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Pathogenesis and Intervention Study of Idiopathic Scoliosis in Elementary and Middle School Students

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Abstract

Scoliosis, also known as lateral curvature of the spine or spinal lateral deviation, is a three-dimensional spinal deformity characterized by the bending of one or multiple segments of the spine to the side accompanied by vertebral rotation. It appears in the shape of an "S" or "C" and can cause pain during standing, walking, or lifting heavy objects, leading to a reduction in physical activity. Scoliosis is the most common spinal disorder among children and adolescents. Adolescent Idiopathic Scoliosis (AIS) refers to scoliosis that occurs during the teenage years and its etiology remains unclear. AIS is a spinal condition characterized by a three-dimensional deformity in the coronal, sagittal, and axial planes, with a Cobb angle of 10 degrees or more. The global prevalence of AIS ranges from 0.47% to 5.2% (Erwin *et al*., 2020; Konieczny *et al*., 2013). According to a study by Qiu Guixing *et al*., the prevalence of scoliosis in China is estimated to be approximately 0.6% to 2.0%, with 90% of cases being AIS. Jia Juanjuan *et al*., conducted a scoliosis screening of 8,026 students in Jiaxing City in 2019, with initial screening identifying 218 positive cases. Among them, 132 cases were confirmed through X-ray examination, estimating a scoliosis prevalence rate of 5.46% among primary and secondary school students in Jiaxing City. Chen Xiaosheng, Ru Shouhang *et al*., conducted a scoliosis survey among students from the fourth grade of primary school to the second grade of high school in various districts of Shenzhen City from January to December 2020, with the results showing a scoliosis prevalence rate of 5.01% among primary and secondary school students in Shenzhen City. The prevalence rate was higher in females than males and increased with age. If scoliosis in adolescents is not promptly and effectively treated during their growth process, the spinal deformity can rapidly progress and lead to various complications. For example, scoliosis can cause changes in the shape of the ribs, resulting in unequal thoracic cavity volume and breathing difficulties. Prolonged restricted breathing can lead to complications such as chest tightness and shortness of breath. Additionally, scoliosis can affect the functioning of abdominal organs, leading to pulmonary dysfunction and hypoxia, and in severe cases, it can cause cardiorespiratory failure. Furthermore, scoliosis not only affects the physical health of patients but also their mental well-being. The physical appearance changes caused by scoliosis deformity can potentially lead to psychological disorders.

Keywords: Scoliosis, Adolescent, Exercise Therapy, Pathogenesis, Idiopathic, Prevent.

1. INTRODUCTION

Adolescent idiopathic scoliosis (AIS) is a three-dimensional malformation that includes scoliosis on the coronal plane, sagittal balance on the sagittal plane, and rotation of the vertebral body on the transverse axis. It is the most common structural scoliosis in clinical practice. The incidence rate of AIS in the adolescent population is about 2%~3%, and it tends to occur in women. The Scoliosis Research Society (SRS) defines scoliosis as the Cobb's method of measuring the curvature of the spine on a standing upright X-ray, with an angle greater than 10°. The pathological occurrence and development of AIS may be related to genetic, biochemical, neurological, skeletal, and biomechanical factors, but its pathogenesis is still unclear, posing certain difficulties for the diagnosis and treatment of AIS. At present, AIS is generally corrected through surgical or non surgical treatment. In 2011, the International Association for Scoliosis Orthopedics and Rehabilitation Therapy pointed out that when the Cobb angle is<10°, regular observation can be performed; Exercise intervention can be selected between 10°and 20° Support therapy combined with exercise therapy can be chosen at 20° to 45° At 45°, surgical treatment can be considered. In non surgical treatment plans, scoliosis can reduce the pathological degree of AIS through exercise intervention, which has many advantages such as low cost, few side effects, high efficiency, and strong operability. Therefore, it is important to conduct in-depth research on the pathogenic factors of AIS and the mechanism of action of exercise therapy on AIS.

2. RESEARCH METHODOLOGY

2.1 Literature Review Method

Relevant studies were retrieved from commonly used electronic literature databases, including PubMed, Web of Science, Elsevier, CNKI, and Wanfang Database, to conduct a comprehensive search. The search terms used in English were "Adolescent idiopathic scoliosis," "Student," "Endocrine hormones," "Biomechanics," and "Exercise therapy." In Chinese, equivalent terms were used. Relevant literature was carefully reviewed, and in-depth analysis and organization were conducted. Adolescent Idiopathic Scoliosis (AIS) Pathogenesis.

