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Review Article

The Diurnal Variation "accordion"-like Phenomenon of Wedged Intervertebral Discs: A Progression Factor in Idiopathic Scoliosis

Theodoros B. GRIVAS*

Department of Orthopedics & Traumatology, "Tzaneio" General Hospital of Piraeus, Greece

***Corresponding author**

Theodoros B. GRIVAS, Department of Orthopedics & Traumatology, "Tzaneio" General Hospital of Piraeus, Piraeus, Tzani and Afendouli 1 st, Piraeus 18536, Greece, Email: grivastb@gmail.com

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Abstract

This report presents a concept for idiopathic scoliosis (IS) progression, which refers to the role of the diurnal variation on the asymmetric water distribution of the eccentric nucleus pulposus of the deformed scoliotic IVD, and the subsequent alteration of the mechanical environment, due to caused intermittent forces, on the adjacent vertebral growth plates. The result of these intermittent forces, due to the diurnal variation, is an asymmetrical vertebral growth and progression of the deformity. This is terms the "accordion-like phenomenon".

The concisely discusses data used to lend support to the presented concept, relate to the mechanobiology, the mechanotransduction process, and fundamentals of the embryology and biology of the spinal column. It also relates to the normal and deformed intervertebral disc, the diurnal variation phenomenon, concepts of IS scoliogeny, the three-joint complex concept, the sleep phases and muscular tone. This background knowledge tries to make clear and apprehensible the concept of "the diurnal variation accordion-like phenomenon of wedged intervertebral discs", which is argued to constitute a key progression factor in IS. This concept seems to be original, existent and it will clinically be very useful for tailoring the treatment of the children suffering IS. The treatment methods currently used to reverse this progression of the IS mechanism are also mentioned. The final great benefit for this group of children will be an unfused spine, as mother nature created it, yet the economies of the national health systems, will be prevented by the high expenditures of traditional surgical treatment, if non operative treatment will properly be applied, based on this concept.

INTRODUCTION

Mechanobiology

Mechanical biology, or the so-called mechanobiology, of the development of skeletal deformity, is an important relatedly novel area of study. Mechanobiology combines biology, engineering, and physics [1]. It is interesting to understand the mechanisms by which cells react to mechanical signals a phenomenon termed mechanotransduction. Mechanotransduction seems to be involved to the development of deformity [2].

Willem Roux,[3], first published on the developmental mechanics of organisms including how mechanical stimuli mediated also on the shaping of muscles and bone. This work inspired the Hueter-Volkmann principle [4-7], Pauwel's theory [8,79] and Wolff's law [9]. Deposition of new bone is the result of increased loading on bone tissue while decrease in mechanical loading causes resorption of bone tissue, [10].

Connective tissue adaptation, including the development of cartilaginous anlagen into bones, is related to dynamic, intermittent load and stress application, while static stress, acts deleteriously for tissue adaptation, [11]. The architecture of trabecular bone, the porous bone found in the spine and at articulating joints, provides the requirements for optimal load transfer, by pairing suitable strength and stiffness to minimal weight according to the rules of mathematical design, [9,12-16]. However, it was reported that it is unlikely that the architecture is fully encoded in the genes, [17]. Additionally it is reported that epigenetics play a role in the IS phenotype [18-25]. The answer of how the bone cells are informed and drive the architecture, may based on the relationship between bone architecture and mechanical usage [26]. While strenuous exercise increases bone mass, [27], disuse, as in microgravity and inactivity, reduces it [28]. It has also been proposed a computational model of the metabolic process in bone, which confirms that cell coupling is governed by feedback from mechanical load transfer [29-31]. The regulatory process that was proposed involves the following hypotheses: a. the mechanical factor that activates response from the external forces to bone metabolism is a typical strain-energy density (SED) rate in the mineralized tissue, b. osteocytes respond to the loading in their local environments by producing a biochemical messenger in proportion to the typical SED rate, c. the biochemical messenger triggered by the osteocytes causes signals to be dissipated through the osteocytic network towards the bone surface, where they create an osteoblast recruitment stimulus [32], d. to portray resorption in the model, the probability *p* of osteoclast activation per surface site at any time is considered to be regulated either by the presence of micro-cracks within the bone matrix (hypothesis I) or by disuse (hypothesis II) [33].

