IDIOPATHIC SCOLIOSIS AS A MULTIFACTORIAL DISEASE: SYSTEMATIC REVIEW OF CURRENT LITERATURE

A.P. Gorbach, O.M Sergeenko, E.N. Shchurova
National Ilizarov Medical Research Centre for Orthopaedics and Traumatology, Kurgan, Russia

Objective. To analyze the current literature dedicated to the etiopathogenesis and development of idiopathic scoliosis.
Material and Methods. The analysis includes studies on the etiological factors of idiopathic scoliosis. The search was carried out on eLibrary, PubMed and Google Scholar databases. The review includes research and experimental studies, as well as systematic reviews and meta-analyses. The exclusion criterion is a theoretical work without practical research/experiment to confirm the theory. The depth of analysis is 30 years.
Results. Out of 456 papers on the research topic, 153 were selected as meeting the inclusion/exclusion criteria. The main theories of the occurrence of idiopathic scoliosis are identified: genetic, neurogenic, theory of bone and muscle tissue defects, biomechanical, hormonal, evolutionary, and the theory of environmental and lifestyle influences.
Conclusions. The term "idiopathic scoliosis" combines a number of diseases with different etiopathogenetic mechanisms of development. Idiopathic scoliosis has a polygenic inheritance. Different genes are responsible for its occurrence in different populations, and the progression mechanisms are triggered by various epigenetic factors. Bone and muscle tissue defects, pathology of the central nervous system, biomechanical disturbances, hormonal and biochemical abnormalities may play a dominant role in some cases of idiopathic scoliosis.
Key Words: idiopathic scoliosis, etiology of idiopathic scoliosis, pathogenesis of idiopathic scoliosis, theories and hypotheses of the development of idiopathic scoliosis.
Please cite this paper as: *Gorbach AP, Sergeenko OM, Shchurova EN. Idiopathic scoliosis as a multifactorial disease: systematic review of current literature. Hir. Pozvonoc. 2022;19(2):19–32. In Russian.*
DOI: http://dx.doi.org/10.14531/ss2022.2.19-32.

Idiopathic scoliosis (IS) is a three-dimensional spine deformity of unknown etiology, characterized by lateral deviation in the frontal plane (⩾10° according to Cobb), axial rotation in the horizontal plane (torsion) and abnormal sagittal profile of the spine [1]. It is generally accepted that deformity less than 10° according to Cobb is not considered as structural scoliosis [1]. IS incidence in populations across different regions of the world is 2–5 % [2].

According to the onset age, IS is divided into infantile (in children 0–3 y.o.), juvenile (4–9 y.o.) and adolescent (from 10 y.o. and older). There are also scoliosis with early onset (before 10 y.o.) and adolescent idiopathic scoliosis with onset after 10 y.o. [3]. In 20 % of patients with early scoliosis onset, pathology of the spinal cord and brain is detected which specifies mandatory MRI.

It is customary to treat IS as a diagnosis of exclusion – when anamnesis, clinical and introscopic data, as well as genetic analysis data do not provide clear evidence of any specific etiology of disease development [4], attributed to a lot of genetic and epigenetic factors [5]. Numerous theories of IS origin can be divided into the following groups: genetic, neurogenic, the theory of bone and muscle tissue defects, biomechanical, hormonal, biochemical, evolutionary and the theory of the influence of the environment and lifestyle [6].

The objective is to analyze the current literature on etiology and development of idiopathic scoliosis.

When planning this study, we tried to answer the following question: is IS a single nosological unit or does it combine several conditions with different pathogenesis?

Material and Methods

An analysis of research publications over the past 30 years on IS etiology and pathogenesis is carried out. The search was performed by three independent authors using eLibrary, PubMed, and Google Scholar databases. The analysis covers research and experimental work, as well as systematic reviews and meta-analyses. The exclusion criteria were the theoretical nature of a work (advancing a particular theory without confirmation through practical research/experiments) and the papers published more than 30 years ago.

Results and Discussion

A total of 456 papers on the research topic were found. Having excluded the publications (already included in systematic reviews and meta-analyses), the list was reduced to 153 (Fig.). The review also includes 5 papers published more than 30 years ago that are of fundamental historical value.

Publications have been analyzed in accordance with the above mentioned theories of idiopathic scoliosis development.

Genetic theory

Modern studies demonstrate that chromosomal anomalies, as well as anomalies of gene loci, cause primary expression changes, while epigenetic changes caused by environmental factors additionally regulate gene expression. Most likely, these elements work together in different combinations, causing dysfunction of the cellular activity of various (bone, muscle, fat, nervous) tissues, that leads to the development of idiopathic scoliosis [7].

Chromosomal abnormalities and genetic mutations. The genetic prerequisites for the development of IS are known and proven, however, the most clinically significant causative loci are still not clear, and additional studies are needed to understand their molecular pathways.

In 1875, after studying twins with IS, Galton [8] first noted the role of the genetic factor in the development of spinal deformity. One of the most recent studies by Simony et al. [9] showed a higher degree of concordance in monozygotic pairs of twins (0.13) than in dizygotic twins (0.00). However, not all monozygotic twins are completely identical phenotypically, despite the same set of genes, which demonstrates the influence of epigenetic factors that already exist at the stage of intrauterine growth (for example, differences in blood supply, in the composition of amniotic fluid and fetal position).

Studying the genes and degree of relationship of 145 patients with adolescent IS from the United States, Ogilvie et al. [10] found that many of them had common relatives – early settlers from Europe. In almost all (97 %) patients in this group the disease was of family origin. The authors noted the existence of at least one major gene, while the differences in penetrance and expressivity in two large unrelated pedigrees may indicate the presence of more than one gene. Genetic relationship between families of patients with adolescent IS from close regions was also noted by other researchers [11]. Inheritance can be recessive, dominant, codominant, or X-linked.

