Advances in Idiopathic Scoliosis Etiology

Advances in Idiopathic Scoliosis Etiology:

A Comprehensive Monograph

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Dedicated to the research professionals, medical/surgical specialists, residents and fellows in training, and health care professionals in training who devote their careers to the well-being of our children.

“First, Understand”
—Prof Jean Dubousset

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FOREWORD

RENÉ M. CASTELEIN, MD AND JOHN F. SARWARK, MD

The cause of adolescent idiopathic scoliosis (AIS) has intrigued researchers for centuries, dating back to its initial description by Hippocrates. Why does a child develop normally until puberty, only to experience the rapid onset of a complex, three-dimensional spinal curvature? Scoliosis influences self-image during the crucial and highly vulnerable episode of puberty. Treatment often involves intensive bracing or surgery, and in severe cases, the condition can impair chest development and compromise cardiac and pulmonary function.

This book is the culmination of eight years of 'Advances in Idiopathic Scoliosis Etiology Knowledge' symposia that were organized yearly by Dr. Sarwark, funded by a grateful family donor. This research group met every September, coincident with the annual meetings of the Scoliosis Research Society (SRS), to discuss etiologic theories of AIS.

To improve treatment strategies and move toward secondary prevention, a deeper understanding of the factors that initiate and drive scoliosis progression is essential. This book aims to synthesize current knowledge on AIS etiology, enhance understanding of its underlying mechanisms, and refine approaches to evaluating and managing scoliosis in children and adolescents. As an interdisciplinary effort, it emphasizes the critical roles of multiple fields in advancing care. We quote: "First, understand," from Jean Dubousset. This book is the first publication of its kind dedicated to this comprehensive perspective.

ABBREVIATIONS

AF: Annulus fibrosus

AIS: Adolescent idiopathic scoliosis

AISE: Advances in Idiopathic Scoliosis Etiology

ASD: Adult spinal deformity

BMD: Bone mineral density

BMI: Body mass index

CAP: Curve acceleration phase

CNS: Central nervous system

ECM: Extracellular matrix

GWAS: Genome-wide association studies

HRQoL: Health-related quality of life

IS: Idiopathic scoliosis

IVD: Intervertebral disc

KO: Knockout

NGS: Next-generation sequencing

NM: Neuromuscular

PGA: Peak growth age

PHV: Peak height velocity

PRS: Polygenic risk score

RASO: Relative anterior spinal overgrowth

FEM: Finite element model

SEAS: Scientific exercises approach to scoliosis

SECTION 1:

FEATURED ARTICLES

CHAPTER 1

INTRODUCTION AND OVERVIEW

JOHN FRANCIS SARWARK, MD

Editors' Note

Idiopathic Scoliosis is not a disease; it is a final common pathway that may result from any disturbance of spinal stability.

The human spine has a natural tendency to develop the rotatory deformity that we call scoliosis, and the characteristics of different types of scoliosis with different etiologies are remarkably similar. Two critical periods increase the risk of scoliosis development: puberty, when loads rise rapidly on still maturing intervertebral discs, and senescence, when these discs lose their mechanical properties, which leads to a higher risk of decompensation.

In that sense scoliosis is primarily a biomechanical issue, a matter of (dis)balance between ever existing rotation-inducing and rotation-resisting forces; contributing factors for induction of IS are related to bone metabolism, multifactorial genetic factors and neurosensory (proprioceptive) factors.

J. F. Sarwark & R.M. Castelein

The objectives of this publication follow the objectives of the AISE (Advances in Idiopathic Scoliosis Etiology) project underway for the past 7 years:

- Further advance specific knowledge on etiology of Idiopathic Scoliosis
- Optimize evaluation and management, care, and treatment across the care spectrum

The Editors state, as is shown in the monograph, intervention optimizations should be aimed at early intervention.

