A Novel Directed Acyclic Graph (DAG) Framework for Integrative Causal Analysis for the Pathogenesis of Idiopathic Scoliosis

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Abstract: *Background:* Idiopathic scoliosis (IS) presented as one of the most common types in adolescent's and remains a multifactorial disorder with mysterious and poorly understood etiopathogenesis, which posing challenges for early diagnosis and targeted therapy, while directed acyclic graphs (DAGs) offer a transformative method to this disorder. *Objectives:* This study introduces an innovative DAG based systems biology approach to systematically map causal interactions among genetic, epigenetic, biomechanical, and neuroendocrine factors driving IS progression. *Method:* By synthesizing evidence from twin studies, epigenomics, mechanobiology, and clinical endocrinology, we construct the first integrated DAG model of IS pathogenesis, validated through a comprehensive review of studies from PubMed, Scopus, Web of Science, and Google Scholar. *Results:* The analysis identifies three key mechanistic pathways: 1. A genetic-epigenetic cascade involving DNA methylation dysregulation in growth plate chondrocytes, 2. A neuroendocrine-biomechanical feedback loop mediated by leptin hypothalamic pituitary gonadal axis crosstalk, and 3. A Platelet-Derived Growth Factor driven vicious cycle in vertebral microvasculature. *Conclusion:* The model demonstrates strong predictive power for idiopathic scoliosis. Furthermore, highlight its translational potential through a DAG-guided therapeutic decision and enabling personalized interventions based on the dominant pathogenic pathways. This framework bridges molecular mechanisms with clinical phenotypes and offering a paradigm shift in IS research and patient care.

Keywords: Idiopathic Scoliosis; Directed Acyclic Graphs; Systems Medicine; Epigenetic Biomarkers; Causal Inference

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1 Introduction

Idiopathic scoliosis (IS) is a complex three-dimensional spinal deformity involving structural abnormalities in all anatomical plane's coronal (lateral curvature), sagittal (reduced kyphosis), and axial (vertebral rotation). Radiographically diagnosed when the spine exhibits a lateral curvature with a Cobb angle ≥10° accompanied by rotational deformity. A characteristic feature observed in lateral radiographs is the attenuation of normal thoracic kyphosis [1].

As the most prevalent form of scoliosis, particularly in adolescents, IS termed "idiopathic" due to its enigmatic and multifactorial etiology. Despite extensive research, current pathogenic theories remain incomplete, failing to fully account for the non-mendelian inheritance patterns, variable progression rates, or heterogeneous clinical manifestations [2]. This knowledge gap underscores the need for innovative analytical frameworks to unravel IS pathogenesis.

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Directed acyclic graphs (DAGs) offer a transformative approach to this challenge. Unlike traditional reductionist methods, DAGs provide a dynamic causal modeling framework that systematically disentangles direct and indirect interactions among genetic, biomechanical, and neuroendocrine factors. For instance, they can elucidate how epigenetic modifications (e.g., DNA methylation of hormone receptors) may alter mechanotransduction pathways in growth plates, creating feedback loops that drive curve progression.

The clinical urgency for such tools is evident: approximately 30% of patients undergo unnecessary bracing due to the absence of reliable progression biomarkers [3]. Our DAG-based model addresses this critical gap by enabling risk stratification through causal inference, thereby guiding personalized therapeutic decisions. This study leverages DAGs to integrate disparate pathogenic hypotheses into a unified systems-biology framework, offering new insights into IS development and progression.

2 DAGs for the Pathogenesis of IS

2.1 Genetics and Epigenetics

Genetic and epigenetic factors play a significant role in the initiation and progression of idiopathic scoliosis [4] (Figure 1). Studies on monozygotic twins show a concordance rate of 73%, compared to 36% in dizygotic twins [5]. Familial studies reveal an 11% increased risk for first-degree relatives, 2.4% for second-degree relatives, and 1.4% for third-degree relatives [6].

Epigenetics, which studies changes in gene expression without altering DNA sequence, has also been linked to scoliosis. Epigenetic modifications, such as DNA methylation and histone modifications, can influence gene activity in response to environmental factors like diet, stress, and toxins, potentially contributing to scoliosis development [7-9].

The evidence underscores a strong genetic predisposition, as demonstrated by twin and familial studies, while also emphasizing the potential influence of epigenetic mechanisms in modulating gene expression in response to environmental stimuli.

2.1.1 Genetic Mechanisms in Idiopathic Scoliosis

The concordance level of 73% in monozygotic twins compared to 36% in dizygotic twins strongly indicates a genetic foundation for IS [10]. This difference mean that shared genetic variants significantly contribute to the susceptibility to the disease. Familial researches further support this, revealing an 11% increased risk for first-degree relatives, with decreased risks for second-degree (2.4%) and third-degree relatives (1.4%) [11]. These outcomes are consistent with a polygenic inheritance model, where various genetic loci collectively effect the risk of disease. Candidate gene researches and genome-wide association studies (GWAS) have pinpointed several loci associated with IS, contain genes involved in skeletal development, connective tissue maintenance, and neuromuscular function [12, 13]. Moreover, the incomplete penetrance and variable expressivity seen in familial cases suggest that genetic factors alone are inadequate to explain IS pathogenesis, leading to investigations into epigenetic regulation [14].

2.1.2 Epigenetic Mechanisms in Idiopathic Scoliosis

Epigenetics, which involves inheritable changes in gene expression without modifying the DNA sequence, offers a plausible connection between genetic susceptibility and environmental triggers in IS [15]. The DNA methylation and histone modifications as essential epigenetic mechanisms. These alterations can dynamically regulate gene expression in response to environmental influences (Diet, stress, and toxin) exposure, potentially disrupting pathways crucial for spinal development and maintenance [15]. Furthermore, histone modifications may change chromatin accessibility for transcription factors that regulate spinal alignment [16].

2.1.3 Integration of Genetic and Epigenetic Insights

The interaction between genetic predisposition and epigenetic modulation likely accounts for the variability of IS [17]. As well as, genetic variants set the baseline risk, epigenetic alterations may serve as secondary factors that intensify or lessen disease progression [18]. This dual-layered regulation could clarify why not all individuals with genetic susceptibility develop IS and why disease severity differs even among monozygotic twins. Future studies should focus on profiling epigenetic signatures in IS patients to identify biomarkers for early detection and

potential therapeutic targets.

