

# Scoliosis Ethiopathogenesis: Changing Paradigms Through The Evidence

## Skolyoz Etiyopatogenezi: Kanıtlara Göre Değişen Paradigmalar

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### SUMMARY

Scoliosis defined as side curvatures of the spine, is a deformity investigated since ancient times but without definitive findings. Although easily diagnosed clinically and radiologically, it's difficult to clarify the etiology and treatment. Many theories have been proposed regarding the etiology. However, studies at molecular level and genetic studies have shown complex etiology but not helped for a permanent treatment plan. Ahead of, treatment modalities concerning calmodulin, gene therapy or melatonin will revive non-invasive cures.

**Keywords:** adolescent idiopathic scoliosis, etiopathogenesis, genetics

### INTRODUCTION

In a healthy vertebral column, the vertebrae are in a neutral position in the coronal and the transverse planes. It can be observed in a radiography obtained from the anteroposterior axis, that all vertebrae between C1-L5 are aligned in the same direction. Disruption, for any reason, of the alignment that should have been in the same direction in the coronal axis, and appearance of a curvature is called scoliosis. Scoliosis, the most common deformity of the spine, is not a disease but rather a deformity or a symptom. In most patients, a rotational deformity accompanies scoliosis. Early diagnosis usually ensures prevention of interventional treatments and enhances the effectiveness of the rehabilitation program (1,2,3).

### ETIOLOGY AND CLASSIFICATION

Classification is generally performed based on etiology. The etiology-based classification by the Scoliosis Research Society (SRS), founded in 1966 in the USA,

### ÖZET

Omurganın yana olarak eğrilikleri olarak tanımlanan skolyoz, eski zamanlardan beri sebebi araştırılan ancak henüz kesin bulgular elde edilemeyen bir vücut deformitesidir. Klinik ve radyolojik olarak kolayca tanı konabilmesine rağmen, etyolojiyi aydınlatılabilmek ve tedavi edebilmek o kadar kolay olamamaktadır. Etiyoloji ile ilgili birçok teori öne sürülmüştür. Ancak zaman içinde ilgili moleküler seviyede bir takım çalışmalar, genetik araştırmalar etyolojinin kompleks bir yapıya sahip olduğunu göstermiş olmakla birlikte kalıcı tedavi planı oluşturulmasında pek bir fayda sağlayamamıştır. İlerleyen zamanlarda gen tedavileri veya kalmomodulin, melatonin gibi bir takım moleküller üzerinden yapılacak tedaviler girişimsel olmayan ve kalıcı tedavileri gündeme getirebilir.

**Anahtar sözcükler:** adolesan idiyopatik skolyoz, etiopatogenez, genetik

is frequently used and classifies scoliosis into two main groups, namely structural scoliosis and non-structural scoliosis (Table 1).

**Structural scoliosis:** This group comprises the majority of all scoliosis cases. Idiopathic scoliosis is the most frequently observed case. Other frequently observed causes are neuromuscular and congenital scoliosis. Structural scoliosis is the asymmetric lateral curvature of the spine.

Rotational deformity in the vertebrae may additionally be seen. The vertebrae usually shift to the convex side. In cases of multiple curvatures, the middle curvature/curvatures is/are structural. Structural curvatures do not straighten by bending sideward(4).

**Non-structural scoliosis:** No intrinsic changes or fixed rotational deformities exist in the spine or the structures around the spine. The curvature completely straightens by bending to the side opposite the curvature, by contraction of the muscles of the opposite side, or by traction(4).

<b>Structural Scoliosis</b>	<b>Non-Structural Scoliosis</b>
Idiopathic	Postural
Neuromuscular	Hysterical
Congenital	Nerve Root Irritation
Trauma	Inflammation
Mesenchymal Disorders	Limb Length Inequality
Rheumatic Diseases	Hip Contractures
Extra spinal Contractures	
Osteochondrodystrophies	
Bone Infection	
Metabolic disorders	
Lumbosacral Region Pathologies	
Tumors	

**Table I.** Classification of Scoliosis

**Idiopathic Scoliosis**

Idiopathic scoliosis with 1-20 degree curvatures comprise 80% of all scoliosis cases(5). Etiology is multifactorial, where postural balance factors and reactions, vestibular mechanisms, metabolic and chemical factors may be responsible with regard to the central nervous system. Various systems are used for the classification of idiopathic scoliosis. Ponseti (6), King (7), Lenke (8), PUMC (Peking Union Medical College) (9) and 3-dimensional classification (10) systems are available, and deciding on the treatment protocols is important with respect to the follow-up of the clinic and progress of patients. However, the most practical and frequently-used classification is that performed based on the onset age of the disease. Idiopathic scoliosis is classified into three, based on the age of onset (3);