FUNDAMENTALS OF THE EMBRYOLOGY AND BIOLOGY OF THE SPINAL COLUMN

Based on this basic embryological development [34], it is clear that any asymmetrical loading on the spine during growth when IS develops, mainly occurs on secondary ossification centers, that is upon the still open ring epiphyses. During growth, if the loading on ring epiphyses is imbalanced or asymmetrical, then a continuous compressive loading decelerates the growth, according to Hueter-Volkmann principle, and any intermittent loading promotes the growth, according to Pauwel's law. However, during the period of pubertal growth, any asymmetrical loading will mainly disturb the growth at the secondary growth centers of the vertebrae, that is the two ring epiphyses and the other three secondary ossification centers. The results of Wolff's law will apparently be evident after bone maturation in the spine.

THE INTERVERTEBRAL DISC (IVD) (OR INTERVERTEBRAL FIBROCARTILAGE)

The IVD lies between adjacent vertebrae in the vertebral column. Each disc forms a fibrocartilaginous joint, to allow slight movement of the vertebrae, to act as a ligament to hold the vertebrae together, and to function as a shock absorber for the spine. The IVD consists of the annulus fibrosous (AF), and the nucleus pulposus (NP). The NP functions to distribute hydraulic pressure in all directions within each IVD under compressive loads. Among other molecules the NP contains aggrecan, a proteoglycan that aggregates by binding to hyaluronan. Attached to each aggrecan molecule are glycosaminoglycan (GAG), chains of chondroitin sulfate and keratan sulfate. The GAGs play a role in osmotic pressure, resulting in a shift of extracellular fluid from the outside to the inside of the nucleus pulposus. The amount of GAGs (and hence water in the IVD) decreases with age and degeneration, [35-37]. The GAGs imbibe water when they are unloaded and expel it when the disc is loaded. The swelling of IVD correlates directly with GAG content, [38-40]. In IS the IVD is grossly deformed. On the concave side of the IS curve the disc height is markedly reduced, while on the convex side it is increased, so that much of the deformity of scoliosis lies in this change in the disc, [41]. The NP in IS, mainly at the apical but at the neighboring IVDs, migrates to the convex side, as it is surgically confirmed [42].This migration is also confirmed in MRI studies. It is reported that deterioration of IS has been associated with displacement of the NP towards the convex side, [43,44]. Yet the GAGs composition and content on the concave side of the IVD is different to that on the convex of the NP, [45]. It has been shown experimentally that proteoglycan synthesis and composition may be affected by altered mechanical stresses. Thus, the changes found in the proteoglycan content of the IS discs may result from changed mechanical environment. These changes will also influence disc hydration, [41,46].

THE DIURNAL VARIATION PHENOMENON RELATED TO THE SPINE

Human stature varies throughout the 24-hour period, lengthening when a subject lies down and shortening the upright position. This is termed *diurnal variation*, (DV) [47]. It was suggested, that this *DV* is due to fluctuation in the water content of the IVD [48].

The DV and changes in body height were studied, using physical measurements and imaging techniques, [49-53]. This DV phenomenon is attributed to the property of proteoglycan macromolecules in the NP. Proteoglycan macromolecules imbibe water when they are not loaded and expel the water under compression loads, due to the so-called Gibbs Donnan effect [54]. Dangerfield et al, 1995, reported that the spinal length changes with respect to upright and recumbent position; these changes are considered to have important clinical significance in the context of 3D IS aetiology, as the spine may be affected in different ways depending on the position adopted by the body' [47]. However, in this report no explanatory mechanism for this consideration was proposed. Czaprowski et al., 2019 reported that body height decreases in children and adolescents with IS during daytime; the height change mostly occurs in the spine and is not related to the curve type or magnitude of IS [55]. However the amount of DVis larger in children as compared to adults [56]. This difference in DV in height between children and adults could be attributed to greater concentrations of purified proteoglycan macromolecules in the NP of children compared with adults. This would allow for more drawing in the water into the IVD during periods of rest, in other words when IVD is not loaded with compressive forces [57].

