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A Multi-Factorial Perspective on Idiopathic Scoliosis: Beyond Orthopedics

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ABSTRACT

Idiopathic scoliosis, a complex spinal deformity, has long been viewed primarily through an orthopedic lens. However, recent research has unveiled a multitude of factors contributing to its development, including hormonal imbalances, bone density variations, emotional and digestive symptoms, genomic variants, and neurotransmitter abnormalities. This narrative review aims to highlight the multi-factorial nature of idiopathic scoliosis, emphasizing the common abnormalities that exist in patients with idiopathic scoliosis that occur outside of the vertebral column itself. Given that these abnormalities seem to be consistent with previously published etiopathological models of scoliosis development and progression, it is feasible to deduce that a more comprehensive idiopathic scoliosis treatment model, one that extends beyond traditional orthopedics to optimize patient care and outcomes, is needed. This treatment framework is proposed through a functional medicine model of patient management.

Introduction:

Idiopathic scoliosis (IS), characterized by an abnormal lateral curvature of the spine, has traditionally been perceived as a musculoskeletal disorder. Historically, clinical management and research efforts have been predominantly centered on structural abnormalities within the spine and the associated musculoskeletal challenges. However, recent advancements in our understanding of this complex condition have illuminated a narrative that transcends the confines of the skeletal system. Idiopathic scoliosis is not solely a deformity of the spine; it represents a dynamic interplay among various systems within the human body. This recognition carries significant implications for the holistic approach to managing patients with idiopathic scoliosis.

Although the musculoskeletal aspects of idiopathic scoliosis remain of paramount concern in clinical practice, it has become increasingly apparent that this condition exerts a pervasive influence on multiple physiological and psychosocial facets. From cardiorespiratory function to psychological well-being, from neurodevelopmental considerations to overall quality of life, idiopathic scoliosis extends its influence across a range of dimensions of an individual's health and overall experience. Understanding these multifaceted impacts is pivotal for providing comprehensive care and optimizing patient outcomes.

This narrative review paper aims to delve into the intricate web of interactions that idiopathic scoliosis engenders throughout the human body. By exploring the broader array of systems and functions affected by this condition, the goal of this review is to emphasize the importance of adopting a holistic approach to patient management. Beyond the conventional musculoskeletal interventions, our review will illuminate the relevance of considering cardiovascular, pulmonary, neurological, psychological, and sociocultural dimensions in the care of individuals with idiopathic scoliosis. Recognizing that idiopathic scoliosis is a multisystem disorder, a shift in the paradigm of patient management is suggested – to one that prioritizes a comprehensive understanding of the condition's impact on all aspects of the patient's well-being.

In this endeavor, we will synthesize the existing body of literature, drawing upon both clinical evidence and emerging research findings. Our objective is to equip clinicians, researchers, and healthcare practitioners with a more holistic perspective on idiopathic scoliosis, ultimately promoting a patient-centered approach that acknowledges and addresses the far-reaching impacts of this condition. By acknowledging that idiopathic scoliosis extends beyond the musculoskeletal system, a multi-disciplinary approach to idiopathic scoliosis management becomes desirable.

Hormone Imbalance in Idiopathic Scoliosis:

Hormonal imbalances, particularly involving melatonin and sex hormones, have emerged as potential contributors to IS. Melatonin, a hormone primarily involved in regulating sleep-wake cycles, has been associated with disrupted circadian rhythms in IS patients[1]. Moreover, sex hormones, such as estrogen, may play a role in skeletal growth and development[2]. Understanding these hormonal influences is crucial for a holistic perspective on IS.

Bone Density Differences in Scoliosis:

Bone density variations have been observed in individuals with IS. Lower bone mineral density in certain regions of the spine may predispose individuals to scoliosis or exacerbate its progression. Incorporating assessments of bone health is essential in the evaluation and management of IS patients.

In recent years, researchers have uncovered intriguing evidence suggesting that individuals with idiopathic scoliosis (IS) may exhibit bone density differences compared to their peers without the condition[3]. These disparities in bone health and metabolism have significant implications for both the etiology and management of scoliosis. Studies investigating bone density in IS patients have reported variations in bone mineral density (BMD) within the spinal column and other skeletal regions[4]. While the exact mechanisms and causes are still under investigation, several key findings have shed light on this aspect.

Research has indicated that in the regions of the spine affected by scoliosis curvature, there may be localized reductions in BMD. Han et al[5] found that the highest BMD occurred on the concave side of the curve apex when compared to the convex side or the uninvolved segments of the spine. The apical BMD was negatively correlated to age and height. They also found that the overall vertebral BMD gradually decreased from the top to the bottom of the spine.