1. Infantile idiopathic scoliosis: Occurs before the age of 3. Mother being of old age may be a factor. May be of progressive or recessive type. The progressive type progresses fast, whereas the recessive type recesses by treatment or spontaneously. 70-90% of all idiopathic scoliosis cases are recessive type idiopathic infantile scoliosis (3).
2. Juvenile Idiopathic Scoliosis: This is the type of structural scoliosis which onsets between the age of 3 and 10, where the curvature is generally to the right side (3).
3. Adolescent Idiopathic Scoliosis: This is the scoliosis that occurs within the period between the age of 10 and the completion of ostosis.

Seen 3.6 to 5 times more frequently in girls. Scoliosis most frequently occurs rightward in the thoracic region, and leftward in the lumbar region. The pre-menarche period with fast growth is the period in which scoliosis progresses most rapidly (3).

Besides, idiopathic scoliosis seen mostly in adults in the 6th decade mostly occurs due to degenerative changes and usually in the lumbar region. Asymmetric degeneration occurring in the vertebrae is generally a factor (3).

**Neuromuscular Scoliosis**

This may accompany the clinical picture during the course of diseases. In such cases, scoliosis and other spinal deformities occur in the earlier periods in life, they are progressive and usually result in serious disability (1).

**Congenital Scoliosis**

Congenital scoliosis generally occurs due to formation flaws that occur during the intrauterine life. Generally hemi vertebrae and block vertebrae occur, and pathological curvatures may appear due to discontinuation of growth in a certain region (1).

**CLINICAL FINDINGS AND DIAGNOSTIC PROCEDURES**

Patients generally do not have any complaints during the early phases. Parents consult physicians mostly upon noticing the posture irregularity in their child. Besides, curvatures may be discovered through radiographs taken for other purposes. Back aches generally appear during the later phases, upon occurrence of degenerations in the facet joints. One shoulder being positioned higher than the other may also draw the patients' attention (1, 11).

Physical examinations may reveal scapula asymmetry, array disorders in spinous processes, one-sided pelvic tilt, asymmetric posture of the ribs and relative shortness of extremities. A comprehensive neurological examination is required in order to distinguish neuromuscular scoliosis. Adam's test may be utilized both in diagnosis and as a general screening test (1, 11).

Radiography plays an important role in radiological diagnosis. Radiography enables determination of the terminal and apical vertebrae, as well as measurement of the Cobb angle. In addition, Risser findings are monitored for the follow-up of spinal development. This helps building predictions for the progress of scoliosis and the planning of a strategy (4).

Advanced techniques such as magnetic resonance imaging and scintigraphy may be utilized in addition to radiography, in cases where difficulties are experienced in definitive diagnosis or interventional treatments are planned (4).

Increases of 5 degrees or more in the Cobb angle at two or more consecutive examinations are indicators of progressing scoliosis. Although the rate and duration of the progress not known, it is known

that the curvature increases in girls at young ages, when growth progresses rapidly, or during adolescence. Moreover, double curvatures progress faster than single curvatures, and thoracic curvatures progress faster than lumbar curvatures(1).

#### **ETIOPATHOGENESIS**

Research conducted especially on adolescent-type idiopathic scoliosis indicate a complex etiopathogenesis. Known facts about etiopathogenesis include that some idiopathic scoliosis cases are familial, girls suffering adolescent idiopathic scoliosis are taller and leaner than their peers, such girls also suffer osteopenia and have their menarche later than their peers.

#### **Genetic mechanisms**

Various clinical and genetic studies proved familial susceptibility in patients with idiopathic scoliosis. Scoliosis prevalence was detected as 27% in the sisters of patients with scoliosis of more than 15 degrees. The said ratio rises to 36% in dizygotic twins, and as high as 73% in monozygotic twins. The studies conducted indicate an "X-linked" genetic disorder with a complex structure (12, 13). Various studies conclude that the genetic locus 19p13 of chromosomes 6p, 10q and 18q may be related to the occurrence of scoliosis (14). Besides, it was detected that the Xq23-26 regions may be responsible for the expression of the deformity (13). There are also studies suggesting that chromosomes 5 and 13 are in connection with kyphoscoliosis(15). On the other hand, recent studies have focused on single nucleotide polymorphism, and suggest that polymorphism of the Estrogen receptor-a (ERa), Estrogen receptor-b (ERb), tryptophane hydroxylase-1 (TPH-1), Melatonin Receptor 1B (MTNR1B) and Matrillin-1 (MATN-1) genes may result in susceptibility to the occurrence of scoliosis or curvatures (16).