The possibility of X-linked inheritance is under scrutiny precisely because adolescent IS occurs more often in girls [12]. Justice et al. [12] demonstrated the presence of a region on the X chromosome that may be associated with adolescent IS. However, Ward et al. [13] pointed to a more likely polygenic inheritance of adolescent IS by presenting examples of its transmission from male to male, refuting the hypothesis of exclusively X-linked inheritance.

In recent decades, the hereditary nature of scoliosis has been investigated along the lines of genome-wide associated studies (GWAS) and candidate-genes analysis. Genetic studies point to many genes associated with IS. At the same time, genes that correlate with IS severity rather than simply with its presence can be put in a separate group. Correlation with the presence of IS in at least one study was revealed in relation to the MAPK7 genes [14] and the DS1034 allelic ladder in the chromosome 19p13.3 [15], LBX1 [16], MATN1 (matrilin 1) [17], ESR2 (estrogen receptor beta) [18], BMP4, IL-6 (interleukin-6), leptin, MMP3, MTNR1B (melatonin receptor 1b) [19], CALM1 (calmodulin 1) [20], VDR (vitamin D receptor) [21], TPH1 (tryptophan hydroxylase 2) [22], FBN1 (fibrillin-1) and FBN2 (fibrillin-2) [23], COL11A1, COL11A2 and TGFBR2 [24], GPR126 (G protein-coupled receptor 126) [25], PAX1 (paired box 1) [26], TGFB1 (transforming growth factor beta 1) [27], C17orf67 and DOT1L [28], IL-17RC (interleukin 17 receptor C) [29], POC5 (centriole protein) [30], NUCKS1 (nuclear casein kinase and cyclin-dependent kinase substrate 1) [31], homeobox genes HOXB8, HOXB7, HOXA13, HOXA10), ZIC2, FAM101A (filamin A protein regulator), COMP (cartilage oligomeric matrix protein) and PITX1 (paired-type homeodomain transcription factor 1) [32, 33].

Epigenetics. Epigenetics studies inherited changes in gene activity during cell growth and division, namely, changes in protein synthesis caused by mechanisms that do not change the nucleotide sequence in DNA [34]. Fendri et al. [33] found 145 genes differently expressed in osteoblasts in adolescent IS, which may be related to the peculiarities of epigenetic regulation. Mao et al. [35] noted that during DNA methylation, positive methylation of the cartilage oligomeric matrix protein (COMP) promoter led to low expression of the COMP gene affecting bone formation, which correlated with younger age and more pronounced deformity in patients with IS. The correlation between the severity of spinal deformity and site cg01374129 hypomethylation is indicated by Meng et al. [36].

The role of mesenchymal stem cells (MSC) of the bone marrow in IS development. This theory can be considered to be a part of the genetic theory, but since the volume of studies in this field is currently quite significant, we considered it right to cover it separately.

Multipotent MSC differentiate into osteoblasts, chondrocytes or adipocytes. Reduced osteogenetic ability of MSC and the tendency of MSC towards adipogenic differentiation were found in patients with IS [37, 38]. Impaired MSC differentiation can impact bone mass formation in IS patients, thereby participating in its development. This is further supported by the fact that patients with adolescent IS show a decrease in bone mineral density [39, 40].

Proteomic analysis of MSC in patients with adolescent IS revealed defects in the regulation of a number of proteins that affect bone growth [41]. It is noted that enhanced activity of one of these proteins causes increased cell proliferation, while the reduced activity of other proteins decreases ossification and bone mass. The authors continued their study and identified several differentially expressed genes associated with the onset of adolescent IS [42].

Chen et al. [43] found that expression of melatonin receptors in MSC in patients with adolescent IS is suppressed, which can lead to a decreased response to melatonin, and since melatonin increases the activity of alkaline phosphatase, enhances the synthesis of glycosaminoglycans (GAG) and other factors influencing gene differentiation, this may affect endosmal and endochondral ossification.