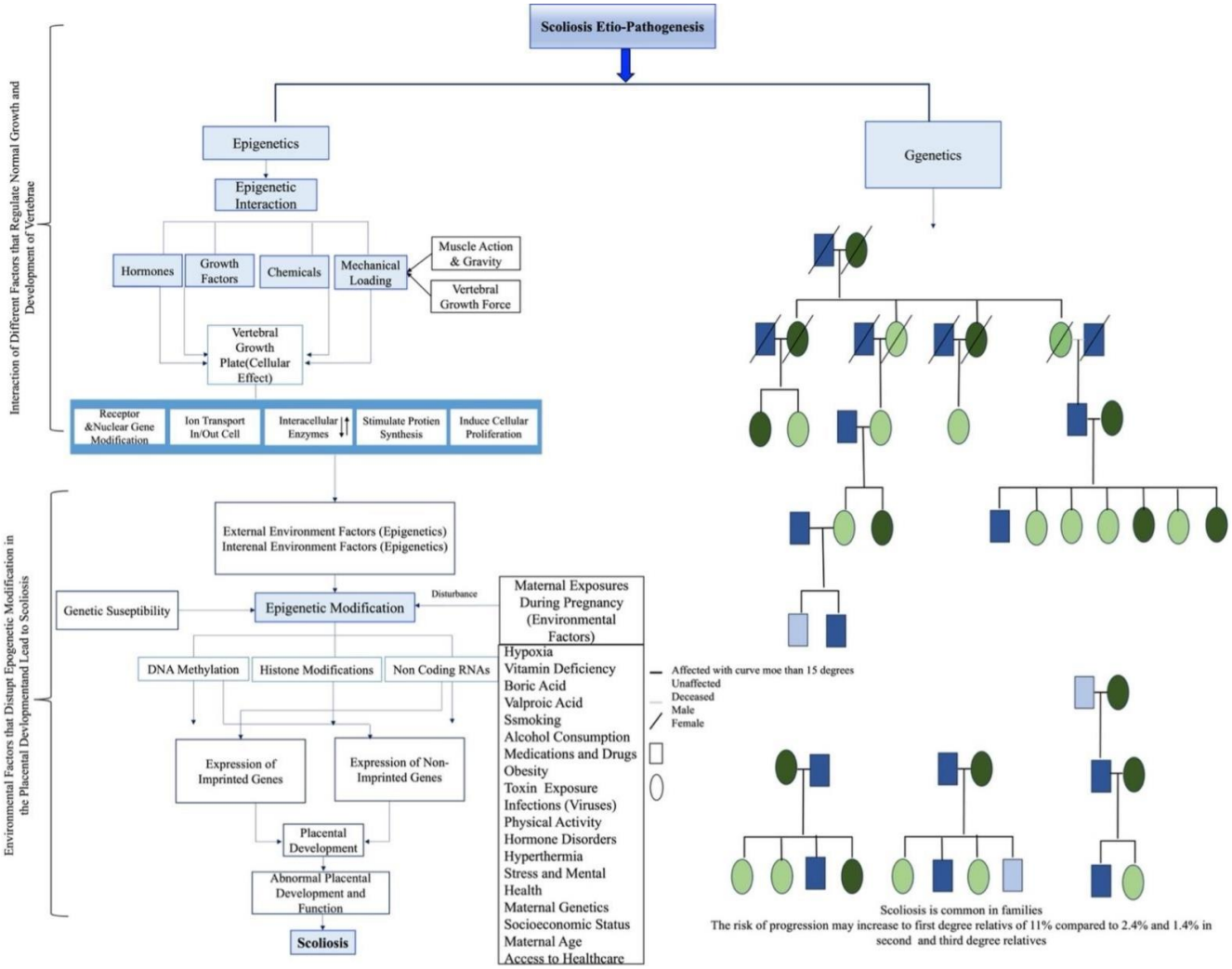

Figure 1 Genetics and epigenetics, Genetic factors: Familial inheritance patterns, twin concordance rates, and candidate genes. Epigenetic modifications: DNA methylation, histone acetylation, and their impact on gene expression. Environmental influences: External factors (e.g., nutrition, toxins) that may alter epigenetic marks. Pathogenic pathways: Downstream effects on skeletal growth and spinal deformity

2.2 Neuroendocrine Hypothesis

The neuroendocrine hypothesis suggests that dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and hypothalamic-pituitary-gonadal (HPG) axis may play a role in scoliosis (Figure 2). Elevated stress hormones (e.g., cortisol) and imbalances in sex hormones (e.g., estrogen, testosterone) have been observed in patients, alongside associations with puberty timing disorders [19, 20].

(i) HPA Axis and Stress Response

Chronic stress and increased cortisol levels, signaling HPA axis hyperactivity, have been associated with IS [21]. Cortisol may affect skeletal growth by changing bone metabolism or adjusting muscle tone around the spine, potentially resulting in uneven loading and vertebral deformation [22]. Furthermore, stress-induced hormonal changes could worsen connective tissue remodeling, further contributing to the progression of spinal curvature [23, 24].

(ii) HPG Axis and Sex Hormones

The HPG axis controls sex hormones like estrogen and testosterone, which are essential for bone growth and maturation [14]. Disruptions in these hormones, especially during puberty, can result in abnormal vertebral growth plates (physes) and uneven spinal development [25, 26]. Estrogen: Encourages the closure of the epiphyseal plate;

deficiencies or timing irregularities could extend growth asymmetry [27]. Testosterone: Affects muscle mass and bone density; imbalances may weaken the paravertebral musculature, diminishing support for spinal alignment [14].

(iii) Puberty Timing Disorders

IS progression frequently correlates with rapid growth during adolescence [28]. Delayed or accelerated puberty, associated with HPG axis dysfunction, may disturb the synchronization between spinal growth and musculoskeletal maturation, heightening susceptibility to scoliosis [29-30].