Cheng et al[6] found that the asymmetrical loss of vertebral bone mineral density is correlated with scoliosis curve severity and may require specific modifications in surgical techniques for scoliosis fusion surgery. Patients with more severe scoliosis curves tend to exhibit greater reductions in BMD. This association suggests that bone density may play a role in the progression of scoliosis.

Several hypotheses have been proposed to explain these observations. The altered mechanical forces experienced by the vertebral bodies in scoliosis may lead to uneven loading on the spine[7]. This uneven loading could potentially influence bone remodeling processes, resulting in localized decreases or asymmetries in BMD. Neurological dysregulation[8] and altered muscle activation patterns[9], which are common in IS, could affect bone health. The nervous system plays a role in regulating bone density through the control of muscle contractions and mechanical loading on bones. As mentioned earlier, hormonal imbalances[2] have been implicated in IS. Hormones like estrogen and growth hormone are key regulators of bone density. Variations in these hormones in IS patients may contribute to altered bone metabolism.

The observed bone density differences in IS patients may have important clinical implications. Assessing bone density in IS patients may aid in risk stratification. Those with lower

BMD in critical regions of the spine may be at greater risk of curve progression and fractures into adulthood, highlighting the need for tailored treatment approaches.

Orthopedic interventions, such as bracing or surgery, should consider the bone health of IS patients, examples of such treatment adaptations/modifications have been reported[6]. Strategies to improve or maintain bone density may be incorporated into treatment plans.

Further research is needed to elucidate the underlying mechanisms of bone density differences in IS. This may involve exploring the role of mechanical, neurological, and hormonal factors, as well as investigating potential therapeutic interventions to optimize bone health in scoliosis patients.

Bone density differences observed in IS patients compared to their peers is a notable characteristic of this multi-factorial condition. While much remains to be uncovered regarding the precise mechanisms and clinical implications, understanding these variations is vital for comprehensive scoliosis care and may offer new avenues for research and therapeutic interventions aimed at improving the quality of life for individuals with idiopathic scoliosis.

Emotional Symptoms in Scoliosis Patients

Scoliosis also seems to have far-reaching effects on psychological and emotional aspects of patients' lives. Understanding these multifaceted symptoms and their implications is crucial for providing comprehensive care to individuals with scoliosis. Scoliosis can lead to noticeable changes in body shape and posture. Adolescents may experience body image concerns, leading to reduced self-esteem and body dissatisfaction[10]. Cognitive symptoms related to body image can have long-term psychological effects but seem to be mitigated by participation in sports activities[11]. Scoliosis patients, especially adolescents, are at an increased risk of developing anxiety and depression[12]. This is not only for the disorder itself, but can also be due to bracing treatment[13]. Collectively, these mental and emotional symptoms associated with scoliosis can significantly reduce a patient's quality of life[14]. Quality of life is significantly impacted even in children with untreated IS compared to healthy controls[15].

Comprehensive care for scoliosis patients should extend beyond the orthopedic aspects of the condition to address these neurological, cognitive, and emotional symptoms.

Digestive Symptoms Associated with Idiopathic Scoliosis:

Digestive disturbances, such as functional dyspepsia and irritable bowel syndrome, are collectively referred to as functional gastrointestinal disorders (FGID)[16]. These disorders are caused by dysfunctional, bidirectional regulatory mechanisms of the gut-brain axis, and are associated with psychological comorbidities[17]. Adolescent patients with gastrointestinal symptoms without clear causes are often patients who also have a history of idiopathic scoliosis[16]. A 5-year study comparing two groups of adolescent patients showed that those with idiopathic scoliosis were significantly more likely to be diagnosed with concomitant FGIDs[16]. Although this study does not examine causality, it considers the possibility that both idiopathic scoliosis and FGIDs may be caused by the same underlying factors, including gut-brain dysregulation. The gut-brain connection may also have impacts on neurotransmitter metabolism, including melatonin and serotonin, two neurotransmitters that have long been on the radar of scoliosis researchers[8]. These will be discussed in more detail later in this paper.