The risk of progression of the IS is closely related to the longitudinal growth of the spine, the gravity and muscular tone [58,59].

IS aetiology is unclear so far and figuring it out is a great challenge. Up to the present time, the majority of research and reports on pathophysiology of IS are based on IS cases suffering more or less severe deformity when the current indication of treatment is surgery, and not when the curve commences or in mild IS cases, when non-operative treatment is indicated. This discrimination might be significant, because this rather multifactorial condition seems to be dictated from different causes/factors when it commences than when it progresses. There is a view that there are two scoliogenic processes for IS, namely the initiating (or inducing) and those that cause curve progression [20]. These two hypothesized scoliogenic processes for IS, namely the initiating (or inducing) and those that cause curve progression, have been confirmed through imaging studies of the sagittal and frontal views a) in children suffering from mild or moderate AIS referred from school screening programs and b) in severe AIS cases directed to theater. The results are not similar in these two cohorts of IS children. Analyzing the radiographic imaging and the Diers surface topography recordings in children suffering from commencing or mild IS, it was reported that the sagittal profile was not statistically significant different with the peer non-scoliotic children, and not correlated with Cobb angle [60,89]. According to this report' s conclusions, the minor hypokyphosis of the thoracic spine and its minimal differences observed in the studied small IS curves compared with non-scoliotics add to the view that the reduced kyphosis, by facilitating axial rotation, could be viewed as being permissive, rather than as aetiological, in the pathogenesis of IS. This is dissimilar to what was reported elsewhere, that is, that in progressed cases of IS, the sagittal profile is considered as a primary causal factor in IS progression [61-63]. Similarly, in the imaging studies of the coronal deformity, in mild IS curves, when the deformity is initiating, the IVD is found to be wedged, but not the vertebral body. This interesting finding led to the conclusion that the spine initially becomes deformed at the level of the IVD, probably due to the increased plasticity of the IVD, in the way of either torsion or wedging, as an expression of other initiating factors that may result in IS; then, the vertebral bodies are patho-remodeled and deformed [64,65]. This IVD deformation has also been observed and discussed earlier [66,67]. Dissimilarly, in reports concerning progressed and severe cases of IS, the authors suggested that there is an inherent growth bone defect in the vertebrae. It is reported that, although the aetiology of AIS has not been documented, the sagittal profile of the spine is proposed to play a major aetiological role in spinal biomechanics, rotational stability, and the development and progression of spinal deformities [68-73].

THE THREE-JOINT COMPLEX CONCEPT

In 1983, Kirkaldy-Willis described the *intervertebral articulation* as a "**three-joint complex**", including the disc anteriorly and the two facet joints posteriorly [74], Figure 1.

Sleep phases and muscular tone. The sleep phases are the non-REM and the REM one. The subject can have intense dreams during REM sleep, since the brain is more active. Most of the dreaming occurs during REM sleep, although some can also occur in non-REM sleep. The muscles become temporarily atonic / "paralyzed", which prevents the subject from acting out his/her dreams. This lack of tone is very important for scoliogenesis and it will be considered below as part of the **diurnal variation "accordion" like phenomenon of wedged intervertebral discs: a progression factor in IS.** As a person ages, sleeps less of the time in REM sleep. Memory consolidation most likely requires both non-REM and REM sleep. Babies can spend up to 50% of their sleep in the REM stage, compared to only about 20% for adults, [75].