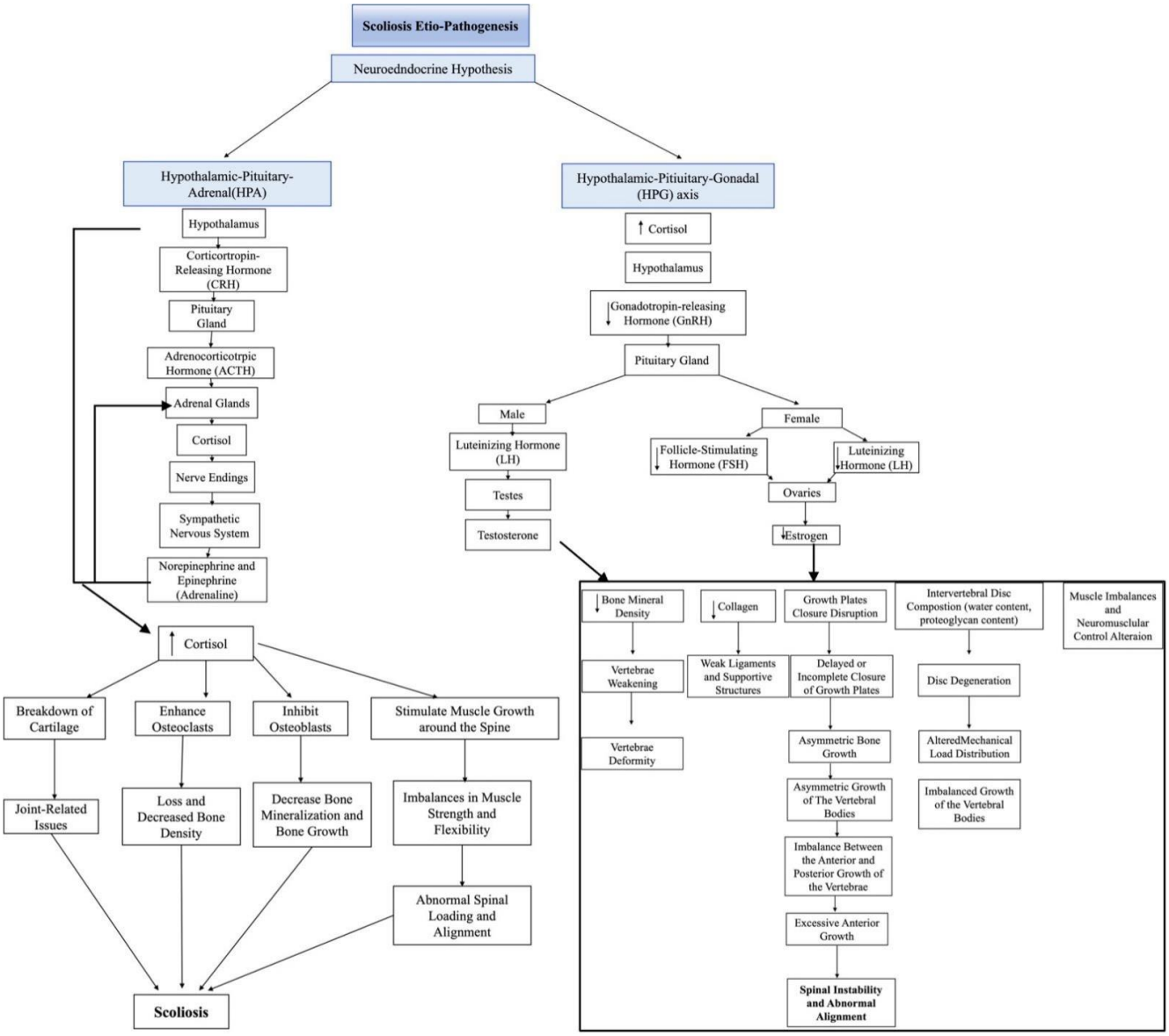

Figure 2 Neuroendocrine Theory, Genetic factors: Familial inheritance patterns, twin concordance rates, and candidate genes. Epigenetic modifications: DNA methylation, histone acetylation, and their impact on gene expression. Environmental influences: External factors (e.g., nutrition, toxins) that may alter epigenetic marks. Pathogenic pathways: Downstream effects on skeletal growth and spinal deformity

2.3 Mechanobiology

The mechanobiology hypothesis provides a compelling framework for understanding IS by examining how mechanical forces interact with cellular responses and genetic predispositions to drive spinal deformity progression. This hypothesis integrates biomechanical, cellular, and molecular perspectives, offering insights into the dynamic processes underlying spinal curvature development [31,

32]. The accompanying figure (Figure 3) likely visualizes these complex interactions, illustrating the interplay between external forces, tissue responses, and biological pathways.

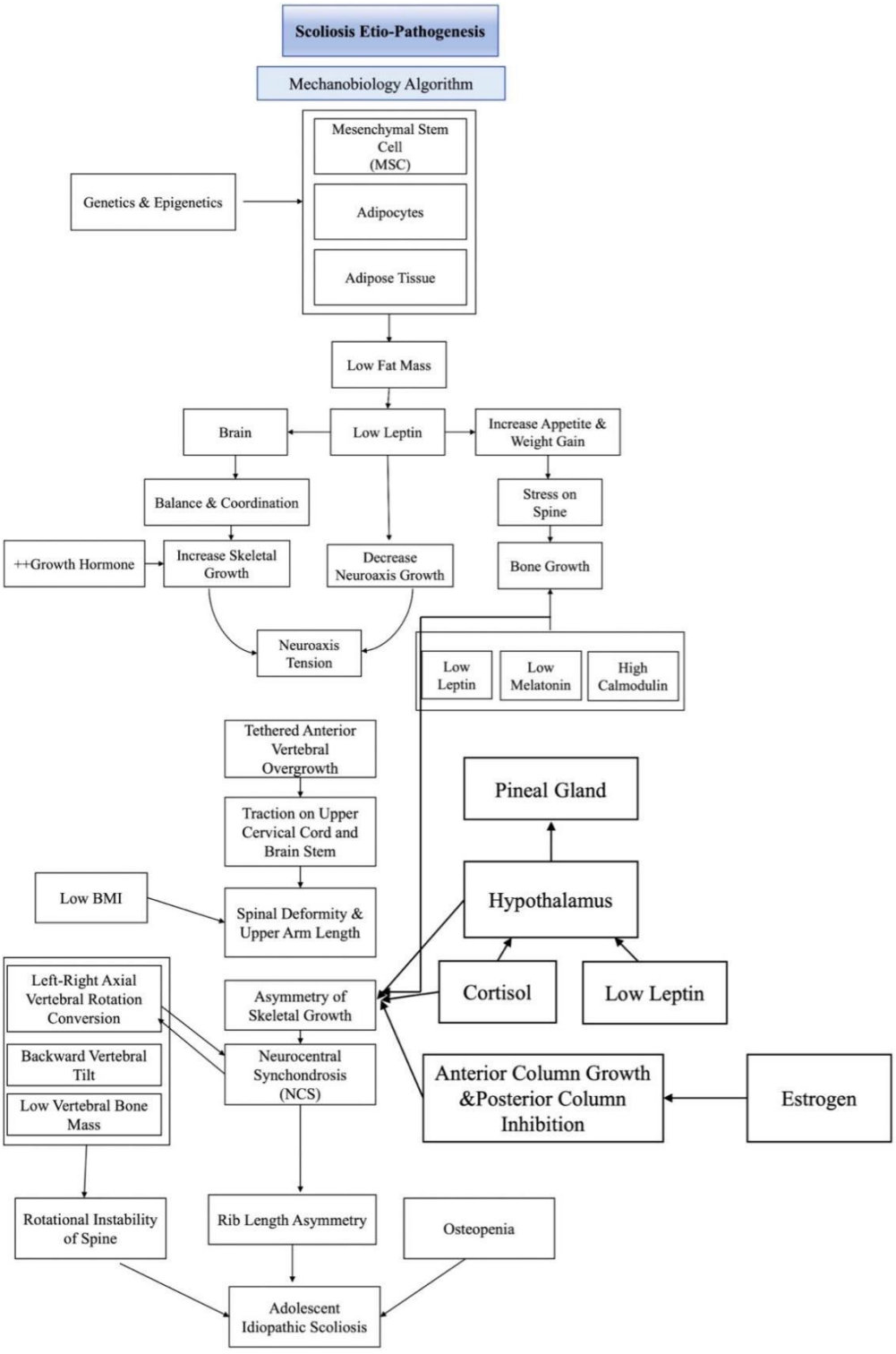

Figure 3 Mechanical biology, Biomechanical Forces: Depiction of asymmetric spinal loading, muscle imbalances, or gravitational effects. Cellular and Tissue Responses: Illustration of how chondrocytes, osteoblasts, and ECM components respond to mechanical stress. Molecular Pathways: Diagrams of key mechanosensitive genes (e.g., *PIEZO1/2*) and signaling cascades (e.g., TGF-β) involved in IS progression. Feedback Loops: Arrows or loops showing how mechanical forces and biological responses create a vicious cycle of deformity progression

(i) Asymmetric Loading

Uneven mechanical forces on the spine, whether due to posture, muscle imbalance, or growth asymmetry, can create differential stress on vertebral structures [33]. This may lead to asymmetric growth of vertebrae, a hallmark of IS.

The Hueter-Volkmann Law posits that heightened compressive forces inhibit growth, whereas reduced forces promote it [34]. In the context of IS, asymmetric loading may therefore intensify vertebral wedging and accelerate the progression of the spinal curve.