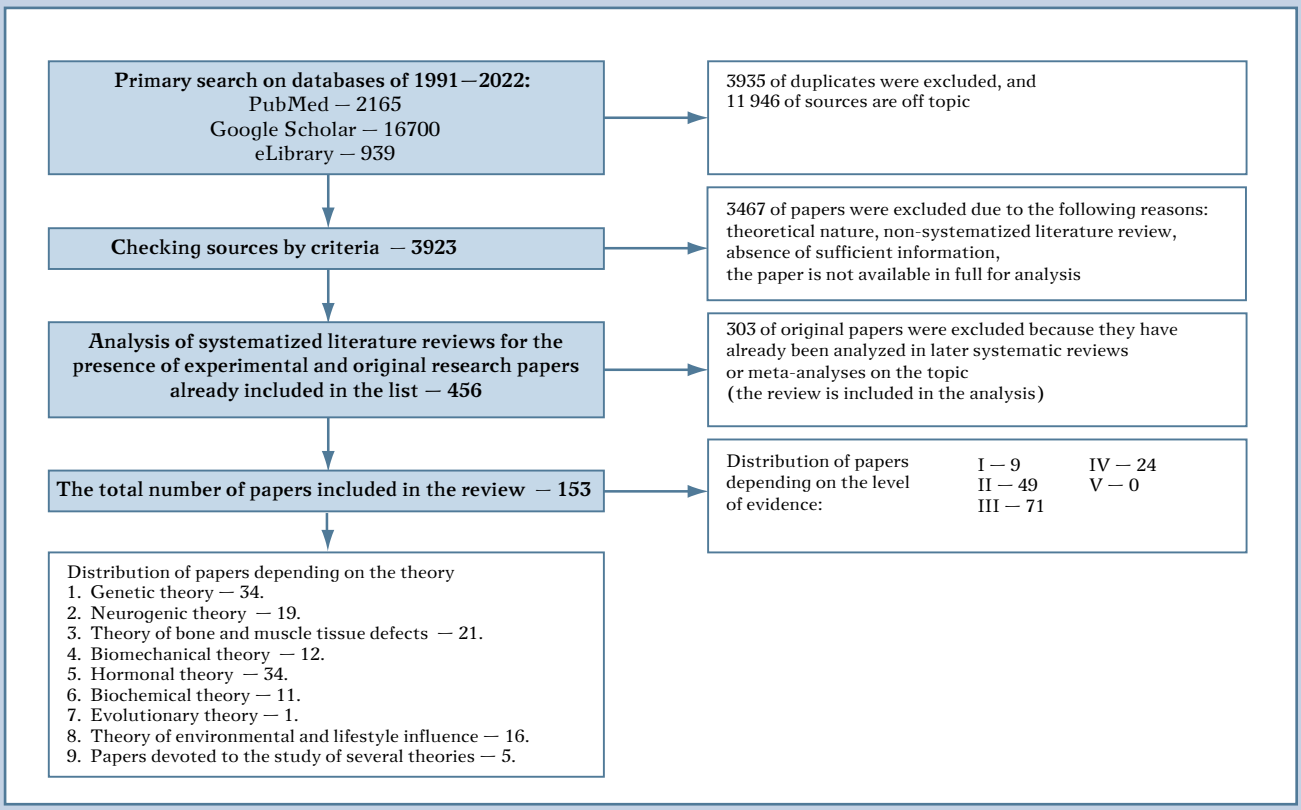

Fig.
Scheme for selection of literature for systematic review

Another study noted that leptin receptors in MSC in patients with adolescent IS are suppressed which, in turn, may lead to hyposensitivity of MSC to circulating leptin [37].

Spot14 nuclear protein and its messenger RNA (mRNA) are more expressed in adipogenic MSC in patients with adolescent IS than in the control group. Their higher expression was also found in the adipose tissue of patients with adolescent IS that reflects an abnormal adipogenic differentiation [44].

Lower expression of the MAPK7 protein was found in MSC with adolescent IS; it affects the osteogenic differentiation of MSC [45].

The GPR126 gene has a higher expression in the vertebral bodies on the convex side of scoliosis, and its malfunction impacts MSC ossification [46].

The following long non-coding RNAs (lncRNAs) and microRNAs (miRNAs) have been identified. They are epigenetic factors associated with MSC differentiation: lncAIS (associated with osteopenia) [47], miR-17-5p, miR-106a-5p, miR-106b-5p, miR-16-5p, miR-93-5p, and miR-181b-5p (suppress osteogenic differentiation of the MSC and impair bone formation), miR-15a-5p (regulates cell apoptosis) [48].

Neurogenic theory

Brain. Research on relationship between the influence of brain on IS development is focused mainly on neuroanatomical and neurofunctional changes observed in brain, brainstem and cerebellum.

Examining brain MRI scans in patients with adolescent IS with the left-sided lower thoracic curve, Shi et al. [49] revealed thinning of white matter in corpus callosum and left internal capsule in patients. The same group of authors confirmed the difference in cortical thickness in patients with adolescent IS in comparison with the normal control group, mainly in the region associated with motor and vestibular functions [51]. Liu et al. [51] noted regional differences in brain volume in patients with adolescent IS, as well as neuroanatomical asymmetries in brain regions functionally associated with somatic motor control and coordination.

When analyzing EEG in 106 patients with IS and in 35 without pathology (aged from 6 to 16 years), Dudin et al. [52] revealed various deviations more often in the study group, for example, signs of neurodynamic disorders with a shift towards the predominance of excitatory processes over inhibition processes, more often noting impairment of cortical-subcortical relationships at the level of diencephalic formations, epileptiform manifestations and the predominance of neurophysiological signs of CNS dysfunc-

tion at the level of the oral parts of the brain stem.

Brain stem and cerebellum. In patients with adolescent IS, in comparison with the control group, asymmetry of the ventral pons and medulla oblongata in the region of the cortical-spinal tract was found [53], a lower level of the cerebellar tonsils, including when examined on a vertical tomographic scanner [54, 55], a relative increase in several regions of the cerebellum [56], a significantly larger diameter and area of the foramen magnum, while the peak rates of cerebrospinal fluid flow through it did not have a significant difference [54].

In addition, girls with adolescent IS showed a prolonged latency of somatosensory evoked potentials, while cerebellar tonsil ectopia was found in 58% of patients with abnormal responses [57].

At the same time, no significant differences in glucose metabolism were discovered in the brains of patients compared with healthy people [58].

Thus, abnormalities in the structure of the brain of patients with adolescent IS were exposed, however, currently there is no convincing evidence that they are the cause of scoliosis development. Many experts are inclined to believe that in some cases scoliosis may be associated with abnormal development of cerebellum and/or latent Chiari malformation (Chiari 0) or asymptomatic Chiari type I malformation.

Asynchronous neuroosseous growth (hidden tethered spinal cord syndrome). The hypothesis of asynchronous neuroosseous growth suggests that small length of a spinal cord can lead to hypokyphosis and, consequently, to the initiation of a curve with or without scoliosis progression [59]. Chu et al. [60] noted a relative segmental elongation of the spinal column at the thoracic level in IS patients with a significant decrease in the ratio of spinal cord length to spinal column length.

Vestibular system and IS. Asymmetry of vestibular system can lead to an asymmetric increase in the tone of paraspinal muscles and development of scoliosis [61–65], however, there is no sufficient evidence for this theory [66].