THE HYPOTHESIS/THEORY

Up to this point, we have reviewed some related topics and issues on mechanobiology, mechanotransduction process, some fundamentals of the embryology and biology of the spinal column, details on the intervertebral disc, the DV phenomenon, concepts on IS scoliogeny, the three-joint complex concept and sleep phases and muscular tone. Based on this review we will describe and analyze the concept of the diurnal variation "accordion"-like phenomenon of wedged intervertebral discs, which is proposed to constitute a key progression factor in idiopathic scoliosis. In Lyon, 2009, a concept was proposed suggesting one mechanism for progression of idiopathic scoliosis (IS) under the title "A comprehensive model of idiopathic scoliosis (IS) progression, based on the patho-biomechanics of the deforming "three joint complex". This presentation suggested an innovative comprehensive model of IS curve progression, based on IVD diurnal variation and the subsequent patho-biomechanics of the deforming "three joint complex". So far, only the abstract of the presentation has been published [76]. This report is an enriched, extensive and elaborated analysis of this concept, as it has not been detailed hitherto in the literature.

In the mild IS curve, the imbibed water in the convex-wise migrated NP, the GAGs mainly in the apical IVD, but also in the adjacent to the apex discs, are in a greater amount than in the concave site. This is done due to convex-wise asymmetrical distribution of glycosaminoglycans (GAGs) in NP collagen network type II. This results in an asymmetrical pattern of water distribution and consequently to an asymmetrical swelling of the IVD. Throughout the day and night, due to sustained loading and unloading, the wedged IVDs in the IS patient expel fluid and imbibe it more in the convex side. Owing to the 24h DV, in line with above described increased swelling, the loads to the convex

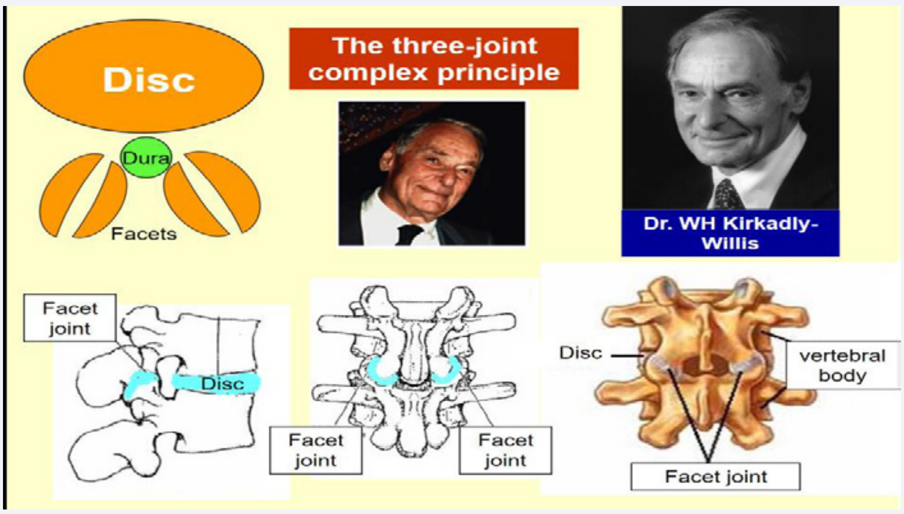

Figure 1 The Three-joint complex principle, including the disc anteriorly and the two facet joints posteriorly.