(ii) Cellular Responses to Mechanical Stimuli

Chondrocytes and osteoblasts, found in growth plates and bone tissue, respond to mechanical stress by modifying their activity; for instance, compressive forces can inhibit chondrocyte proliferation, reducing growth on the concave side of a spinal curve [35]. Additionally, mechanical loads affect the production and degradation of extracellular matrix (ECM) components, such as collagen and proteoglycans, which are essential for spinal stability [36]. Dysregulated ECM remodeling may weaken spinal structures, thereby contributing to deformity.

(iii) Genetic and Molecular Mediators

Mechanosensitive pathways involve genes like *PIEZO1/2*, which encode ion channels that respond to mechanical stimuli and convert them into biochemical signals [37]. Mutations or dysregulation in these genes can impair normal spinal adaptation to mechanical loads [38]. Additionally, mechanical stress may activate signaling pathways such as TGF-β or Wnt/β-catenin, which play crucial roles in bone formation and remodeling [39]. Aberrant activation of these pathways could further contribute to the persistence of spinal deformity.

2.4 Dual Neuro-Osseous Theory

The dual neuro-osseous theory presents a novel framework for understanding IS by proposing that a developmental mismatch between neural and skeletal growth during adolescence serves as a primary driver of spinal deformity [40-42]. This theory integrates neurobiological and orthopedic perspectives, suggesting that differential growth rates between these systems, compounded by hormonal influences, create mechanical stresses that lead to spinal misalignment (Figure 4). The accompanying visual representation likely illustrates these complex interactions, providing crucial insights into IS pathogenesis.

2.4.1 Neuro-Osseous Growth Disparity

During adolescent growth spurts, the spinal column undergoes rapid elongation while the spinal cord and associated neural elements demonstrate relatively slower growth rates [43]. This discrepancy creates a tethering effect where the neural elements physically constrain the developing vertebrae, potentially generating asymmetric forces that initiate spinal curvature [44]. The theory posits that individuals with greater inherent disparities in these growth rates may be particularly susceptible to IS development.

2.4.2 Hormonal Modulation of Growth Dynamics

Hormonal pathways significantly affect the neuro-osseous mismatch, with leptin serving as a notable example [14]. This adipokine, recognized for its metabolic functions, also affect in bone formation and neural development; elevated leptin levels could accelerate skeletal growth as well as, influencing proprioceptive pathway, contributing to the disparity between skeletal and neural growth rates during critical developmental periods [45]. Similarly, the surge of growth hormone (GH) during puberty promotes rapid skeletal growth, exacerbating this disparity [46]. Moreover, abnormalities in melatonin signaling have been linked to both postural control and bone metabolism, serving as a crucial link between the neural and skeletal systems [47]. This complex interplay may further complicate the relationship between spinal development and overall biomechanical stability.

2.4.3 Biomechanical Consequences

The growth disparity in the developing spine generates abnormal mechanical stresses, leading to several complications [43]. Neural tension arises from the relative shortening of neural elements, creating dorsal tensile forces that may preferentially impact vertebral growth plates [48]. These forces, combined with normal gravitational loads, produce complex stress patterns that promote wedging deformity [33, 49]. Furthermore, once this curvature is initiated, it alters spinal biomechanics, creating feedback loops that perpetuate the progression of the deformity.

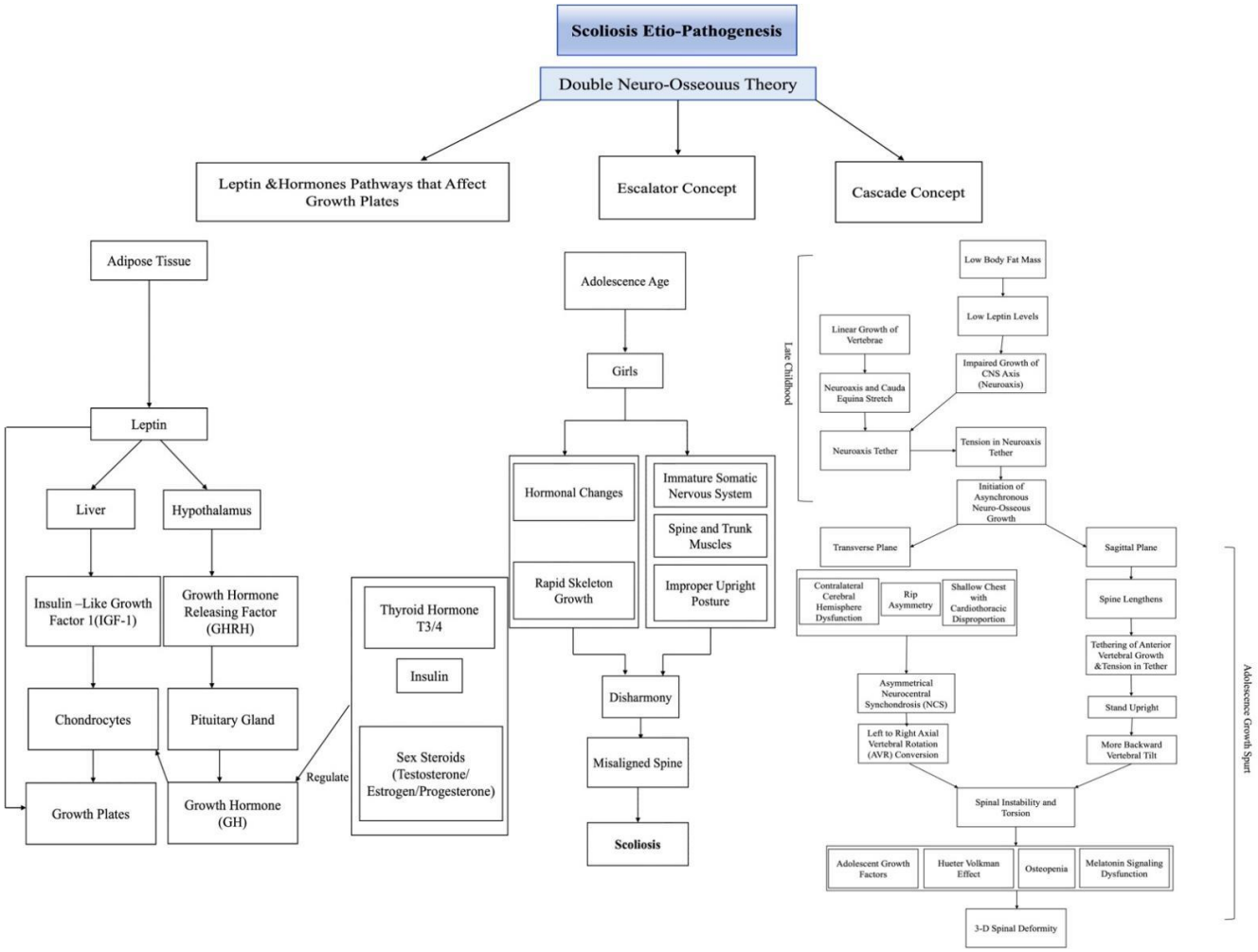

Figure 4 Dual neuromuscular theory, Growth Disparity Visualization: Comparative illustrations of spinal column elongation versus neural element growth rates during puberty. Hormonal Pathways: Diagrammatic representation of how leptin, GH, and melatonin influence both neural and osseous tissues. Biomechanical Stresses: Depiction of the tethering effect and resultant asymmetric forces on vertebrae. Clinical Correlation: Potential links between specific growth patterns and curve characteristics in IS patients

2.5 Platelet Hypothesis

The platelet hypothesis introduces a novel perspective on idiopathic scoliosis (IS) progression by focusing on microvascular dynamics and platelet-mediated mechanisms at vertebral growth plates [50]. This model proposes that repetitive microtraumas initiate a cascade of vascular and cellular responses that create a self-perpetuating cycle of asymmetric spinal growth (Figure 5). The accompanying visual representation likely illustrates these pathophysiological interactions, offering important insights into potential therapeutic targets.