Tissue defect theory

Bone tissue. At present, bone malformations in IS at the morphological level have been identified [67–72], and it has been established that osteopenia is a prognostic factor for scoliosis progression.

According to Tanabe et al. [73], examining the segmented spinal processes of patients with IS taken intraoperatively, 67% of specimens showed a reduced bone volume and 76 % showed high bone tissue metabolism.

Examining growth plate cells taken from 50 children with IS, Zaidman et al. [74, 75] found cells similar to glio- and neuroblasts on the concave side of the deformity, while cells similar to chondroblasts were found on the convex side. The authors suggested that the etiological factor of scoliotic disease may be ectopic localization in the vertebral body growth plate of neural crest-derived cells that are not genetically determined to chondrogenic differentiation and to the growth process.

Muscular tissue. Studies of paravertebral muscles in IS patients demonstrate structural changes and muscle asymmetries that can either cause scoliosis or be caused by scoliosis. Morphological changes in the muscles in IS are predominantly of a nonspecific diffuse nature [76, 77], and the performance asymmetry of paraspinal muscles is confirmed by EMG data [78, 79].

On the convex side of the deformity in patients with adolescent IS, a higher concentration of calmodulin was found which affects muscle contractility [80]. At the same time, muscles on the convex side contain more type I fibers than those on the concave side that may be due to their higher fatigue and resistance at a lower rate of contraction [81].

Changes in paravertebral muscles have also been confirmed at the genetic level: Buchan et al. [82] identified rare FBN1 and FBN2 variants that correlated with deformity progression, while Nowak et al. [83] – a high content of TGF- 2, TGF-3 transcripts and transforming growth factor beta receptor 2 (TGF-BR2) in muscles on the concave side of the deformity.

Genetic studies have also shown that some risk loci for IS onset and progression have formed in zones located near or within genes associated with muscle biogenesis [84, 85].

Having performed dopplerography of the vessels of extremities, as well as ultrasound of the heart and abdominal organs and spirometry to 598 pupils of the European North of Russia, 160 of whom had scoliosis [86], Chernozemov and Dudin found that children with scoliosis have a lower rate of blood flow in extremities, a greater frequency of mitral valve dysfunction and pulmonary valve regurgitation, as well as a decrease in spirometry and a pathology of biliary tract, which may indicate generalized connective tissue dysplasia.

Biomechanical theory

Accelerated growth of the anterior column. Back in 1996, Murray et al. [87] found that in IS there is an increase in the anterior column of the spine relative to the posterior one. The discrepancy between the growth of the anterior and posterior elements of the vertebral bodies, as well as the growth of the vertebral bodies and their posterior elements, leads, first of all, to thoracic hypokyphosis. Increased pressure on the epiphyseal plate of the vertebra slows down its growth, while the reduced pressure accelerates it. Theory assumes that on the concave side of the curve, the epiphyseal plates experience abnormally high pressure that leads to a decrease in the growth rate, while on the convex side the pressure is lower which leads to accelerated growth [88]. Shi et al. [89] confirmed this model experimentally and suggested that the increase in the anterior support column in IS may be secondary, since the model with previously established hypokyphosis did not develop scoliosis during the study. The theory of the accelerated growth of the anterior supporting column was also confirmed by the model of developing hypokyphotic spine deformity with an anterior restraining band that imitates the contraction of the anterior muscles and ligaments, even without the preset left-right asymmetry that caused the deformity to form in the frontal plane [90].

Guo et al. [91] found that enchondral ossification of the vertebral bodies in patients with adolescent IS is the main type of ossification and occurs faster than membranous (endesmal) ossification of the pedicles, which explains the principle of the theory on accelerated growth of the anterior supporting column in IS.

Wedging of the intervertebral discs (IVD). Some authors note that IVD growth and formation can play the leading role in IS development. Will et al. [92] and Brink et al. [93] revealed a more pronounced wedging of the intervertebral discs than the wedge shape of the bodies in adolescent IS at the beginning of the growth spurt.

Thorax and limbs. In addition to three-dimensional changes in the spine, IS has deviations in the positioning and biomechanics of other segments (shoulders, shoulder blades, pelvis) that may be a consequence or initial trigger of spinal deformity. Thus, asymmetry in the rib length may be a secondary change [94], or asymmetry in chest formation may contribute to IS development [95]. Left-handedness and the peculiarities of chest organs location can play a role in the nature of the curve in adolescent IS [96]. The same authors suggested that right-handedness is associated with stronger muscles in the right half of the back, which may cause a convexity to the right side.

Hormonal theory

Melatonin and calmodulin. Changes in melatonin metabolism can lead to an imbalance in cell proliferation and differentiation in various cell types which disrupts the normal formation of bone mass and can cause IS [97–101]. The question of whether melatonin deficiency is the cause of adolescent IS remains controversial, since studies of the level of this hormone in the blood serum show completely opposite results [102, 103].

The first studies on melatonin and its supposed influence on IS development have been performed on chickens [104, 105], rats [106] and rabbits since 1995. Experimental pinealectomy in animals led to the development of scoliosis [107].

Pinchuk et al. [108] suggested that the cause of scoliosis may be a dysfunction of the biorhythm of secretion as a result of an imbalance in the activity of the suprachiasmatic nucleus/pineal gland but not melatonin deficiency. At the same time, impairment in melatonin signaling were revealed in cultures of osteoblasts, when examining bone tissue samples taken during spinal surgery in patients with IS [109].

During the study the level of melatonin in patients with IS, both negative [110, 111] and positive results [112] were obtained, which may be due to the polymorphism of the disease. Mutations possibly associated with impaired melatonin metabolism have been identified in the Chinese population of patients with IS [100, 113], while no potentially significant mutations have been identified in other studies [114, 115].