**Genes in relation with connective tissue structure:** Numerous studies conducted on FBN1, ELN, COL1A1, COL1A2, COL2A1, ACAN, MATN1, LOX1, LOX2, LOX3, LOX4, LOX 5, TIMP2, MMP3, DPP9 genes failed to reveal any relation of such genes with scoliosis. Only the MATN-1 gene, which is in connection with the support provided by the support elements of the spine, is found to be related with the progress of scoliosis (17).

**Genes in relation with bone formation and metabolism:** BMP4, LEP, CALM1, IL6, VDR, TNFRSF11B, RANKL, RANK genes are genes concerning bone formation and metabolism. With CALM1 being slightly more among these, some studies have indicated that IL6, LEP and VDR genes are slightly related to the increase in susceptibility to curvature (17).

**Genes in relation with melatonin pathway:** MTNR1A, MTNR1B, TPH1, ASMT, AANAT, GPR50 genes were studied. Among these, studies on MTNR1B and TPH1 genes revealed more relevant results regarding susceptibility to curvature (17).

**Genes in relation with puberty and growth:** CYP17, ESR1, ESR2, GPER, GHR, IGF1 genes were studied. Whereas, hypotheses regarding dysfunction of estrogen receptors, which were considered

to have been the most relevant, failed to provide adequate number of positive outcomes, except for a small number of weak studies (17).

#### **Mechanisms in relation with connective tissues and the spine**

Collagen and elastin fibria are the main components that support the vertebral column. It was discovered, in scoliosis patients, that nucleus pulposus has been pushed to the convex side of the curvature, annulus fibrosus has stretched towards the concave side, and compressed by the neighboring vertebrae. It was demonstrated that disc samples taken from patients with idiopathic and neuromuscular scoliosis had reduced glycosaminoglycan and increased collagen content. However, all such changes have been considered as changes occurring due to scoliosis, rather than initiating changes (5).

Hung et al detected reduced bone mineral density in progressive scoliosis patients, compared to the control group. Osteopenia appears to be responsible for progression, rather than being an initiator. Although a disruption in the vitamin D gene or metabolism is blamed for the condition, no defect could be proved to be related to such a disruption (18).

#### **Mechanisms in relation to the paravertebral muscles**

The fact that the vertebral column carries a load of only 2 kilograms when stripped from its muscles and left only with bones and ligaments is an indication of the significance of the paravertebral muscles (19). Although reductions were detected in miscellaneous studies by Spencer et al on the two types of muscle fibers in adolescent idiopathic scoliosis, namely slow-type 1 and rapid-type 2, a common outcome could not be obtained from such studies (17, 20). Some researchers discovered separations in the contraction bands of the tubular bodies of paravertebral muscles, formation of central cores in certain fibers, shortening of sarcomeres, array disorders in myofilaments, as well as increased intracellular calcium levels. Such changes may be related to a defect in the calcium pump (5).

#### **Neurological mechanisms**

Pincott et al demonstrated, through experimental damages formed in various regions of the central nervous system, that scoliosis occurred with its convexity directed towards the location of the damage (21).

Research demonstrated that patients with scoliosis had more vestibular dysfunction compared to normal humans. Nystagmus, an indication of oculovestibular dysfunction, is observed more frequently in scoliosis patients. It is proposed that axial posture resulting from oculovestibular asymmetry, high cortical proprioception and sensory perception deficiency may trigger scoliosis (22).

Some researchers suggest that a short spinal cord would stretch the posterior elements during growth and result in the curvature and rotation of the vertebral column(23).