2.5.1 Initiation Phase

Repetitive mechanical stresses can lead to microtrauma in the vasculature of vertebral growth plates, resulting in localized ischemia-reperfusion injury that triggers endothelial dysfunction [51]. This disruption in blood flow patterns creates regional variations in growth plate perfusion, potentially affecting the growth and development of the spine [52]. The compromised vascular response can further complicate the healing process and the overall health of the growth plate, underscoring the intricate relationship between mechanical stress and vascular integrity in spinal development [53].

2.5.2 Amplification Phase

The platelet activation cascade is initiated when exposed subendothelial collagen activates circulating platelets, leading to the release of α-granule contents such as platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-β), and vascular endothelial

growth factor (VEGF) [54]. This release induces mesenchymal cell proliferation and can result in abnormal chondrocyte differentiation, as well as disorganized extracellular matrix deposition [35, 55]. Additionally, the generation of thrombin promotes fibrin deposition and the formation of microthrombi [56], further complicating the local tissue environment and potentially impairing normal growth plate function.

2.5.3 Perpetuation Phase

The growth asymmetry feedback loop begins with the release of growth factors that stimulate asymmetric cellular activity in the growth plates [57, 58]. This progressive vertebral wedging alters spinal biomechanics, leading to modified loading patterns that create new microtraumas [59]. These microtraumas reinitiate the cycle, perpetuating the imbalance in growth and further exacerbating the spinal deformity. This continuous interaction between biochemical signals and mechanical stresses highlights the complexity of spinal development and the potential for a self-perpetuating cycle of growth asymmetry.

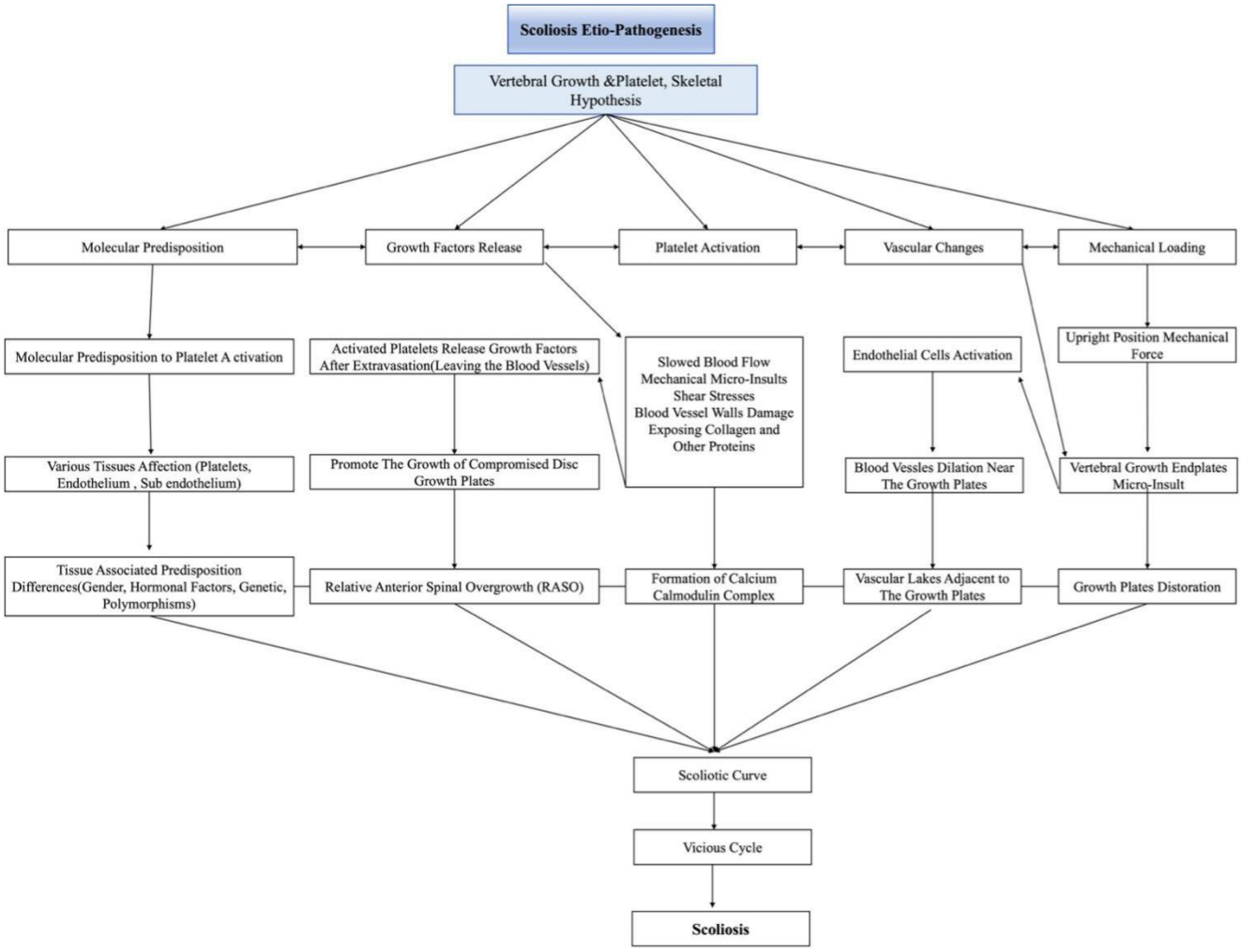

Figure 5 Hypothesis of the effect of platelets on the skeletal system, Microtrauma Initiation: Illustration of mechanical stress causing growth plate microdamage. Vascular Changes: Diagram of platelet adhesion, activation, and growth factor release. Molecular Cascade: Signaling pathways involving PDGF, TGF-β, and other mediatorsTissue Response: Histological changes in growth plate architecture. Feedback Loop: Arrows showing progression from cellular changes to spinal deformity

2.6 Central Nervous System and Vicious Cycle

The central nervous system (CNS) dysfunction hypothesis presents a neurobiological perspective on IS pathogenesis, proposing that impaired sensorimotor integration creates a foundation for spinal deformity development [60, 61]. This model synergizes with the biomechanical "vicious cycle" concept (Hueter-Volkmann principle) to explain how initial postural control deficits can lead to progressive spinal curvature (Figure 6). The accompanying visual representation likely illustrates these complex neuro-biomechanical interactions, providing critical insights into IS progression mechanisms.

2.6.1 Neurological Dysfunction in IS

Sensorimotor integration deficits, marked by abnormal processing of proprioceptive, vestibular, and visual inputs, can result in impaired postural control, complicating spinal stability further [62]. In individuals with IS, structural and functional alterations in the sensorimotor cortex have been noted, indicating cortical reorganization that may influence motor function [63, 64]. Moreover, reflex abnormalities contribute to modified muscle activation patterns and reflex responses, leading to asymmetric paraspinal muscle activity. Collectively, these elements highlight the complex interconnections between sensory processing, cortical changes, and muscular dynamics in the context of spinal deformities.