What has been learned in last 5-10 years of the AISE project:

- That an integrated interdisciplinary approach, thoughtfully developed, is critical to the study of IS Etiology and this approach is proposed here.
- That there are important INHERENT FACTORS of human spine morphology.
- That ANTHROPOLOGY has a role.
- That BIOMECHANICS of the fully upright human spine (as distinct from other spines) has a role.
- That GROWTH ACCELERATION in PUBERTY has a role.
- That factors that impact BONE HEALTH have a role.
- And GENETICS has a role, and is under much study. Furthermore, the genetics role is multifactorial and continues to be elucidated.

In developing concepts of understanding IS Etiology, the following Phases and Themes are proposed:

Phases:

- An INDUCTION PHASE (early, or an 'early bird phase' associated in variable degrees with the 5 key integrated themes below)
- A PROGRESSION PHASE (occurs later; the so-called VICIOUS CYCLE described by Stokes et al.)

Themes:

This book is developed in the format of 5 Key Integrated Themes.

1. Body Morphology and Anthropology
2. Biomechanics
3. Puberty and Accelerated Growth
4. Genetics
5. Metabolism

Editors' comments

The Editors state that: We know that the immature developing spine in *those susceptible* may undergo deformation in certain phases, particularly the pre-pubertal and pubertal accelerated growth phase. This susceptibility, in context of other factors, may result in IS induction. By stating *in those susceptible,* the editors allow for future discoveries of genetic influences, yet to be determined. These genetic influences are discussed later in this monograph.

The Utrecht Theory (inherent factors)

Inherent Right Torsion. There is a natural and inherent Right thoracic torsion of the adolescent and adult human spine (and contralaterally, in situs inversus cases.) The presentation of Right thoracic IS is well known, classic and taught everywhere. When induction begins, the torsion is directed to continue as a Right torsion as discussed in this monograph. Furthermore, the human spine is intrinsically unstable to rotation due to its fully upright loading, with the center of gravity straight above the pelvis.

The Hueter-Volkman Principle

Asymmetric loading of the growing spine (progression phase) occurs as follows: initially, the discs are deformed and contribute much more to the deformity than the bony changes. At a later stage, onset of (physeal) growth retardation of the concavity as well as posteriorly leads to further torsion and hypokyphosis in the sagittal profile and perpetuates the *Vicious Cycle* (Stokes et al.). Relative anterior spinal overgrowth (anterior column lengthening, or RASO) and negative spine balance (loss of sagittal harmony) are then observed compared to the normal spine. This phenomenon occurs in all types of scoliosis (not exclusively in idiopathic) and is discussed in detail in the monograph.

On Genetic Multifactorial Contributions to IS Etiology and the Null Hypothesis

The Genetic contributions to development of IS are well discussed in detail in this monograph by authorities on the topic. The Editors wish to state in this regard and with respect to the Null Hypothesis concept, there are arguments pro and con relating to genetic influences to IS etiology. Pro: the condition is well known to be familial in varying degrees (although it is common, it should occur even more broadly, e.g. many or most individuals go through growth acceleration in puberty without developing IS). Is there in fact some underlying factor *in those susceptible*? There may be. The discussions in this monograph allow for genetic influences for the induction of IS. Con: the condition is remarkably common. The condition occurs in previously fully well, healthy teens and pre-teens. The condition reverses itself (in mild presentations) with early treatment. There is little evidence of adult degenerative disc spine disease. Concordance rate in identical twins is not as significant as one would expect. The biomechanics of induction of the condition, outlined here, explain well the induction of deformity in the normal healthy state *in those susceptible* without defined genetic causes.