3. Pathogenesis

3.1 Genetics

Extensive clinical, epidemiological, and basic scientific research has been conducted to investigate the pathogenesis of AIS. However, the exact mechanisms underlying AIS development remain unclear. AIS is often associated with a certain degree of familial inheritance, suggesting a genetic component. Kesling *et al*., conducted a meta-analysis of twins and found concordance rates of 73% in monozygotic twins and 36% in dizygotic twins with AIS. Gao *et al*., identified a potential CHD7 gene polymorphism that was over-transmitted to affected individuals' offspring and predicted a binding site for the caudal-related homeobox (Cdx) transcription factors, suggesting its association with AIS susceptibility. Justice *et al*., implicated a region on the X chromosome potentially linked to AIS. Sharma *et al*., performed a genome-wide association study (GWAS) on 3,102 individuals and identified a single nucleotide polymorphism (SNP) in the promoter region downstream of the PAX1 gene on 20p11.22 that was associated with AIS, which was further validated using a zebrafish model. Ikuyo Kou *et al*., conducted a GWAS on Japanese women with AIS and identified a single locus on chromosome 10q24.31, providing new insights into the pathogenesis of AIS. Takahashi *et al*., expanded the GWAS through stepwise association studies and replication studies in Japanese, Chinese, and European populations, identifying a novel AIS susceptibility locus on chromosome 6q24.1. GWAS has identified several candidate genes for AIS, including CHL1, LBX1, GPR126, BNC2, and PAX1 (Sharma *et al*., 2015; Ogura *et al*., 2015). However, their functional impairments and potential synergistic effects within one or multiple biological pathways in causing AIS remain unclear, offering new avenues for studying the pathogenesis of AIS.

3.2 Endocrine Hormones

3.2.1 Androgens in AIS

Androgens primarily secreted by testicular stromal cells in males and synthesized by the ovaries and adrenal cortex cells in females, play a role in bone metabolism, skeletal growth and development, and protein synthesis (Almeida *et al*., 2017). Androgen receptors (AR) are concentrated in the growth plate of bone tissue, promoting cartilage proliferation and endochondral ossification, thus ensuring normal skeletal growth and development. Studies have shown that AIS patients have lower levels of androgens compared to non-AIS individuals. Yuan-Tao Wu *et al*., collected blood samples from 301 female participants, divided them into AIS and non-AIS groups, and found significantly decreased serum androgen levels in the AIS group compared to the non-AIS group (1.94±0.09 vs. 2.284±0.103). AIS patients showed increased levels of interleukin (IL)-6 and matrix metalloproteinase (MMP)-13 in cartilage, along with decreased AR levels. In cell experiments, androgens activated the AR/IL-6/signal transducer and activator of transcription 3 (STAT3) signaling pathway, reducing the extent of abnormal cartilage development in female AIS patients (Yuan-Tao Wu *et al*., 2021). Although there is limited literature on how androgens contribute to AIS, it is evident that AIS patients have lower androgen levels compared to non-AIS individuals, suggesting that abnormal androgen levels may affect normal bone and cartilage development leading to AIS occurrence.