Koyama et al. [116] demonstrated that melatonin is involved in stimulating bone cell proliferation and type I collagen synthesis in osteocytes and inhibiting bone tissue resorption by suppressing RANKL-mediated osteoclasts.

Calmodulin is a calcium-binding protein that regulates the actin-myosin complex associated with skeletal muscle contraction and platelet aggregation. Calmodulin regulates muscle function and bone formation, participates in various metabolic systems as a second messenger, it is widely expressed in various cells and takes part in the contractile system of cells and is also a melatonin inhibitor [97, 113]. Several studies have found elevated concentration of calmodulin in platelets in patients with adolescent IS [117]. In addition, its imbalance in the paraspinal muscles was found in patients with adolescent IS [118], as well as a decrease in the level of calmodulin after spinal fusion [119].

A case-control study showed a relationship between the level and form of spinal deformity with different subtypes of the calmodulin gene [20].

Leptin. Leptin influences functioning of the nervous system (the central function of leptin), as well as has a direct impact on the skeletal system (peripheral function). Ultimately, leptin is a hormone involved in bone formation regulation. Its production is regulated by the nuclei of the hypothalamus and the sympathetic nervous system [120]. It is mainly secreted by adipocytes, and the leptin receptor (OB-R) is found in chondrocytes and osteoblasts. Leptin regulates osteogenic differentiation of bone marrow stem cells and chondrocyte function by directly binding to the OB receptor [121].

In patients with adolescent IS a decrease in circulating leptin level was found, which is believed to be associated with lower body mass index (BMI) and bone density [122]. The change in the level of circulating leptin in adolescent IS may be secondary, caused by a low capacity for adipogenesis which is the result of their lower fat accumulation [37]. A study of the level of leptin and its soluble receptors (OB-R) in girls with adolescent IS compared with healthy girls showed that lower body weight in girls with scoliosis was due to both lower skeletal muscle mass and lower body fat content. Altered leptin bioavailability also exists in girls with adolescent IS and may lead to weight loss [123]. Hyposensitivity to it is a plausible explanation for the abnormally low bone mineral density observed in IS patients [124].

Wang et al. [121] found a lower expression of membrane leptin receptors in chondrocyte cells of the facet joints of patients with adolescent IS.

Low BMI can be directly related to low leptin levels and it is usually lower than average in IS patients. Does low leptin cause of low body weight and reduced fat accumulation or is it an inverse relationship? The answer to this question is not clear yet. It is likely that IS patients have higher leptin utilization due to higher levels of the soluble leptin receptor (OB-R). In addition, as BMI decreases in IS patients, the fat content decreases that probably leads to a decrease in leptin secretion. Although the trigger for lower leptin levels and lower BMI in IS is unclear, the effects appear to be mediated by increased leptin utilization, reduced secretion, and abnormal downstream signaling in the leptin pathways [37].

Sex hormones. It is known that IS is more common in women than in men

[12]. Estrogen performs a lot of functions and its lack leads to a deficiency in bone maturation that can further lead to IS development. Estrogens affect bone tissue remodeling and growth by interacting with factors that modulate bone growth, their biomechanics and structure.

Estrogens suppress production of cytokines, including interleukin-6 (IL-6), interleukin-1 (IL-1), nuclear factor B ligand receptor activator (RANKL) from immune cells and osteoblasts, enhance osteoblast proliferation, reduce osteoblast and osteocyte apoptosis and induce osteoclast apoptosis.

Kulis et al. [125] examined IS patients before and after menarche onset, the control group included girls without spinal deformity. In the main group before menarche, the levels of FSH, LH and estradiol were reduced, the levels of progesterone, estrone and estriol were higher, and the concentrations of estrone and estriol were normal, also there were higher levels of RANKL (glycoprotein of the TNF superfamily, produced by osteoblastic cells and activated T-lymphocytes), osteocalcin and alkaline phosphatase in this group. These figures were significantly higher in the group of girls after the menarche onset. The concentrations of FSH, LH, estradiol and progesterone in girls with IS after the onset of menarche were lower, estrone was slightly lower, and estriol was normal.

The cellular response to estrogen in IS patients altered and may lead to delayed menarche and osteopenia. Estrogen receptors can influence the response of vertebral growth sites to stress which affects bone formation. Estrogens also impact the work of other hormones, for example, melatonin and estrogen have the opposite effects on regulation of cAMP level in cells and calmodulin, in turn, can affect the work of estrogen in signaling pathways [126, 127].

Growth hormone. Growth hormone (STH – somatotropic hormone) regulates the overall body growth, changes in its secretion and performance can affect the skeleton growth. Willner et al. [128] found a higher secretion of the growth hormone in adolescent girls with IS than in healthy peers. Yang et al. [129] and Zhuang et al. [130] identified gene polymorphisms of STH receptors in patients with adolescent IS that were associated with higher STH level in blood and low bone mass.

Park et al. [131] found that growth hormone treatment of IS patients did not affect its progression and in the group of children who previously did not have IS, during growth hormone treatment of idiopathic growth retardation, *de novo* scoliosis occurred in 3.7 %. However, Day et al. [132] obtained data that is different from these results.

The conflicting data are explained by the fact that patients treated with growth hormone probably had syndromes when scoliosis is more common than in an age-comparable population. Thus, in Turner syndrome, the prevalence of scoliosis reaches 28.8 % [132].

Through genetic studies, it can be concluded that changes in STH receptors may play a more important role than changes in its secretion or structure. Further research is needed to find out the specific role of STH and interactions between STH and other hormones.