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CHAPTER 2

BIOMECHANICS

Editors' note: Featured Article

The Role of the Intervertebral Disc in the Etiology of Idiopathic Scoliosis

René M. Castelein, MD
Tom Schlösser, MD PhD
Keita Ito, MD DSc

Abstract

Idiopathic scoliosis remains the biggest enigma in orthopaedics. Most evidence indicates that patients develop normally until their spine, and with it the trunk, starts to decompensate into a rotational deformity that has a serious impact on the rest of life. No uniform etiological model has yet been developed, and no animal model can mimic the unique fully upright human spino-pelvic biomechanics. The growing human spine is rotationally more unstable than other spines in nature due to its sagittal alignment. In this chapter we will propose that scoliosis is primarily a biomechanical problem, that rotation-inducing forces continuously act on the human spine throughout life, and that the main reason rotation usually remains within physiological limits is the integrity of the spine's stabilizers, most notably the intervertebral discs. There are two phases in life when that integrity is challenged and the delicate balance between rotation *inducing* and rotation *resisting* forces may be disturbed. The first occurs during puberty, when rapidly increasing spinal loading is accompanied by altered sagittal

alignment as the disc matures, with an increasingly stronger attachment to the vertebral endplates. The endplates transition from cartilage to bone during the same period, although not necessarily at exactly the same time. The second phase occurs when discs degenerate in older age, lose their torsional stiffness and ultimately can no longer resist that ever-present force that wants to induce rotation. Both types represent different ends of the same spectrum and could be called 'discogenic scoliosis.' Both of these phases are limited in time, either ending in a mature and stable disc with a fully ossified and fused ring apophysis as its attachment, or, in later life, in a degenerated, ankylosed and thus also (again) stable disc. Theoretically, only during these transitional phases of temporary instability does the spine need to be protected; once the end stage has been reached, deformity no longer has a chance to develop.

Introduction

The etiology of idiopathic scoliosis has been the topic of research for centuries, and still no generally accepted theory exists. There is no evidence that there is any consistent underlying causative abnormality.[1,2] It is considered a disease of the human race, with no known equivalent in other mammals. In zebrafish, however, a rotational spinal curvature can occur spontaneously that shows similarities to the characteristics of human idiopathic scoliosis.[3,4] Practically all scientific knowledge is derived from established cases; very little is known of the pre-scoliotic spine and unfortunately, no mammalian animal model is known.[5]

The intervertebral disc (IVD) is the most important stabilizer of the spine,[6] and most of the spinal deformity in adolescent idiopathic scoliosis patients is located in the disc; bony changes occur later during the process, and to a much lesser extent.[7-11,18] The human spine is different from other spines in nature, even those of bipedal species, in the sense that it is rotationally much less stable.[12,25] This has to do with its unique sagittal profile, which starts with a pelvic lordosis and continues into a lumbar lordosis and a center of gravity that is straight above the pelvis, unlike all other species, including the bipedal ones. This leads to a variable segment of the thoracic and lumbar spine that is posteriorly inclined, which is uniquely human. We will go into this further in a subsequent paragraph. The normal, non-scoliotic human

spine also exhibits a slight pre-existent rotatory pattern, that is identical in direction (but much less in magnitude) to what is generally seen in most types of scoliosis; to the left in the upper thoracic area, to the right in the mid-and low thoracic spine, and then back to the left around the thoraco-lumbar junction.[13] This rotational pattern changes in direction during growth due to a gradual change in the distribution of body mass and explains the different curve patterns that are characteristic of the infantile and adolescent age groups.[14,15] The most important structure to resist progression of rotation beyond these physiological limits is the well-functioning and mechanically intact intervertebral disc (IVD).

We propose that idiopathic scoliosis has a predominantly mechanical background. It is the result of a temporary mismatch between the ever-present rotation inducing forces that are the result of unique human upright spinal biomechanics, and the stage of maturity of the intervertebral discs (IVD). These forces act on the human spine throughout life and are resisted predominantly by the mechanical properties of the IVD. During two brief periods in life this delicate balance can be disturbed, resulting in spinal decompensation into a pre-defined rotatory deformity. The first period is when, during puberty, the body's dimensions, and thus the loads on the spine, rapidly increase, while the discs go through their own sequence of maturation, not necessarily in a synchronous manner. The second period is when, in older age, the mechanical properties of the disc rapidly deteriorate through disc degeneration, the spine becomes temporarily unstable, and the rotation inducing forces get a chance to manifest themselves. Both types of resulting scoliosis, called respectively Adolescent Idiopathic Scoliosis (AIS) and Adult Spinal Deformity (ASD), represent different ends of the same spectrum, are related to time-dependent disc properties, and are the result of a temporary mechanical overload. They both occur in initially normal spines, in individuals that have no underlying manifest disease that can readily explain the occurrence of the deformity. Therefore, both could be called "idiopathic", but a more appropriate term could be "discogenic".