side of the wedged apical IVD and to the periapical IVDs end plates (ring apophysis), exert asymmetrical convex-wise concentrated cyclical/internment forces. Thus there is greater amount of expansion in this site compared with the convex side. The convex side of the disc sustains a greater amount of cyclic expansion than the concave side. As a result, the convex side end-plates/ring apophyses become intermittently more loaded during the 24-hourperiod, (Pauwel's law). This intermittent loading of the convex-wise of the IVD, which probably falls within the normal limits *of stress and strain,* stimulates the growth in the end-plate of the vertebrae convex-wise. However, the concave site of the IS IVD is more likely to be continuously loaded (Hueter-Volkmann law). The continuous compressive forces transmitted to the growth plates/ring plates in the concave site decrease the rate of proliferation of the chondrocytes in the hypertrophic zone. The imposed, convex-wise, asymmetrically concentrated cyclical loads to the adjacent immature vertebral end plates of the spine lead to an asymmetrical growth not only of the vertebral body, but of its posterior elements as well. More specifically, the loading on the two facet-joins is asymmetrical. The asymmetrical increased loading during the day occurs as the wedged IV space narrows due to the expelled water and decreases asymmetrically during the night as the IVD space swells due to the imbibed water. This results in asymmetrical growth, Figures 2, 3 and 4.

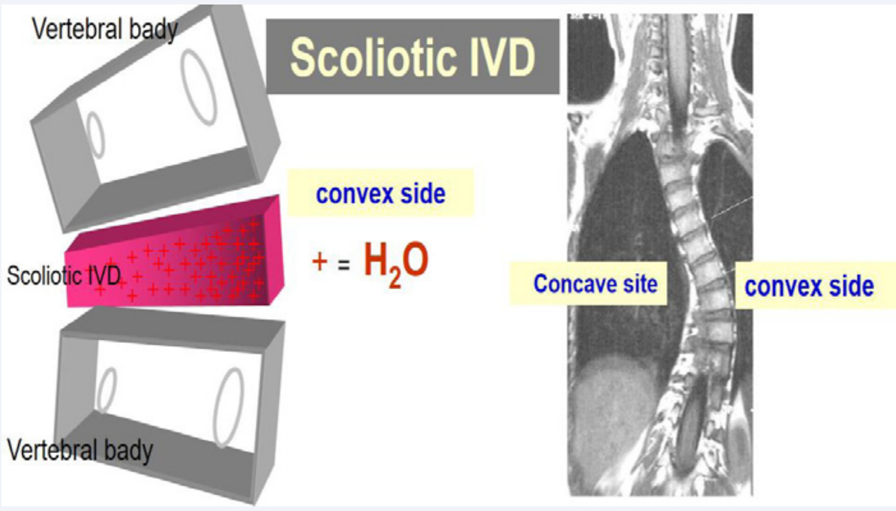

Figure 2 The imbibed water (+ H2O) mainly in the apical IVD but also in the adjacent discs must be in a greater amount in the convex side than in the concave due to convex-wise asymmetrical distribution of glycosaminoglycans (GAGs) in NP collagen network type II. This results in: 1) asymmetrical pattern of water distribution, 2) Due to DV, asymmetrical convex-wise, concentrated cyclical loads to the IVD during the 24h, the convex side of the wedged IVD sustains greater amount of expansion than the concave side and as a eventual result the vertebra deforms.