Biochemical theory

Mineral metabolism of bone tissue. The decrease in bone tissue mass (osteopenia) in patients with adolescent IS has been confirmed by numerous studies. Osteopenia can theoretically lead to curvature appearance and progression. The ligand-receptor system RANK/RANKL/OPG is a key link in bone tissue homeostasis, which directly regulates osteoclast differentiation and osteolysis and plays an important role in bone metabolism. Suh et al. [133] found a relative increase in the concentration of receptor activator of nuclear factor kappa B ligand (RANKL) compared to osteoprotegirin (OPG), as well as low vertebral and femoral neck bone mass. In turn, Zhou et al. [134] found increased expression of RANKL not only in serum, but also in osteoblasts.

Eun et al. [135] confirmed that the OPG gene and the IL-6 gene, which was a candidate gene for osteopenia, have polymorphisms in patients with adolescent IS and may be associated with deformity development. Wang et al. [136] found a decrease of RUNX2 expression in osteoblasts of patients with adolescent IS. It is an important transcription factor regulating osteoblast differentiation and skeletal formation that correlates with decreasing bone mass in the spine and femoral neck. Using finite element modeling, it was possible to confirm that osteopenia on the concave side in thoracic scoliosis can change the bone structure, including the joints structure, their regular growth and cause the deformity progression.

Metabolism of fats and proteins. Impaired serum lipid metabolism found in patients with adolescent IS [138] concerns glycerophospholipids, glycerolipids and fatty acid esters. Lipid metabolism is associated with various types of hormones and regulatory systems, therefore, most likely, these changes are secondary.

The intervertebral disc structure. Biochemical processes can cause histological discs changes which, in turn, can cause biomechanical changes that can lead to scoliosis onset or progression. Ghosh et al. [139] noted pathological distribution of glycosaminoglycans in scoliotic vertebral discs, the concentration of which should initially be the highest in the vertebral pulp.

An increase in the amount of collagen types I and II was found on the convex side of the discs compared to the concave side [140].

Evolution theory

A study of a large sample of monkey skeletons did not identify a single case of scoliosis in chimpanzees or gorillas [141]. This may be due to the anatomy difference, since, compared to humans, they have a shorter and less mobile lumbar spine, and they rarely move on two limbs.

Theory of the environment and lifestyle impact

Nutrition and ecology. The interaction of genes and diet has been observed in many aspects of growth development, most profoundly in adolescence during puberty. Golding [142] drew attention to the sudden increase in IS incidence in Jamaica after 1965, particularly, to endocrine supplements that began to be used to stimulate the growth of livestock.

DNA methylation and epigenetic factors are considered to be the main mechanism underlying these changes, since these epigenetic factors can cause genetic predisposition. In particular, nutritional components thought to play a role include bioactive polyphenols, zinc, selenium, and vitamins A and D [143].

Yang et al. [144] hypothesized that high level of selenium in the environment can cause discoordination of the spine and bones growth, excessive growth of the spine in relation to the spinal cord (hidden tethered spinal cord syndrome), all that, in turn, can cause scoliosis. This assumption is related to the fact that guppy fish developed a S-shaped deformity in an environment with high selenium content.

The cohort study by Ji et al. [145] confirmed that high selenium level was significantly associated with the incidence of adolescent IS, while low level was not significantly correlated.

It is considered that there is a link between IS and anorexia nervosa. Nutritional modification may delay spinal deformity progression [143].

Differences in gut microbiomes were found between patients with and without adolescent IS. Microbiome may influence plasma protein composition, and abundance of fecal prevotella is positively correlated with Cobb angles in patients with adolescent IS [146].

Vitamin D and its metabolites play the key role in bone metabolism and phosphorus-calcium homeostasis, affect the growth and differentiation of cells in various target organs. It is also a ligand for the nuclear receptor encoded by the VDR gene, which, in turn, regulates the activity of many target genes through its interaction with specific DNA sequences in the promoter regions of these genes. Vitamin D deficiency or insufficiency may influence the development of adolescent IS through various mechanisms [147, 148, 150].

Vitamin D correlates with calcium metabolism and may also affect regulation of fibrosis and postural control that may lead to the development of adolescent IS [147]. Probably, it interacts with estrogen, melatonin and leptin affecting bone density [147].

Children may suffer from insufficient level of vitamin D for various reasons: for example, in the cold season due to reduced insolation [149]. According to Mithal et al. [149] the mean vitamin D level in children was 16.6 ng/mL, while Balioglu et al. [150] noted the lowest level (14.41 ng/mL) in patients with adolescent IS in winter. This difference may be related to the location of the study.

The vitamin D receptor (VDR) is another point of interest in vitamin D metabolism. Vitamin D deficiency affects the modulation of brain neurotransmitters such as acetylcholine and catecholamines, and disrupts vitamin D-VDR signaling pathways, resulting in impaired motor function, poor balance and postural control in mice with low vitamin D level [151, 152]. Associations have been found between the risk of IS developing and polymorphisms of the vitamin D receptor (VDR) genes [21, 153]. Until now, this remains controversial: does the VDR gene polymorphism contribute to development of adolescent IS? Some studies do not support this theory [154].

McMaster et al. [155] suggested that chloroform generated in heated pools has a neurotoxic effect causing adolescent IS. In adult healthy swimmers, circulating neurotoxins were detected, among which were found chloroform, bromodichloromethane, dibromochloromethane and bromoform, as well as cyanide chloride and dichloroacetonitrile. It has been noted that in healthy adolescents who exercised in indoor heated pools, as well as in infants, there is a vertical asymmetry of the spinous processes [156].