3.2.2 Estrogens in AIS

Currently, the prevalence of scoliosis is higher in females than males. Warren *et al*., reported a scoliosis prevalence of 24% in 75 female ballet dancers from four professional ballet companies (average age 24.3 years), and the prevalence increased with age at menarche, with 18 out of 75 scoliotic patients experiencing delayed menarche. Ballet dancers with scoliosis had a higher incidence of secondary amenorrhea compared to those without scoliosis. Insufficient estrogen levels may be causally related to AIS. Inoue *et al*., reported an association between estrogen receptor gene polymorphisms and the severity of AIS curves. Estrogens and their receptors are widely distributed in the body and participate in various developmental processes. Increasing evidence suggests that lower estrogen levels may play an important role in the early stages of AIS (Grivas *et al*., 2006). Current research on estrogens in AIS mainly focuses on estrogen levels (Kulis *et al*., 2006; Kulis *et al*., 2015). There are two hypotheses regarding how estrogens are involved in the pathogenesis of AIS. One hypothesis suggests that abnormal estrogen levels can lead to delayed menarche and delayed bone development and maturation, increasing the probability of spinal deformity. The other hypothesis proposes that abnormal estrogen levels directly affect bone metabolism and remodeling, resulting in abnormal skeletal growth and an increased risk of developing AIS (Grivas *et al*., 2006; Leboeuf *et* *al*., 2009; Sandersas *et al.*, 2007). Zheng Shuhui *et al*., divided 120 rats into female, ovariectomy (OVX), OVX+E2 (estradiol), prunin (a drug), and male groups. Based on spinal radiographic analysis, the prevalence and severity of spinal deformities were higher in the female and OVX+E2 groups compared to the OVX, prunin, and male groups. Thus, higher circulating estrogen levels significantly increased the risk of spinal deformities in the rat model, suggesting that estrogen is a factor contributing to AIS (Shuhui Zheng *et al*., 2018). Estrogens influence bone remodeling, growth, and acquisition, which could be contributing factors to AIS development. While estrogens are not the causative agents of AIS, they can affect the progression of spinal curvature through interactions with biomechanical and structural factors, thus influencing the development of scoliosis. Therefore, understanding the role of estrogens is crucial for elucidating the evolution of AIS during skeletal growth and for developing new therapeutic interventions.

3.2.3 Melatonin

A serotonin-derived hormone secreted by the pineal gland, plays a role in regulating circadian rhythms. Apart from its involvement in circadian rhythm regulation, melatonin also participates in various biological processes, including skeletal development. In 1959, Thillard *et al*., first reported a link between melatonin and AIS, observing that pinealectomy in chickens induced spinal deformities similar to scoliosis. Machida *et al*., reproduced this animal model in rats, demonstrating that pinealectomy led to scoliosis in bipedal rats, resembling adolescent idiopathic scoliosis in humans. Changes in melatonin function may disrupt the proliferation and differentiation balance of different cell types, thus interfering with normal bone mass formation. Melatonin promotes osteoblast proliferation and secretion of osteoprotegerin (OPG), which further inhibits the binding of the receptor activator of nuclear factor kappa-B ligand (RANKL) to RANK, reducing osteoclast differentiation (Sanchez-Barcelo *et al*., 2010). Yim *et al*., found lower expression of the melatonin receptor MT2 in osteoblasts from AIS patients compared to controls, suggesting an association with AIS. Man *et al*., demonstrated that AIS osteoblasts lacking MT2 expression had reduced proliferation capacity, and a genetic polymorphism in the MT2 gene, such as rs4753426, was associated with AIS phenotype. Evidence suggests abnormal downstream signaling of the melatonin-MT2/protein kinase C (PKC) pathway may be associated with decreased osteoblastic differentiation and impaired bone tissue mineralization (Azeddine *et al*., 2007; Han *et al*., 2017). Melatonin has also been shown to decrease osteoclast formation by promoting the expression of OPG and inhibiting the expression of RANKL. RANKL promotes osteoclast proliferation and activation by binding to its receptor RANK on osteoclasts, while OPG blocks the RANKL-RANK interaction (Liu *et al*., 2019; Amstrup *et al*., 2013; Histing *et al*., 2012; Koyama *et al*., 2002). These actions of melatonin can enhance bone formation, leading to increased bone density and mass (Liu *et al*., 2019). Decreased melatonin levels and altered MT2 receptor function may result in abnormal skeletal development and contribute to the development of AIS. These studies suggest that transient melatonin deficiency may exacerbate spinal curvature in scoliosis, and melatonin levels could serve as a predictive factor for the progression of low melatonin scoliosis. The results of this research also indicate that if melatonin curves do not exceed 35 degrees, melatonin could be used as a therapeutic and preventive approach for low melatonin scoliosis.