Preexistent Rotation of the Normal, Non-scoliotic Spine

The normal spine is a slightly pre-rotated structure in the transverse plane. Its rotational pattern is identical in direction to what is found in the most

prevalent curve types in scoliosis.[13,14] The direction of this transverse-plane rotation changes with age and is related to a change in the distribution of internal body mass.[15,16] Once the spine decompensates into scoliosis, this preexistent rotation increases, simply following the already built-in pattern. The occurrence of preexistent rotation in the normal spine explains the predominant curve patterns at different ages. Gradually, irreversible changes are induced, predominantly in the shape of the discs but later also in the bony anatomy of the vertebrae.[11,17,18] Bone metabolism plays a role in scoliosis, through the adaptation of the shape of the vertebrae due to asymmetric growth according to Hueter-Volkmann's law as well as bone adaptation through Wolff's law.[1,19-23] Since discs and vertebral bodies originate from closely related embryological structures, it is logical to assume that the same agents that govern bone metabolism may also have a -*still rather unknown*- effect on the mechanical properties of the discs as well as other stabilizing soft tissue structures around the spine.

Rotation-inducing Dorsal Shear Forces

The human sagittal spino-pelvic alignment and subsequent biomechanical loading is unique and cannot be compared to any other vertebrate, not even bipedal species.[1,12,24-26] This unique alignment originates in the shape of the human pelvis, which has developed a lordosis between the ischial and iliac bone during its evolution.[27,28] Combined with the lumbar lordosis, and the fact that humans can simultaneously extend their hips and knees, these features have brought the human body's center of gravity more dorsal than in any other species, principally changing the biomechanical environment (Fig. 2-1). All spines in nature are subject to axial compression and anterior shear, but by its sagittal alignment, the human spine is the only one on which a third force comes into play: a posteriorly directed force acting on the backwardly inclined segments. This force, acting on that pre-rotated structure, unlocks the facet joints, decreasing the rotational stability of the involved segments.[12,25,26] The existence of these shear forces, both anteriorly and posteriorly directed, has been questioned because the spine is conceptualized to undergo a follower load.[29] This follower load simulates the co-contraction compression forces of muscles necessary to stabilize the spine. In this concept, forces are ideally always tangential to the spine's sagittal curvatures along the trajectory of the paraspinal muscles. However,

there is no doubt that, in real life, in the sagittal plane shear loads in opposing directions exist. It is relatively common, especially in the degenerative spine, for vertebrae to slide either anteriorly or posteriorly, dependent on their orientation in the sagittal plane (Fig. 2-2), and this resultant ante- or retro-listhesis is caused by the anterior or posterior shear component of the combination of muscle tension and gravitational force.

Kouwenhoven and colleagues, in an ex vivo experiment, demonstrated that, under the influence of posterior shear loading, a reduction of rotational stability of the involved spinal segments occurs.[12] The longer the backwardly inclined area of the spine is, or the higher the backward inclination angle, the more these segments are prone to develop a rotational deformity, i.e. scoliosis.[26,30] Janssen and colleagues showed in an in vivo upright MRI study that rotation of the spine increases in healthy, non-scoliotic young adult volunteers if they moved from a quadrupedal-like to a human, fully upright position.[30] Homminga and colleagues showed in a biomechanical modeling study that also in old age, due to disc degeneration in combination with the ever-existing posterior shear loads, the rotational stability of the exposed spinal segments is significantly reduced, leading to degenerative scoliosis along the same mechanism.[31]