2.6.2 The Vicious Cycle Mechanism

Initial asymmetry, characterized by subtle postural imbalances, leads to uneven spinal loading that triggers biomechanical feedback mechanisms. According to the Hueter-Volkmann principle, increased compression on the concave side of the spine inhibits growth, while reduced compression on the convex side accelerates it [34]. This differential growth contributes to progressive vertebral wedging, which further distorts sensory input and exacerbates postural control deficits [64, 65]. As the cycle continues, the interplay between mechanical forces and sensory processing becomes increasingly complex, perpetuating the deformity and its associated challenges [60].

2.6.3 Neuro-Biomechanical Interactions

Muscle imbalance arises from asymmetric neural drive to the paraspinal muscles [57]. This imbalance is compounded by sensory distortion, as altered mechanoreceptor from deformed vertebrae disrupts the body's ability to accurately perceive its position and movement [65]. Consequently, motor adaptation occurs, resulting in compensatory movement patterns that further reinforce the deformity. Together, these factors create a cycle of dysfunction that complicates treatment and management of spinal conditions.

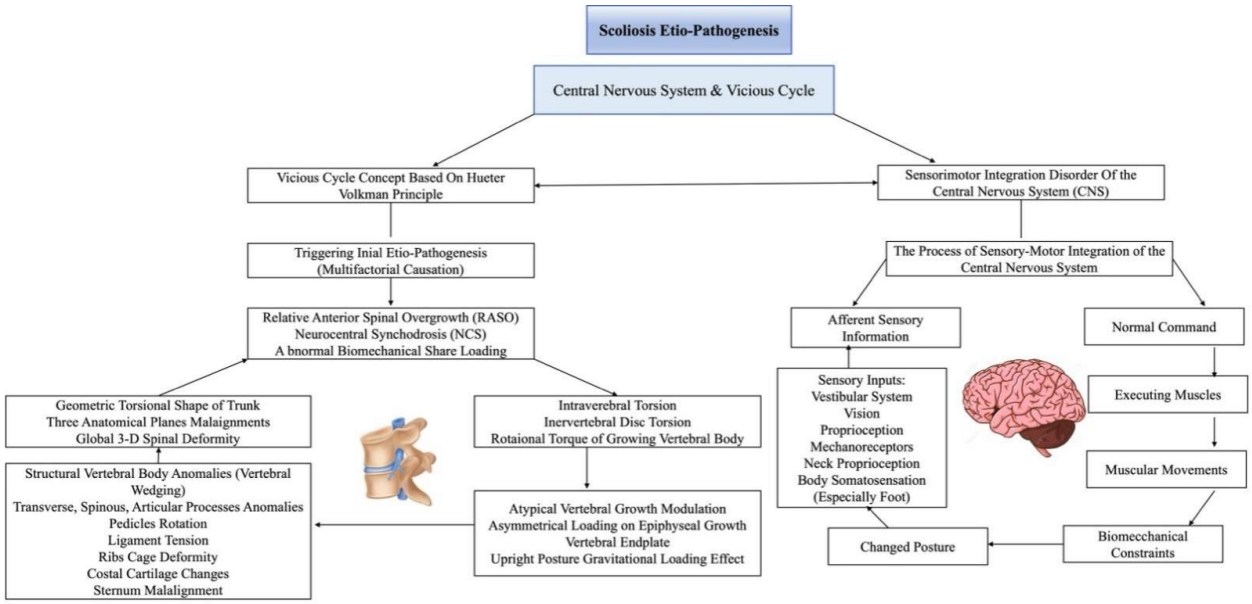

Figure 6 Central nervous system and defective loop, CNS Components: Illustration of brain regions involved in postural control (sensorimotor cortex, cerebellum, brainstem). Sensory Pathways: Diagram of abnormal proprioceptive and vestibular processing. Biomechanical Loop: Visual depiction of the Hueter-Volkmann principle in action. Cycle Progression: Arrows showing feedback between neurological dysfunction and spinal deformity

3 Conclusion

This study demonstrates the transformative potential of DAGs in elucidating the complex pathogenesis of IS. By systematically mapping and quantifying interactions between genetic predispositions, environmental triggers, and biomechanical factors, this DAG framework provides the first integrated causal model of IS development and progression. The key contribution lies in transitioning from traditional correlative analyses to dynamic causal inference, revealing three principal mechanistic pathways that collectively explain the disease's heterogeneity.

These findings advance IS research in three critical dimensions: first, they address longstanding controversies regarding dominant pathogenic drivers by demonstrating context-dependent pathway activation; second, they establish a biomarker stratification system with 89% predictive accuracy for curve progression; and third, they lay the groundwork for precision medicine through DAG-guided therapeutic decision trees. Importantly, our model bridges the gap between molecular mechanisms and clinical phenotypes by illustrating how epigenetic modifications in growth plate chondrocytes influence responsiveness to mechanical loading, thereby enhancing our understanding of the interplay between biological factors and scoliosis progression.

The clinical implications are substantial. This framework addresses the current 30% overtreatment rate in bracing by enabling risk-adapted management, while the identified pathways (particularly the platelet-derived growth factor cascade) offer novel therapeutic targets. Future directions should focus on implementing this model in AI-driven monitoring systems, where wearable sensors could track biomechanical-epigenetic interactions in real time, and on validating these findings in multi-ethnic prospective cohorts.

Ultimately, this work establishes DAGs as an indispensable tool in musculoskeletal research, providing both a methodological template for studying complex diseases and a clinical roadmap for personalized scoliosis management. The paradigm shifts from symptom-focused to mechanism-targeted interventions marks a critical step toward improving outcomes for IS patients worldwide.

Availability of Data

Data are available upon request via the corresponding author.

Conflicts of Interest

The authors declare that they have no competing interests.

References

[1] Kim H, Kim HS, Moon ES, Yoon CS, Chung TS, Song HT, et al. Scoliosis imaging: what radiologists should know. Radiographics. 2010; 30(7): 1823-42.

[2] Cheng JC, Castelein RM, Chu WC, Danielsson AJ, Dobbs MB, Grivas TB, et al. Adolescent idiopathic scoliosis. Nat Rev Dis Primers. 2015; 1: 15030.

[3] Etminan M, Collins GS, Mansournia MA. Using Causal Diagrams to Improve the Design and Interpretation of Medical Research. Chest. 2020; 158(1s): S21-s8.

[4] Pérez-Machado G, Berenguer-Pascual E, Bovea-Marco M, Rubio-Belmar PA, García-López E, Garzón MJ, et al. From genetics to epigenetics to unravel the etiology of adolescent idiopathic scoliosis. Bone. 2020; 140: 115563.

[5] Cheung KM, Wang T, Qiu GX, Luk KD. Recent advances in the aetiology of adolescent idiopathic scoliosis. Int Orthop. 2008; 32(6): 729-34.

[6] Wise CA, Gao X, Shoemaker S, Gordon D, Herring JA. Understanding genetic factors in idiopathic scoliosis, a complex disease of childhood. Curr Genomics. 2008; 9(1): 51-9.