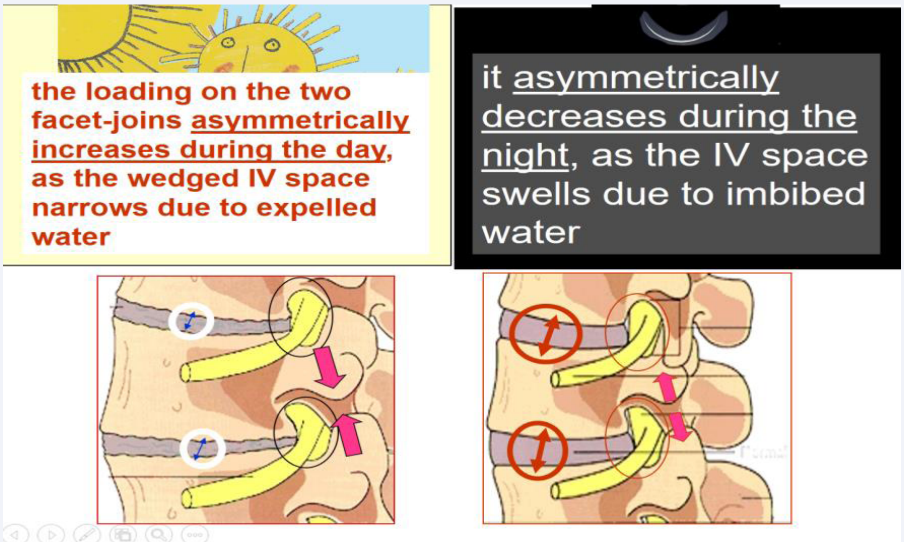

Figure 3 The loading on the two facet-joins and IVDs is asymmetrical. The asymmetrical loading during the day occurs as the wedged IVD space narrows due to the expelled water, and decreases asymmetrically during the night as the IVD space swells due to the imbibed water. This results in asymmetrical growth of vertebral bodies and their posterior elements and also this is reflected in minor fluctuation of Cobb angle during the 24hour period, as was reported in Zetterberg et al 1983, [91], in the younger and more skeletally immature individuals.

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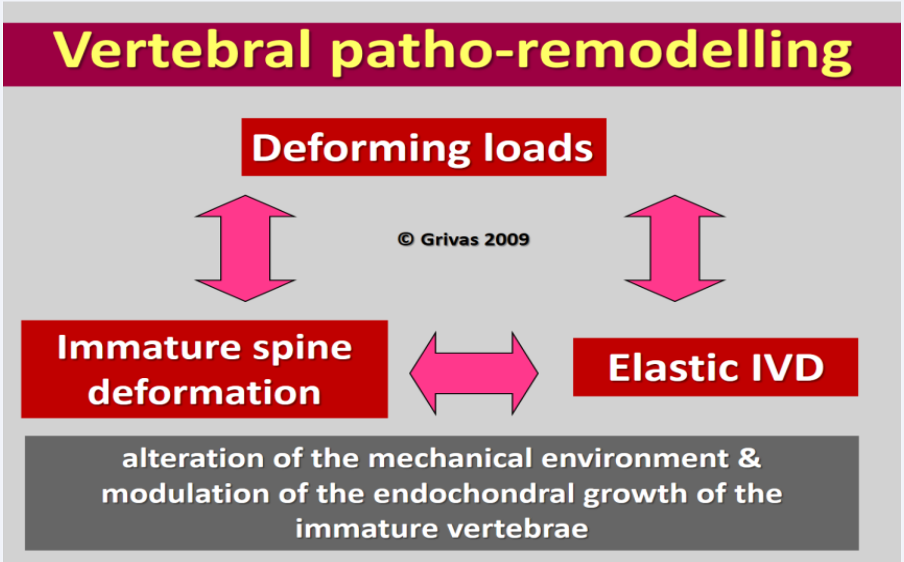

Figure 4 The vicious cycle of patho-remodelling in apical and adjacent vertebrae in a IS curve, due to alteration of the mechanical environment & modulation of the endochondral growth of the immature vertebrae.

