growth plate, ultimately leading to slippage at the growth plate.

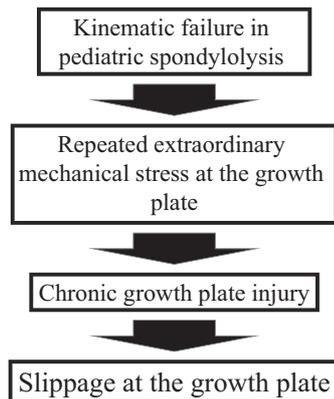


Figure 11 : The Tokushima theory of growth plate slippage in pediatric spondylolisthesis.

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