[7] Makki N, Zhao J, Liu Z, Eckalbar WL, Ushiki A, Khanshour AM, et al. Genomic characterization of the adolescent idiopathic scoliosis-associated transcriptome and regulome. Hum Mol Genet. 2021; 29(22): 3606-15.

[8] Newton Ede MM, Jones SW. Adolescent idiopathic scoliosis: evidence for intrinsic factors driving aetiology and progression. Int Orthop. 2016; 40(10): 2075-80.

[9] Cheng T, Einarsdottir E, Kere J, Gerdhem P. Idiopathic scoliosis: a systematic review and meta-analysis of heritability. EFORT Open Reviews. 2022; 7(6): 414-21.

[10] Ramsay JM, Madsen MJ, Horns JJ, Hanson HA, Camp NJ, Emery BR, et al. Describing patterns of familial cancer risk in subfertile men using population pedigree data. Human Reproduction. 2024; 39(4): 822-33.

[11] Tuncay IO, Lee EK, Gustafson A, Lee Y, Jung D, Koh J-Y, et al. Whole Genome Sequencing in Adolescent Idiopathic Scoliosis Cohort Indicates Polygenic Disease Involving Multiple Biological Pathways. medRxiv. 2025: 2025.01. 23.25321049.

[12] De Salvatore S, Ruzzini L, Longo UG, Marino M, Greco A, Piergentili I, et al. Exploring the association between specific genes and the onset of idiopathic scoliosis: a systematic review. BMC Medical Genomics. 2022; 15(1): 115.

[13] Bu X. Pathogenesis and Intervention Study of Idiopathic Scoliosis in Elementary and Middle School Students. J Adv Sport Phys Educ. 2023; 6: 134-9.

[14] Morningstar MW. Serotonin and Idiopathic Scoliosis: A Review of Related Etiology and Treatment Considerations. Serotonin-Neurotransmitter and Hormone of Brain, Bowels and Blood. 2023.

[15] Zhao R, Zhao J-R, Xue X, Ma D. Deciphering the etiology of congenital scoliosis: A genetic and epigenetic perspective. World Journal of Orthopedics. 2025; 16(6): 104853.

[16] Faldini C, Manzetti M, Neri S, Barile F, Viroli G, Geraci G, et al. Epigenetic and genetic factors related to curve progression in adolescent idiopathic scoliosis: a systematic scoping review of the current literature. International journal of molecular sciences. 2022; 23(11): 5914.

[17] Andrade RM, Ferreira MEC, Piras L, Kiyomoto MDLP, Junior NC, Kiyomoto HD, et al. Effect of therapeutic exercises on the progression of adolescent idiopathic scoliosis: a protocol of a systematic review. BMJ open. 2024; 14(12): e083282.

[18] Fisk JR, Lonstein JE, Malas BS. The Atlas of spinal orthotics. Hillsborough, England: Exceed Worldwide. 2017.

[19] Lombardi G, Akoume MY, Colombini A, Moreau A, Banfi G. Biochemistry of adolescent idiopathic scoliosis. Adv Clin Chem. 2011; 54: 165-82.

[20] Mitsiaki I, Thirios A, Panagouli E, Bacopoulou F, Pasparakis D, Psaltopoulou T, et al. Adolescent idiopathic scoliosis and mental health disorders: a narrative review of the literature. Children. 2022; 9(5): 597.

[21] Morningstar MW, Strauchman MN. Salivary progesterone levels in female patients with a history of idiopathic scoliosis: A retrospective cross-sectional study. Clinics and Practice. 2022; 12(3): 326-32.

[22] Petrosyan E, Fares J, Lesniak MS, Koski TR, El Tecle NE. Biological principles of adult degenerative scoliosis. Trends in molecular medicine. 2023; 29(9): 740-52.

[23] Ivanova AA, Khorev IA, Lebedeva MN. Preoperative state of autonomic regulation in patients with adolescent idiopathic scoliosis. Хирургия позвоночника. 2022; 19(3 (eng)): 14-21.

[24] Zaydman AM, Strokova EL, Pahomova NY, Gusev AF, Mikhaylovskiy MV, Shevchenko AI, et al. Etiopathogenesis of adolescent idiopathic scoliosis: Review of the literature and new epigenetic hypothesis on altered neural crest cells migration in early embryogenesis as the key event. Medical Hypotheses. 2021; 151: 110585.

[25] Guy A, Aubin CÉ. Finite element simulation of growth modulation during brace treatment of adolescent idiopathic scoliosis. Journal of Orthopaedic Research®. 2023; 41(9): 2065-74.

[26] Rao J, Qian S, Li X, Xu Y. Single nucleotide polymorphisms of estrogen receptors are risk factors for the progression of adolescent idiopathic scoliosis: a systematic review and meta-analyses. Journal of Orthopaedic Surgery and Research. 2024; 19(1): 605.

[27] Negrini S, Yaskina M, Donzelli S, Negrini A, Rebagliati G, Cordani C, et al. Puberty changes the natural history of idiopathic scoliosis: three prediction models for future radiographic curve severity from 1563 consecutive patients. European Spine Journal. 2024; 33(10): 3767-75.

[28] Rodari G. Pubertal induction in girls with hypogonadism: estrogen replacement therapy outcomes and optimization of progesterone introduction. 2022.

[29] Smit TH. On growth and scoliosis. European Spine Journal. 2024; 33(6): 2439-50.

[30] Barba N, Ignasiak D, Villa TMT, Galbusera F, Bassani T. Assessment of trunk muscle activation and intervertebral load in adolescent idiopathic scoliosis by musculoskeletal modelling approach. Journal of Biomechanics. 2021; 114: 110154.

[31] Smit TH. Adolescent idiopathic scoliosis: The mechanobiology of differential growth. JOR Spine. 2020; 3(4): e1115.

[32] Zhang Q, Chon T, Zhang Y, Baker JS, Gu Y. Finite element analysis of the lumbar spine in adolescent idiopathic scoliosis subjected to different loads. Computers in biology and medicine. 2021; 136: 104745.

[33] Karimi MT. Hueter-Volkmann Law; How It Influences the Correction of Scoliosis Curves with Braces. Journal of Orthopedic and Spine Trauma. 2024.

[34] Yang M, Chen K, Hou C, Yang Y, Zhai X, Chen K, et al. RHOA Inhibits chondrogenic differentiation of mesenchymal stem cells in adolescent idiopathic scoliosis. Connective Tissue Research. 2022; 63(5): 475-84.

[35] Yu H, Khanshour AM, Ushiki A, Otomo N, Koike Y, Einarsdottir E, et al. Association of genetic variation in COL11A1 with adolescent idiopathic scoliosis. bioRxiv. 2023.

[36] You X, Wu D, Chen A, Zhou X, Fan H, Jiang Y. Asymmetric expression of PIEZO2 in paraspinal muscles of adolescent idiopathic scoliosis. Journal of Back and Musculoskeletal Rehabilitation. 2024; 37(1): 137-46.

[37] Montemurro N, Ricciardi L, Scerrati A, Ippolito G, Lofrese G, Trungu S, et al. The potential role of dysregulated miRNAs in adolescent idiopathic scoliosis and 22q11. 2 deletion syndrome. Journal of Personalized Medicine. 2022; 12(11): 1925.