Physical activity. Physical activity with different training strategies can give different results in IS. IS is less common among girls who go in for dancing, as well as among adolescents who are fond of gymnastics, karate, horseback riding and speed skating. There was no statistically significant association with previous regular football or ice hockey. IS occurred 8 times more often in children who started swimming at the age of less than one year in comparison with those who did not go the pool at this age [157], an explanation of this hypothesis is presented above. Watanabe et al. [158] found that the likelihood of developing IS raised with an increasing frequency of child's training in classical ballet, as well as with the duration of ballet lessons.

Conclusion

The common term "idiopathic scoliosis" most likely combines a number of diseases with different etiopathogenetic mechanisms of development. The most popular hypothesis at present is that there is no single gene responsible for scoliosis formation and, most likely, IS is a polygenic inheritance, which development is triggered by epigenetic factors.

Such causes of IS development as bone and muscle tissue defects, pathology of the central nervous system, biomechanics disorders, hormonal and biochemical abnormalities may play a dominant role in some cases of IS development.

Genetic and neurogenic theories, the theory of bone and muscle tissue defects, biomechanical, hormonal and biochemical, evolutionary, environmental and lifestyle theories are closely related to each other and intersect in many key points.

Searching for an etiological factor and studying factors that play a certain role in IS progression will remain relevant from both scientific and clinical points of view.

The study had no sponsors. The authors declare that they have no conflict of interest.