3.2.4 Leptin

Leptin improves muscle quality in muscle development by inhibiting myosin degradation and promoting muscle cell proliferation (Sáinz *et al*., 2009). Besides low BMI, low leptin levels or reactive changes in AIS may result in low muscle quality and strength, ultimately leading to postural imbalance in AIS patients. Imbalanced paraspinal muscle development is an important factor in scoliosis progression (Li *et al*., 2019). Leptin may be involved in this asymmetric development of paraspinal muscles, but further research is needed to determine whether OB-Rs are expressed asymmetrically in the spine adjacent muscles. 2.2.5 Vitamin D and Calcium-Phosphate Balance in AIS Defects in trabecular bone structure and mineralization are important features of scoliosis. In addition, hormonal disturbances, particularly estrogen, and abnormal connective tissue structure and function are implicated (Porter, 2001). Vitamin D plays a crucial role in maintaining calcium-phosphate balance, regulating bone matrix mineralization through its actions in calcium absorption in the intestine (Suh *et al*., 2010). Some studies have observed lower vitamin D levels in AIS patients, and these levels have been associated with the development of AIS. 2.3 Biomechanics Humans, as bipedal animals, have a unique verticality, with the trunk directly positioned above the pelvis. In other vertebrates, whether bipedal or quadrupedal, the trunk is positioned anterior to the pelvis (Cheng *et al*., 2015; Janssen *et al*., 2010). When considering the etiology of AIS, the verticality of the human body has been overlooked. Taylor proposed that the vertical growth of intervertebral discs and the anterior-posterior growth of vertebral bodies and intervertebral discs depend on activities associated with weight-bearing in an upright posture (Taylor, 1975). Load and rotational stability on susceptible immature vertical spines are key concepts to consider. The anterior pelvic tilt, combined with lumbar lordosis and the ability of humans to fully extend their hips and knees, places the body's center of gravity directly over the pelvis. This increases the biomechanical loads on the human spine, which is fundamentally different from all other vertebrates in the animal kingdom. In other vertebrates, the vertebral column bears axial and anterior loads, while the human vertebral column bears posterior loads (referred to as back stress loads). It has been demonstrated that these stress loads decrease the rotational stiffness of the exposed segments (Kouwenhoven *et al.*, 2007). This unique verticality determines that the human spine is essentially a rotationally unstable structure (Brink *et al.*, 2019). The regions of the spine affected by shear loads are poorly defined because little is known about the sagittal shape of the spine at different ages, as it transforms from the overall posterior convexity at birth to the anterior convexity of the pelvis, lumbar spine, and cervical spine in adulthood (Gardner *et al.*, 2018). The regions where rotation is likely to occur depend on the sagittal shape of the spine during growth. Studies have shown substantial differences in sagittal shape between the early stages of primary thoracic scoliosis development and the early stages of lumbar scoliosis development (Schlösser *et al.*, 2014). Furthermore, the incidence of pelvic involvement differs between lumbar and thoracic scoliosis (Brink *et al.*, 2018). Rotations of susceptible vertebrae occur around the rigid posterior ligaments, resulting in rotation away from the midline, where the anterior elements define a longer arc than the posterior elements. This leads to anterior convexity, which is the result of initial rotation. The anterior part of the intervertebral disc has the opportunity to expand passively under reduced medio-sagittal loads, producing asymmetric loading at the vertebral growth plate defined by Hueter-Volkmann's law, which states that bone growth is relatively inhibited in regions of increased pressure and stimulated in regions of decreased pressure or tension (Schlösser *et al.*, 1997). This sequence ultimately leads to increased anterior segment length, largely due to the passive action of early intervertebral discs exceeding the active action of bone. However, according to Hueter-Volkmann's law and depending on the patient's bone quality, further asymmetric bone development may occur as the deformity progresses, triggering AIS (As a journal reviewer, the translation of the provided text into English is as follows) (Brink *et al.*, 2018).

4. Intervention Measures

4.1Testing and Assessment

The most commonly used method for screening scoliosis is the forward bending test, often combined with the use of a scoliometer or Moiré topography. In order to perform the test, the patient stands upright while the examiner observes the back for any noticeable curvature (Reamy *et al.*, 2001). The patient is then asked to bend forward, aligning the spine parallel to the floor, with arms hanging freely, palms together, and knees flexed forward, while the examiner checks for any thoracic or lumbar prominence from behind to determine the presence of scoliosis. The sensitivity of this test for thoracic scoliosis in patients with Cobb angle greater than 20 degrees ranges from 92% to 100% (Côté *et al.*, 1998). However, the Adam's forward bending test is less reliable for detecting lumbar scoliosis, and if a curvature is suspected, the use of a scoliometer is often employed to aid in determining the need for radiographic imaging to confirm the diagnosis. The scoliometer is used to measure the angle of trunk rotation, and this measurement can then be used to estimate a more precise Cobb angle, which is measured through radiographic imaging. In summary, positive cases identified through initial screening should undergo further testing to determine the extent of the scoliosis. Early screening for scoliosis in children and adolescents allows for early prevention, diagnosis, and treatment.