Genomic Variants in Idiopathic Scoliosis

A single nucleotide polymorphism (SNPs) is a variation in a single nucleotide that occurs at a specific position in the genome. SNPs are the most common type of genetic variation among people and can be found in both coding regions (which affect gene function) and non-coding regions (which may affect gene regulation or have no apparent effect). Because of their prevalence and variability, SNPs are important in the study of personalized medicine, especially as it relates to idiopathic scoliosis. Several SNPs have been previously identified among idiopathic scoliosis patients, including LBX1, GPR126, BNC2, PAX1, LBX1-as1, BCL2, AJAP1, PAX3, TNIK, MEISI, MAGI1, TGFB1, MIR4300HG, and TPH1, from Caucasian, Japanese, and Chinese populations[18, 19]. A systematic review by De Salvatore et al[20] examined 24 studies and found that CHD7, SH2B1, ESR, CALM1, LBX1, MATN1, CHL1, FBN1, and FBN2 were associated with idiopathic scoliosis in various ethnicities. Another review by Al Mekkawi et al[21] examined 43 studies and found that only LBX1 and MATN1 were associated with an increased risk of IS in at least one of five different genetic models they used. However, when these same SNPs were examined in multi-ethnic populations, the results were difficult to replicate[22].

It is possible that the reason for this replication difficulty is that several SNPs have distinct interactions with one another[23]. Morningstar et al identified 19 SNPs that were associated with idiopathic scoliosis in Caucasian patients[24]. They did not look at any singular SNPs, but rather looked at groups of SNPs related by common metabolic purposes, such as methylation or histamine production. They found that idiopathic scoliosis patients had 7 of more of the 19 SNPs in about 91% of cases, and those with 14 or higher were significantly more likely to have surgical threshold curves. These data suggest that it is a combination of SNPs that lay the groundwork for the development or progression of idiopathic scoliosis, and not any single SNP. The presence of SNPs do not seem to cause idiopathic scoliosis by themselves. Rather, it is thought that epigenetic influence on multiple SNPs is a significant factor. Perhaps the most direct test of this is in monozygotic twins, where it was shown that epigenetic impacts can cause one twin to develop scoliosis and not the other[25].

Physiological Implications of Genomic Variants

Genomic variants, which include single nucleotide polymorphisms (SNPs), can lower the threshold for various

aspects of health, development, and disease susceptibility. Within the context of idiopathic scoliosis, many SNPs are associated with downstream physiological observations such as: osteopenia[26], lower progesterone[27], altered melatonin receptor binding[28], fibrillin-related disorders[29], abnormal calmodulin metabolism[20], muscle progenitor cell migration and neuronal determination processes[30], and cartilage strength[31]. As a result, individuals with these variants may experience abnormalities in the structure of their spine, thus predisposing them to idiopathic scoliosis.

Genomic variants associated with IS often exhibit pleiotropy, where a single genetic change affects multiple organ systems. This explains why IS can be associated with additional conditions, such as craniofacial abnormalities[32], in individuals with specific genetic mutations. Understanding the physiological impact of these variants may help guide physicians to select more comprehensive management strategies for idiopathic scoliosis, especially in earlier stages of IS development. Individuals with affected genes may have a higher risk of passing on these variants to their offspring, leading to a familial predisposition to scoliosis. A deeper understanding of the physiological impact of these variants may pave the way for targeted therapies that address the specific genetic mechanisms underlying IS.

Neurotransmitter Abnormalities in Scoliosis:

The roles of various neurotransmitters and hormones have been studied in relation to idiopathic scoliosis (IS), shedding light on their potential involvement in the onset or progression of the condition. Here, the roles of melatonin, serotonin, norepinephrine, histamine, and glutamate in the context of IS are highlighted.

Melatonin, a hormone primarily known for its role in regulating circadian rhythms and sleep-wake cycles, has been a focus of IS research. Studies have shown that individuals with IS often exhibit disrupted melatonin secretion patterns, including lower nighttime melatonin levels and altered circadian rhythms. Melatonin is involved in regulating bone growth and development. Disrupted melatonin levels can influence the process of bone formation and remodeling. Some researchers hypothesize that melatonin's role in bone metabolism may contribute to the development or progression of scoliosis by affecting vertebral growth plates. It has garnered attention from studies involving the Machida pinealectomized chicken and mouse models[33]. In these studies, the removal of the pineal gland led to significant alterations in melatonin levels, which correlated with abnormal spinal curvature in the affected animals. Research demonstrated that the lack of melatonin resulted in disrupted bone metabolism and changes in growth plate cartilage, contributing to scoliosis development. Specifically, the Machida chicken model revealed that melatonin deficiency was associated with asymmetrical growth of vertebrae, while similar findings in mouse models highlighted the hormone's role in regulating spinal growth and alignment. These studies suggest that melatonin may play a crucial regulatory role in maintaining spinal integrity, offering insights into the pathophysiology of idiopathic scoliosis.