Sagittal profiles in children, especially the ones that develop scoliosis, were shown to differ significantly by Abelin-Genevois in her classification system and by Pasha.[32-34] Schlösser and colleagues found that in non-scoliotic subjects, spines of girls are more backwardly inclined than the spines of boys at the moment of maximal growth velocity, making them more susceptible to develop a rotational deformity, i.e. scoliosis.[35] Brink and colleagues showed that the pelvic incidence, the determinator of sagittal spinal alignment, is significantly higher in lumbar than in thoracic scoliosis and controls.[36,37] Schlösser and colleagues showed that early lumbar scoliosis has a different sagittal profile than does early thoracic scoliosis,[38] and de Reuver and colleagues showed that degenerative de novo scoliosis has similar spino-pelvic configuration as adolescent Lenke 5 scoliosis (de Reuver S et al., manuscript in preparation, 2020). Furthermore, de Reuver et al. showed in a syndromic population that the early sagittal profile of the spine was predictive of scoliosis development, as well as of the ensuing

different curve patterns.[39] This all points to the role of sagittal spino-pelvic alignment in the etiology of different types of scoliosis.

The Disc as the Primary Stabilizer of the Spine During Different Phases in Life

Next to its ability to function as a shock absorber, the IVD, especially the annulus fibrosus (AF), should primarily be considered as a ligament that connects the vertebrae and stabilizes the spine. Much more is known of IVD degeneration during later life than of IVD maturation during puberty. It is known, however, that in infancy the AF anchors through the Sharpey fibers and attaches at the -initially cartilaginous- endplate into the vertebrae. The physis at the cranial and caudal end of each vertebral body gradually mineralize at its periphery (the ring apophysis) and ultimately fuse to the vertebral body during the process of puberty, eventually forming stable, bony enthesis anchorage, after which the spine can be considered stable and 'mature'. As has been known for a long time, as soon as spinal maturity has been reached, scoliosis will no longer have a chance to develop (if it already exists, it can of course still progress). Costa et al. have studied the mineralization and fusion of the ring apophysis, which is the discs attachment, on CT scans of a non-scoliotic population and compared their results to the same ossification process in a scoliotic population.[40,41] No scan was taken for the purpose of these studies; they were available in an already existing database. Their findings indicate that maturation of the IVD occurs at a later age and lasts longer in female idiopathic scoliotic patients than in the matched controls, at a time when much of the body's transformation from child to adult has already occurred. Given the fact that the process was not related to concavity or convexity of the curve, it was concluded that the observed differences were most likely not caused by the curvature but were an independent phenomenon. Even at the age of 21, many female AIS patients did not show complete maturation of their mid- and low thoracic ring apophyses. This suggests asynchronous maturation of the primary stabilizers of the spine relative to the (earlier) rapid increase in body height, weight, moment arm, and thus mechanical loads, on the spine. This asynchronous maturation is not at all unusual throughout the human body; we know from Osgood Schlatter's disease that the force of the Quadriceps

muscle is already relatively mature while the attachment of the patellar tendon into the tibia is still immature and cartilaginous. Additionally, avulsions of the Rectus Femoris muscle from the inferior iliac spine can occur because the relatively mature muscle force can exceed the strength of the still immature, cartilaginous attachment, and a similar mechanism occurs in Sever's disease of the Os Calcis or in "little league elbow". These are all examples of forces acting on the skeleton that lead to clinical manifestations, because these forces are more mature and larger than their immature and still cartilaginous attachments can withstand. Along the same mechanism, forces on the spine can also temporarily exceed the capacity of the stabilizers, predominantly the discs, to counteract that continuously present, but during growth rapidly increasing force that wants to initiate rotation of the spine.

Whereas, during puberty, the forces increase rapidly while the stabilizers may still not be mature enough, in older age, this rotation inducing dorsal shear force, that was previously adequately counteracted by the well-developed and mechanically intact disc, can lead to scoliosis when the mechanical disc properties deteriorate through degeneration, and the spine finally decompensates and follows that built-in pre-existent rotation.