4.2 Health Education

With the continuous changes in modern lifestyle, increasing academic pressure, and convenient transportation, children's outdoor activity time has been decreasing. During the COVID-19 pandemic, online classes and home learning further reduced the limited outdoor activity time for children, which has had a negative impact on their physical health. Currently, spinal curvature, myopia, and obesity have become the top three health issues among primary and secondary school students in China. It is urgent to carry out health education to change people's traditional views on spinal curvature, promote an understanding of the concept of scoliosis, and incorporate health knowledge related to body posture into textbooks. It is essential to increase the awareness of parents and schools regarding scoliosis, and provide training on scoliosis health knowledge to parents and physical education teachers in schools. This will establish a "home-school partnership" and encourage parents and schools to actively guide children to develop a sense of responsibility for their own health, actively learn about spinal protection knowledge and skills, and promote communication and education between teachers, parents, and students. In addition to focusing on students' mental health, teachers and parents should actively ensure that students adopt correct body postures to prevent scoliosis. At the societal level, it is important to provide training on children and adolescents' body posture for professionals in sports clubs catering to young people. Efforts should be made to create a child and adolescent spine-friendly environment, where children and adolescents have comprehensive support that includes posture assessment, tracking of test results, guidance on exercise programs, and updated health knowledge.

4.3 Exercise Intervention

The theory of exercise therapy is primarily based on the abnormal regulation of muscle control by the nervous system and the theory of biomechanical abnormalities. As a non-surgical treatment approach, exercise therapy has become an important measure for treating AIS. The main objectives of exercise intervention are to reduce the progression of spinal curvature, lower the risk of secondary complications (including back pain, respiratory problems, and body deformities), and improve the quality of life. It has been concluded that patients with thoracic curvature ≤25 degrees and thoracolumbar or lumbar curvature ≤20 degrees can be effectively treated through exercise alone. The mechanisms of exercise intervention in AIS may involve correcting the abnormality in the nervous system through exercise and improving muscle imbalance through movement (Liao YS *et al*., 2022). Studies have shown that exercise therapy has a certain efficacy in reducing Cobb angle, trunk rotation angle, thoracic kyphosis angle, lumbar lordosis angle, and improving the quality of life in AIS patients (Negrini *et al*., 2008; Fusco *et al*., 2011; Shahnawaz Anwer *et al*., 2015). The "Healthy China Action (2019-2030)" proposes that primary and secondary schools should strictly implement the national curriculum standards for "Physical Education and Health," with three lessons per week for grades 3 to 6 in primary school and three lessons per week for junior high school, and two lessons per week for high school. The investigation results of scoliosis in primary school students in Suzhou City have shown that having three physical education lessons per week can reduce the incidence of thoracolumbar scoliosis, and reducing sedentary time moderately is crucial for preventing the occurrence and progression of scoliosis (Hai Bo *et al*., 2021). The implementation of physical education classes in schools during the school term has a regulatory effect on reducing postural abnormalities, which highlights the importance of conducting physical education in schools.

5. IN SUMMARY

The etiology of AIS is still unclear. However, this paper has provided new insights into the pathogenesis of AIS from genetic, endocrine, and biomechanical perspectives. Similar to other common diseases, the prevention and treatment of idiopathic scoliosis in children and adolescents should not rely solely on the efforts of schools, families, or society, but rather require a comprehensive approach. In the future, the prevention and treatment of scoliosis in primary and secondary schools should be approached from multiple angles, including testing and assessment, health education, and exercise intervention. It is important to create a scoliosis-friendly environment for children and adolescents, focusing on early prevention, early detection, and early treatment, in order to provide comprehensive support for their healthy growth.

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