The asymmetrical anatomical growth changes in the posterior vertebral elements have been confirmed, see Shea et al, 2004 [77]. This report states that on average, the facets on the convex side have an increased porosity and thinner cortical thickness, and vice versa in the concave site. However, the authors studied surgical cases with more or less developed and mature scoliotic bone; in these cases, it would seem more appropriate to apply Wolff's law. In the mature scoliotic vertebra, in compression loads in facets the cortical thickness increases and the porosity decreases; in tension - (less compression, rather than no tension, would be a more accurate term for the description of the forces) - the cortical thickness decreases and the porosity increases. The authors state that in "scoliotic deformities apply eccentric forces to spinal facets and that the concave and convex portions of the curve are subject to compression and tension forces, respectively. "Similarly, Wang et al., 2011 [78], in relation to the vicious cycle and mechano-transduction in the spine, state that "The progression of skeletal deformity during growth is believed to be governed by laws including the "Hueter-Volkmann Law," which states that growth depends on the amount of compression of the growth plate, which can be retarded by increased compression and accelerated by tension."In our opinion, it would be more proper to state that "scoliotic deformities apply eccentric forces to spinal facets and that the concave and convex portions of the curve are subject to compression and "relatively less compression or intermittently more and less compressive forces, respectively." Tension forces can be exerted naturally, if this happens, only during REM sleeping phase, when the atonic phase of the muscles occurs, because tension forces can be exerted on the human body only purposefully or externally or in a no-gravity environment. In all other sleep periods, that is in non-REM phases of sleep but also during daytime in stance posture, only compressive forces are more or less applied, as the muscles always have some degree of tone, no matter if this is strong, mild, or weak. These intermittent, more and less compressive forces, due to the DV phenomenon, apparently according to the Pauwel's low, stimulate growth at the ring epiphyses. We term the results of these intermittent forces, due to the DV, the "**accordion-like phenomenon**". Therefore, during the 24-hour cycle of a child's life, it is not reasonable to state that there is tension placed on the spine, due to the normal tone of muscles inserted in the vertebra or embracing the spine. And most certainly not while they are sitting or standing. Only when lay down during sleeping, tension may be produced, if not, while in the REM phase of sleep, when muscle tone decreases. Pauwel's law, applied to the growing vertebrae end plates, states that "the intermittent pressure within the normal limits of stress and strain stimulates the growth in the end-plate of a normal vertebra", [79]. The proposed model implies/entails the role of the DV and the asymmetric water distribution in the scoliotic IVD and the subsequent alteration of the mechanical environment of the adjacent vertebral growth plates. Hence, the deformation of the IVD contributes to the progression of IS curves. The eccentric NP of the deformed IVD in the IS spine, through DV in its water concentration, produces an asymmetrically cyclical load during the 24-hour period and an asymmetrical growth of the vertebral body and posterior elements, (Hueter-Volkmann and Pauwel's laws). The deformation of the apical IVD and the adjacent to apical discs seems to be an important contributory factor in the progression of a scoliotic curve [80].

Modulation of the IVD mechanical environment by applying corrective forces on the IS curve restores a close-to-normal force application on the vertebral growth plates, and consequently prevents curve progression. The forces are now transmitted evenly to the growth plate and increase the rate of proliferation of chondrocytes at the corrected pressure side, that is the concave side. Application of appropriately directed forces, ideally opposite to the apex of the deformity, likely leads to optimal correction. The wedging of the elastic IVD in the immature IS spine could be reversed by application of corrective forces on it. Reversal of IVD wedging is thus amended into a "corrective", rather than "progressive", factor of the deformity [81]. Through the proposed model, treatment of progressive IS with braces especially during night time period [90], physiotheraputic specific scoliosis exercises (PSSE) and growth modulation fusionless surgery by using stapling, growing rods, convex vertebral body tethering techniques or Vertebral growth modulation by posterior dynamic deformity correction devices, could be effective [82-88].

The study of scoliogeny aims to an aetiological treatment, rather than the currently applied symptomatic treatment. Treatment also aims to decrease the possibility of fusion of the spinal column, and to maintain the mobility of the spine, since the human spine is naturally modeled to be articulated and mobile. Additionally, as professor TKF Taylor stated, "the efficacy of early detection and surgical techniques cannot be denied but orthopaedic surgery is not relieved of the responsibility of pursuing the causation and pathogenesis of scoliotic curvature. Spinal fusion for scoliosis cuts across the fundamental principle of orthopaedic surgery – the preservation of musculoskeletal function. Clearly, a sacrifice of spinal mobility is not a final acceptable solution to the malady" [41].

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AUTHOR CONTRIBUTIONS

TBG conceived the concept of "diurnal variation "accordion"-like phenomenon of wedged intervertebral discs: a progression factor in idiopathic scoliosis", conducted the literature review, drafted the text, and fashioned the figures.

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