#### **Effects of growth and development**

Acceleration of growth in adolescence, as well as

the fact that adolescents with scoliosis are taller than their peers as of the end of puberty suggest that a growth hormone relation such as growth hormone-insulin may be effective in the development of scoliosis. In some researches, growth hormone level is found to be higher compared to the control group. On the other hand, insulin-like growth factor-1 level was found to be high in some researches, and the same as the control group in others (24, 25, 26). According to the Hueter-Volkman principal, increasing compressive pressure in epiphyseal plates slow down growth, while increasing tractional pressure accelerate growth. Existence of asymmetric forces during growth was suggested as a factor that may trigger scoliosis. Although, in scoliosis, accelerated growth in the convex side of the apical vertebra can be thought to result from the existence of less pressure thereon, this situation is acknowledged as a result rather than a cause (27, 28).

It is known that scoliosis patients have hypokyphosis. This is thought to be a result of anterior plates growing more rapidly. Another study revealed that the height of the backbone is greater in girls compared to boys and such difference increases with age, and high-angle scoliosis patients are taller compared to low-angle scoliosis patients. Thoracic kyphosis flattens to a certain extent with rapid growth during adolescence, and recovers to its former condition after completion of growth. It was shown that such flattening occurs at the same period in boys and girls, independent of maturity. Growth acceleration occurs at a later period in boys, following completion of the flattening of thoracic kyphosis. Whereas in girls, such acceleration and flattening coincide, and therefore scoliosis is seen more frequently in girls (29).

#### **Effects of melatonin**

It was demonstrated that scoliosis developed in chickens following pinealectomy, and recovery is observed in scoliosis following re-implantation of the removed pineal gland into the skeletal muscle. However, a similar result could not be achieved in bipedal monkeys. This situation is explained by the melatonin receptors being spread in a broader area (30). Research conducted based on the aforementioned findings revealed that adolescent idiopathic scoliosis patients have melatonin signal dysfunction. Moreau demonstrated that such dysfunction is a result of increased phosphorylation of the serine residues of the Gi inhibitor proteins connected to the MT1 and MT2 receptors. It was also demonstrated that dysfunction in the MT2 receptors can be recovered with 17-beta estradiol. Two types of melatonin receptors were defined in mammals, and among these, it was shown that melatonin receptor 1A (MTNR1A) polymorphism is irrelevant with the development of adolescent idiopathic scoliosis, while melatonin receptor 1B (MTNR1B) gene polymorphism causes susceptibility to the development of adolescent idiopathic scoliosis, however it does not affect the degree of curvature(31).

#### **Thrombocyte changes and calmoduline disorders**

Thrombocytes are considered as skeletal muscles

that do not have axial connections, as they have a contraction function due to the actin and myosin fibrils they carry. Various thrombocyte disorders were reported in many patients with adolescent idiopathic scoliosis. Researches revealed the existence of larger-than-normal thrombocytes, increased intracellular calcium and phosphorus levels, reduced ability of aggregation and abnormal myosin structure (5).

Calmoduline is a protein responsible for regulating the calcium flow from the sarcoplasmic reticulum and the contraction activity between actin and myosin. Kindsfater et al discovered that calmoduline levels in patients with progressing adolescent idiopathic scoliosis are higher compared to patients with stable curvatures (32).

There are experimental studies indicating that the progress of curvature can be reduced as a result of inhibition of the effects of calmoduline using selective estrogen receptor antagonists (SERM). Such observations suggest that estrogen and/or estrogen receptors have an effect on the pathogenesis of idiopathic scoliosis, and may also explain the gender difference in involvement, as well as the osteopenia existing in the patients. The effects of estrogens are thought to occur mostly through osteoblast signal defects (33, 34).

#### **Asymmetric effects of hypothalamus, leptin and the sympathetic nervous system**

Grivas et al demonstrated that girls with relatively lower body-mass index (BMI) have their menarche later and have serious curvatures. It may be possible that leptin levels are lower in girls with lower body-mass index, and thus hypothalamus have grown over-sensitive to leptin. This increased sensitivity may have led to asymmetric stimulation of the sympathetic nervous system, which is under the effect of the hypothalamus, and in turn, the effects of the sympathetic nervous system on paravertebral muscles, costae or the vertebra corpuses may occur asymmetrically. Such asymmetry occurring in the growth period may play a role in the occurrence or development of scoliosis (35).

In conclusion, the etiology of adolescent infantile scoliosis is not yet fully clarified. It is still unclear whether the mentioned mechanisms are causes or results. Currently, adolescent idiopathic scoliosis is assessed as a dominantly-inherited multigenic disease having a variable penetration. Presumably, significant developments would be achieved in the future with further progress in genetic studies. When the effects of melatonin and calmoduline on progression are concerned, it can be presumed that new treatment strategies may be established based on the said molecules.

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