The problem with scoliosis etiology research is that practically all data are collected from already well-established cases; little is known of the very early and pre-clinical stages of the disease. Of course, it is not feasible to study development of the spine in a large cohort of asymptomatic growing children, especially not when ionizing imaging is involved. One way to overcome this, is to study high risk groups, that have a more pronounced advantage in early detection, and in the meantime avoid ionizing radiation. We therefore recently initiated a prospective observational cohort study, in order to capture the Earliest Changes of the Bone and Intervertebral Discs in Children at Increased Risk for Scoliosis Development (the 'EARLYBIRD' study).[42] Given the well-known (but under continued investigation) genetic component of AIS, we are presently following asymptomatic younger sisters and daughters of known AIS patients, starting before adolescence and before scoliosis onset, both clinically and with advanced non-ionizing imaging, using supine (Bone) MRI and upright 3D spinal ultrasound. The primary focus will be the longitudinal, structural

changes in the intervertebral discs and vertebral bodies during growth in subjects that ultimately do, compared to those that do not, develop AIS. In addition, anthropometric changes and spinal sagittal alignment in the upright position are collected for assessment of development of the sagittal profile, and consequent biomechanical loading. With advanced MRI-based synthetic CT scans, also the ring apophyses are visualized to relate the timing of scoliosis onset to spinal skeletal maturity.[43] Interestingly, of the first 40 pre-adolescent, first degree, female family members of AIS patients included in this study, 70% already had a coronal asymmetry at baseline with a (mean ± SD) curve angle of 7±3° on the supine imaging, with most asymmetry/deformation in the discs. Whether these asymmetries observed before the growth spurt become structural and occur more than in the general pre-adolescent population is still unknown and further follow-up will show which will progress into a "true" AIS. For now, it is hypothesized that these pre-scoliotic asymmetries may contribute to increased rotational mechanical stress during the growth spurt, ultimately leading to asymmetrical disc remodeling and scoliosis development.

To further explore how the AF may be overstretched in some of these subjects, patient-specific biomechanical spine models at various time points during growth are created[44] and used to study rotational stability and AF stretching under posture and activities of daily living (manuscript in submission). Although it is not possible to measure the AF tissues and anchorage properties in these subjects, this is done in a more general manner with juvenile human cadaveric specimens where the physical properties are assessed as function of maturity and/or growth (manuscript in submission). Finally, the mechanobiological influence of the physes morphogens on modulation of AF repair/remodeling is explored in vitro.

Of course, many other underlying factors may also play a role in whether the spine will decompensate into scoliosis; genetics, proprioception, metabolomics, and even inflammatory processes may all influence at a certain point and to a certain extent the biomechanical behavior of the tissues concerned and thereby the rotational stability of the spine in the horizontal plane. Whether that will result in a scoliotic deformity depends on a number of these factors coinciding in time, in what can be called a *"perfect storm"*. So, in that sense scoliosis etiology will always be

"multifactorial", but also the other examples given above, such as Osgood Schlatter's disease, are of course multi-factorial. The question should be: "what is not?"

Scoliosis has a chance to develop during a relatively small window of opportunity. In adolescents, it will have no chance to develop once the disc has matured at the end of spinal growth. In old age, once the disc reaches the phase of ankylosis, the system is stable again and it will no longer allow a scoliosis to develop either. Both adolescent idiopathic and adult degenerative scoliosis are a severe burden to the patient and society, treatment is very costly, and the results, although better than ever, are far from perfect. The challenge in scoliosis treatment, both in children and adults should be to better understand its shared patho-mechanism, recognize those individuals that are at risk for developing a progressive deformity, to rationally intervene in this process at an appropriate time and to temporarily protect the spine during this limited window in time, if possible by external means but, if necessary, with temporary and motion-preserving implants. Fusion could then be reserved for severe and recalcitrant cases, rather than being the standard of care. That this is a theoretical concept that needs much more research to become a reality, is evident.