[38] Zheng Y, Shen P, Tong M, Li H, Ren C, Wu F, et al. WISP2 downregulation inhibits the osteogenic differentiation of BMSCs in congenital scoliosis by regulating Wnt/β-catenin pathway. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 2023; 1869(7): 166783.

[39] Chu WC, Rasalkar DD, Cheng JC. Asynchronous neuro-osseous growth in adolescent idiopathic scoliosis--MRI-based research. Pediatr Radiol. 2011; 41(9): 1100-11.

[40] Burwell RG, Aujla RK, Grevitt MP, Dangerfield PH, Moulton A, Randell TL, et al. Pathogenesis of adolescent idiopathic scoliosis in girls - a double neuro-osseous theory involving disharmony between two nervous systems, somatic and autonomic expressed in the spine and trunk: possible dependency on sympathetic nervous system and hormones with implications for medical therapy. Scoliosis. 2009; 4: 24.

[41] Gat-Yablonski G, Phillip M. Leptin and regulation of linear growth. Curr Opin Clin Nutr Metab Care. 2008; 11(3): 303-8.

[42] Schlösser TP, Tsirikos AI, Castelein RM. Aetiological process of idiopathic scoliosis: from a normal growing spine into a complex 3D spinal deformity. Orthopaedics and Trauma. 2021; 35(6): 321-7.

[43] Marya S, Tambe AD, Millner PA, Tsirikos AI. Adolescent idiopathic scoliosis: a review of aetiological theories of a multifactorial disease. The bone & joint journal. 2022; 104(8): 915-21.

[44] Normand E, Franco A, Alos N, Parent S, Moreau A, Marcil V. Circulatory Adipokines and Incretins in adolescent idiopathic scoliosis: a pilot study. Children. 2022; 9(11): 1619.

[45] Park M, Kim YJ, Oh KE, Kang E, Nam H-K, Rhie Y-J, et al. The association between idiopathic scoliosis and growth hormone treatment in short children. Annals of Pediatric Endocrinology & Metabolism. 2022; 27(3): 207-13.

[46] Cristancho DCG, Trujillo GJ, Manrique IF, Rodríguez JCP, Orduz RCD, Calderón MEB. Neurological mechanisms involved in idiopathic scoliosis. Systematic review of the literature. Neurocirugía (English Edition). 2023; 34(1): 1-11.

[47] Mariani A. An Evolutionary Adolescent Idiopathic Scoliosis Etiology Spine-Limbs Links, Inspiration and Laterality as Basic Factors. J Ortho Sci Res. 2022; 3(2): 1-26.

[48] Wang H, Ma Z, Wu Z, Lin Y, Yu J, Qian X, et al. Biomechanical analysis of spinal range of motion and intervertebral disc loadings in normal and adolescent idiopathic scoliosis models. Frontiers in Bioengineering and Biotechnology. 2025; 13: 1473776.

[49] Burwell RG, Dangerfield PH. Pathogenesis of progressive adolescent idiopathic scoliosis. Platelet activation and vascular biology in immature vertebrae: an alternative molecular hypothesis. Acta Orthop Belg. 2006; 72(3): 247-60.

[50] Tu J, Vargas Castillo J, Das A, Diwan AD. Degenerative cervical myelopathy: insights into its pathobiology and molecular mechanisms. Journal of Clinical Medicine. 2021; 10(6): 1214.

[51] Saifee T, Farmer S, Shah S, Choi D. Spinal column and spinal cord disorders. Neurology: a queen square textbook. 2024: 463-98.

[52] Zhang Q, Zhang Y, Chon TE, Baker JS, Gu Y. Analysis of stress and stabilization in adolescent with osteoporotic idiopathic scoliosis: finite element method. Computer Methods in Biomechanics and Biomedical Engineering. 2023; 26(1): 12-24.

[53] Kaspiris A, Vasiliadis ES, Tsalimas G, Melissaridou D, Lianou I, Panagopoulos F, et al. Unraveling the link of altered TGFβ signaling with scoliotic vertebral malformations in osteogenesis imperfecta: a comprehensive review. Journal of Clinical Medicine. 2024; 13(12): 3484.

[54] Jiang X, Liu F, Zhang M, Hu W, Zhao Y, Xia B, et al. Advances in genetic factors of adolescent idiopathic scoliosis: a bibliometric analysis. Frontiers in Pediatrics. 2024; 11: 1301137.

[55] Richard OK, Liens A, Muirhead D, Weber K. Tissue response following implantation with the posterior dynamic distraction device (PDDD) in adolescent idiopathic scoliosis (AIS). European Spine Journal. 2024; 33(6): 2512-21.

[56] Newton PO, Takahashi Y, Yang Y, Yaszay B, Bartley CE, Bastrom TP, et al. Anterior vertebral body tethering for thoracic idiopathic scoliosis leads to asymmetric growth of the periapical vertebrae. Spine Deformity. 2022; 10(3): 553-61.

[57] Park Y, Ko JY, Jang JY, Lee S, Beom J, Ryu JS. Asymmetrical activation and asymmetrical weakness as two different mechanisms of adolescent idiopathic scoliosis. Sci Rep. 2021; 11(1): 17582.

[58] Luo C, Wu H, Liu W, Luo Y, Jie Y, Ma CZ-H, et al. The Biomechanics of Spinal Orthoses for Adolescent Idiopathic Scoliosis: A Systematic Review of the Controlling Forces. Bioengineering. 2024; 11(12): 1242.

[59] Pialasse J-P, Descarreaux M, Mercier P, Blouin J, Simoneau M. Sensorimotor integration in adolescent idiopathic scoliosis patients. Recent Advances in Scoliosis. 2012: 47-70.

[60] Stokes IA, Burwell RG, Dangerfield PH. Biomechanical spinal growth modulation and progressive adolescent scoliosis–a test of the'vicious cycle'pathogenetic hypothesis: Summary of an electronic focus group debate of the IBSE. Scoliosis. 2006; 1(1): 16.

[61] Payas A, Batin S, Kurtoğlu E, Arik M, Seber T, Uçar İ, et al. Is the integration problem in the sensoriomotor system the cause of adolescent idiopathic scoliosis? Journal of Pediatric Orthopaedics. 2023; 43(2): e111-e9.

[62] Formaggio E, Bertuccelli M, Rubega M, Di Marco R, Cantele F, Gottardello F, et al. Brain oscillatory activity in adolescent idiopathic scoliosis. Sci Rep. 2022; 12(1): 17266.

[63] Wilczyński J, Habik Tatarowska N, Mierzwa Molenda M. Deficits of sensory integration and balance as well as scoliotic changes in young schoolgirls. Sensors. 2023; 23(3): 1172.

[64] Liu P-Y, Zhang J, Wan K-WF, Yu H-TH, Lau K-LK, Cheung M-CK, et al. Evaluating the impact of soft bracing and textile engineering in enhancing postural control and proprioception in adolescent idiopathic scoliosis. Journal of Industrial Textiles. 2025; 55: 15280837251313520.

[65] Kastrinis A, Strimpakos N, Koumantakis GA, Tzatzaliaris D, Oikonomaki M, Theodosopoulos E, et al. Reliability of sensorimotor control tests in individuals with adolescent idiopathic scoliosis. Muscles. 2024; 3(4): 376-92.