Serotonin is a neurotransmitter primarily synthesized in the brain and the gastrointestinal tract, where about 90% of the body's serotonin is produced by enterochromaffin cells in the gut. In the brain, serotonin is synthesized from the amino acid tryptophan through a series of enzymatic reactions, mainly in the raphe nuclei of the brainstem. This vital neurotransmitter plays a multifaceted role in regulating mood, contributing to feelings of well-being and happiness; imbalances in serotonin levels are often linked to mood disorders such as depression and anxiety. Additionally, serotonin is crucial in regulating the sleep-wake cycle, influencing sleep quality and patterns by modulating the production of melatonin. Beyond its effects on mood and sleep, serotonin also plays a key role in spinal muscle control, as it helps modulate motor function and muscle tone by acting on spinal cord neurons. Research has indicated that IS patients may have lower peripheral levels of serotonin compared to non-scoliosis patients[34]. A deficiency in serotonin can affect muscle tone and neuromuscular coordination. Altered serotonin levels may contribute to the asymmetric muscle development and abnormal muscle activity seen in IS patients. This imbalance in muscle forces could potentially influence the progression of scoliosis.

Norepinephrine, also known as noradrenaline, is a catecholamine neurotransmitter synthesized primarily in the adrenal medulla and in certain neurons of the central nervous system, particularly in the locus ceruleus of the brainstem. Its production begins with the conversion of the amino acid tyrosine into dopamine, which is then further converted into norepinephrine by the enzyme dopamine β-hydroxylase. Norepinephrine plays a crucial role in sympathetic tone, regulating arousal, attention, and stress responses, while also influencing mood and anxiety levels. In terms of neuromuscular function, norepinephrine modulates the excitability of motor neurons and influences muscle contraction by enhancing the efficiency of synaptic transmission at the neuromuscular junction. This neurotransmitter is integral to maintaining alertness and optimizing physical performance, particularly during stressful situations, by increasing heart rate and blood flow to muscles, thereby enhancing overall neuromuscular coordination and responsiveness. These are all particularly important functions as they relate to postural adaptation as well. Since norepinephrine signals for rapid physiological adaptations to sudden postural changes or novel postural tasks, persistent alterations in norepinephrine levels may reduce altered postural control, especially under novel environments such as during accelerated musculoskeletal growth velocity, especially during puberty.

It's important to note that while there is evidence to suggest the involvement of these neurotransmitters in IS, the precise mechanisms and their roles in the condition are still subjects of ongoing research and debate. Idiopathic scoliosis is a complex, multi-factorial condition influenced by genetic, biomechanical, and neurological factors. Understanding the roles of these neurotransmitters may be an important part of unraveling the complex etiology of IS and may provide avenues for future research and potential therapeutic interventions.

Applying these observations to clinical practice

Physicians can synthesize the knowledge of neurotransmitters like serotonin and norepinephrine, along with the hormonal influences of melatonin, to create a comprehensive care plan for patients with idiopathic scoliosis. In conventional Western medicine, care has often become compartmentalized, requiring patients to consult multiple specialists—such as orthopedic surgeons, neurologists, and mental health providers—to address the diverse symptoms and concerns related to scoliosis. This fragmented approach can lead to gaps in understanding how factors like mood, sleep, and neuromuscular function collectively impact spinal health. By recognizing the interconnected roles of serotonin in mood regulation, norepinephrine in neuromuscular function, and melatonin in sleep cycles, physicians can adopt a more holistic treatment strategy. This might involve not only addressing spinal alignment but also considering interventions to enhance emotional well-being, improve sleep quality, and optimize neuromuscular control. Such an integrative approach can ultimately lead to more effective, patient-centered care, improving outcomes and overall quality of life for individuals with idiopathic scoliosis.

Conclusion:

Idiopathic scoliosis is a multi-factorial condition influenced by hormonal imbalances, bone density variations, emotional and digestive symptoms, genomic variants, and neurotransmitter abnormalities. This narrative review underscores the need for a multi-disciplinary approach to idiopathic scoliosis care that extends beyond traditional orthopedics. Involving experts from various fields, including endocrinology, genetics, psychology, gastroenterology, and neurology, can provide a more holistic understanding and management of this complex condition. Such an approach is essential to optimize patient outcomes, enhance the quality of life, and advance our knowledge of idiopathic scoliosis. Future research should continue to explore the intricate interplay of these factors, ultimately leading to more effective treatment strategies.

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