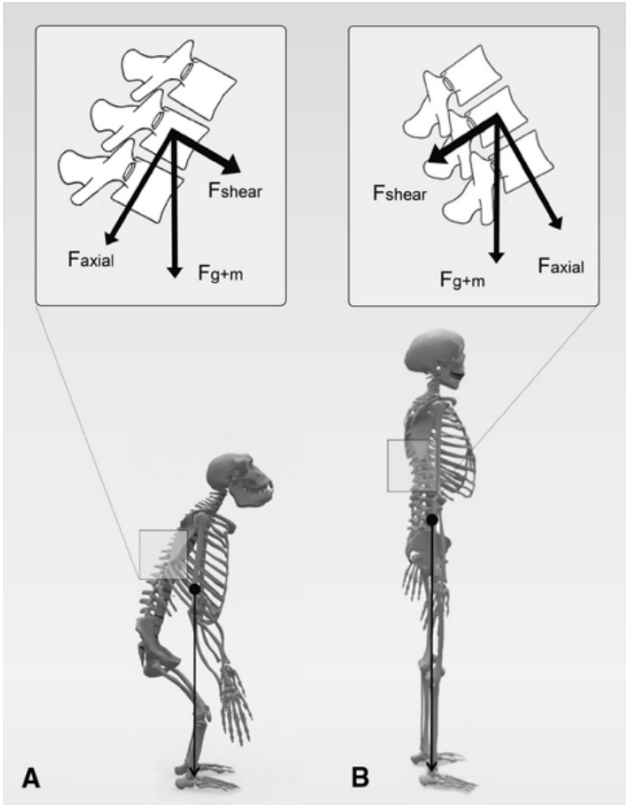

Fig 2-1. Anteriorly inclined vertebrae are affected by an axial force as well as an anteriorly directed shear component of gravity and muscle action. Posteriorly inclined vertebrae are affected by—next to a predominant axial force—a posteriorly directed shear component. The magnitude of each depends on an individual's sagittal spinal profile, the net outcome depends on the balance between the magnitude of the force and the strength of the stabilizing structures, predominantly the intervertebral discs.

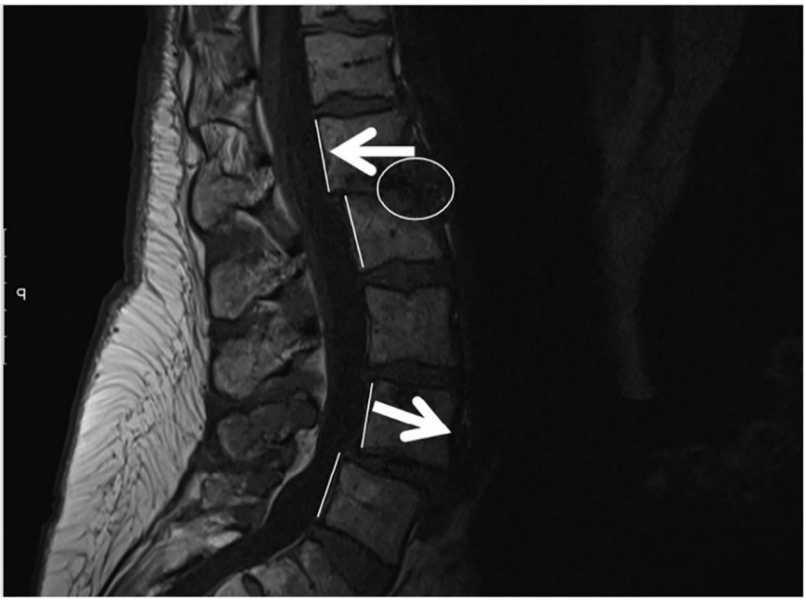

Fig 2-2. An MRI scan of a degenerative lumbar spine, showing at L1 to L2 both disc collapse (oval) as a result of the axial force and retrolisthesis (posterior arrow) as a result of the posterior force, and at L4 to L5 antelisthesis (anterior arrow) as a result of the anterior force.

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