References

1. **Giampietro PF, Pourquie O, Raggio C, Ikegawa S, Turnpenny PD, Gray R, Dunwoodie SL, Gurnett CA, Alman B, Cheung K, Kusumi K, Hadley-Miller N, Wise CA.** Summary of the first inaugural joint meeting of the International Consortium for scoliosis genetics and the International Consortium for vertebral anomalies and scoliosis, March 16–18, 2017. Dallas, Texas. Am J Med Genet A. 2018;176:253–256. DOI: 10.1002/ajmg.a.38550.
2. **Hengwei F, Zifang H, Qifei W, Weiqing T, Nali D, Ping Y, Junlin Y.** Prevalence of idiopathic scoliosis in chinese schoolchildren: a large, population-based study. Spine. 2016;41:259–264. DOI: 10.1097/brs.0000000000001197.
3. **Balsano M, Negri S.** Natural course and classification of idiopathic scoliosis. In: Spine Surgery, ed. by B. Meyer, M.Rauschmann. Springer, Cham. 2019:141–148. DOI: 10.1007/978-3-319-98875-7_19.
4. **Trobisch P, Suess O, Schwab F.** Idiopathic scoliosis. Dtsch Arztebl Int. 2010;107:875–883. DOI: 10.3238/arztebl.2010.0875.
5. **Ogura Y, Matsumoto M, Ikegawa S, Watanabe K.** Epigenetics for curve progression of adolescent idiopathic scoliosis. EBioMedicine. 2018;37:36–37. DOI: 10.1016/j.ebiom.2018.10.015.
6. **Gao A, Li JY, Shao R, Wu TX, Wang YQ, Liu XG, Yu M.** Schroth exercises improve health-related quality of life and radiographic parameters in adolescent idiopathic scoliosis patients. Chin Med J (Engl). 2021;134:2589–2596. DOI: 10.1097/cm9.0000000000001799.
7. **Latalski M, Danielewicz-Bromberek A, Fatyga M, Latalska M, Krober M, Zwolak P.** Current insights into the aetiology of adolescent idiopathic scoliosis. Arch Orthop Trauma Surg. 2017;137:1327–1333. DOI: 10.1007/s00402-017-2756-1.
8. **Galton F.** The history of twins, as a criterion of the relative powers of nature and nurture. Fraser's Magazine. 1875;12:566–576.
9. **Simony A, Carreon LY, Jmark KH, Kyvik KO, Andersen MO.** Concordance rates of adolescent idiopathic scoliosis in a Danish twin population. Spine. 2016;41:1503–1507. DOI: 10.1097/BRS.0000000000001681.
10. **Ogilvie JW, Braun J, Argyle V, Nelson L, Meade M, Ward K.** The search for idiopathic scoliosis genes. Spine. 2006;31:679–681. DOI: 10.1097/01.brs.0000202527.25356.90.
11. **Dausset J, Cann H, Cohen D, Lathrop M, Lalouel JM, White R.** Centre d'etude du polymorphisme humain (CEPH): collaborative genetic mapping of the human genome. Genomics. 1990;6:575–577. DOI: 10.1016/0888-7543(90)90491-c.
12. **Justice CM, Miller NH, Marosy B, Zhang J, Wilson AF.** Familial idiopathic scoliosis: evidence of an X-linked susceptibility locus. Spine. 2003;28:589–594. DOI: 10.1097/01.BRS.0000049940.39801.E6.
13. **Ward K, Ogilvie J, Argyle V, Nelson L, Meade M, Braun J, Chettier R.** Polygenic inheritance of adolescent idiopathic scoliosis: a study of extended families in Utah. Am J Med Genet A. 2010;152:1178–1188. DOI: 10.1002/ajmg.a.33145.
14. **Gao W, Chen C, Zhou T, Yang S, Gao B, Zhou H, Lian C, Wu Z, Qiu X, Yang X, Alattar E, Liu W, Su D, Sun S, Chen Y, Cheung KMC, Song Y, Luk KKD, Chan D, Sham PC, Xing C, Khor CC, Liu G, Yang J, Deng Y, Hao D, Huang D, Li QZ, Xu C, Su P.** Rare coding variants in MAPK7 predispose to adolescent idiopathic scoliosis. Hum Mutat. 2017;38:1500–1510. DOI: 10.1002/humu.23296.
15. **Sadat-Ali M, Al-Omran AS, Al-Othman AA.** Genetic markers for idiopathic scoliosis on chromosome 19p 13.3 among Saudi Arabian girls: a pilot study. Indian J Hum Genet. 2011;17:13–16. DOI: 10.4103/0971-6866.82187.
16. **Ogura Y, Kou I, Matsumoto M, Watanabe K, Ikegawa S.** [Genome-wide association study for adolescent idiopathic scoliosis]. Clin Calcium. 2016;26:553–560.
17. **Zhang H, Zhao S, Zhao Z, Tang L, Guo Q, Liu S, Chen L.** The association of rs1149048 polymorphism in matrilin-1(MATN1) gene with adolescent idiopathic scoliosis susceptibility: a meta-analysis. Mol Biol Rep. 2014;41:2543–2549. DOI: 10.1007/s11033-014-3112-y.
18. **Zhao L, Roffey DM, Chen S.** Association between the estrogen receptor beta (ESR2) rs1256120 single nucleotide polymorphism and adolescent idiopathic scoliosis: a systematic review and meta-analysis. Spine. 2017;42:871–878. DOI: 10.1097/brs.0000000000001932.
19. **Morocz M, Czibula A, Grozer ZB, Szecsenyi A, Almos PZ, Rasko I, Illes T.** Association study of BMP4, IL6, Leptin, MMP3, and MTNR1B gene promoter polymorphisms and adolescent idiopathic scoliosis. Spine. 2011;36:E123–E130. DOI: 10.1097/BRS.0b013e318a511b0e.
20. **Zhao D, Qiu GX, Wang YP, Zhang JG, Shen JX, Wu ZH, Wang H.** Association of calmodulin1 gene polymorphisms with susceptibility to adolescent idiopathic scoliosis. Orthop Surg. 2009;1:58–65. DOI: 10.1111/j.1757-7861.2008.00011.x.
21. **Xia CW, Qiu Y, Sun X, Qiu XS, Wang SF, Zhu ZZ, Zhu F.** [Vitamin D receptor gene polymorphisms in female adolescent idiopathic scoliosis patients]. Zhonghua Yi Xue Za Zhi. 2007;87:1465–1469.
22. **Li J, Yang Z, Yu M.** Association study of single nucleotide polymorphism in tryptophan hydroxylase 1 gene with adolescent idiopathic scoliosis: A meta-analysis. Medicine (Baltimore). 2021;100:e23733. DOI: 10.1097/md.0000000000023733.
23. **Buchan JG, Alvarado DM, Haller GE, Cruchaga C, Harms MB, Zhang T, Willing MC, Grange DK, Braverman AC, Miller NH, Morcuende JA, Tang NL, Lam TP, Ng BK, Cheng JC, Dobbs MB, Gurnett CA.** Rare variants in FBN1 and FBN2 are associated with severe adolescent idiopathic scoliosis. Hum Mol Genet. 2014;23:5271–5282. DOI: 10.1093/hmg/ddu224.
24. **Liu B, Zhao S, Liu L, Du H, Zhao H, Wang S, Niu Y, Li X, Qiu G, Wu Z, Zhang TJ, Wu N.** Aberrant interaction between mutated ADAMTSL2 and LTBP4 is associated with adolescent idiopathic scoliosis. Gene. 2022;814:146126. DOI: 10.1016/j.gene.2021.146126.
25. **Xu E, Shao W, Jiang H, Lin T, Gao R, Zhou X.** A genetic variant in GPR126 causing a decreased inclusion of exon 6 is associated with cartilage development in adolescent idiopathic scoliosis population. Biomed Res Int. 2019;2019:4678969. DOI: 10.1155/2019/4678969.
26. **Liu G, Liu S, Li X, Chen J, Chen W, Zuo Y, Liu J, Niu Y, Lin M, Zhao S, Long B, Zhao Y, Ye Y, Zhang J, Shen J, Qiu G, Wu Z, Wu N.** Genetic polymorphisms of PAX1 are functionally associated with different PUMC types of adolescent idiopathic scoliosis in a northern Chinese Han population. Gene. 2019;688:215–220. DOI: 10.1016/j.gene.2018.12.013.
27. **Nikolova S, Dikova M, Dikov D, Djerov A, Savov A, Kremensky I, Loukanov A.** Positive association between TGFB1 gene and susceptibility to idiopathic scoliosis in Bulgarian population. Anal Cell Pathol (Amst). 2018;2018:6836092. DOI: 10.1155/2018/6836092.
28. **Mao S, Xu L, Zhu Z, Qian B, Qiao J, Yi L, Qiu Y.** Association between genetic determinants of peak height velocity during puberty and predisposition to adolescent idiopathic scoliosis. Spine. 2013;38:1034–1039. DOI: 10.1097/BRS.0b013e318287fcfd.
29. **Zhou S, Qiu XS, Zhu ZZ, Wu WF, Liu Z, Qiu Y.** A single-nucleotide polymorphism rs708567 in the IL-17RC gene is associated with a susceptibility to and the curve severity of adolescent idiopathic scoliosis in a Chinese Han population: a case-control study. BMC Musculoskelet Disord. 2012;13:181. DOI: 10.1186/1471-2474-13-181.
30. **Hassan A, Parent S, Mathieu H, Zaouter C, Molidperee S, Bagu ET, Barchi S, Villemure I, Patten SA, Moldovan F.** Adolescent idiopathic scoliosis associated POC5 mutation impairs cell cycle, cilia length and centrosome protein interactions. PLoS One. 2019;14:e0213269. DOI: 10.1371/journal.pone.0213269.

31. **Xu L, Xia C, Sun W, Qin X, Qiu Y, Zhu Z.** Genetic polymorphism of NUCKS1 is associated with the susceptibility of adolescent idiopathic scoliosis. Spine. 2017;42:1629–1634. DOI: 10.1097/brs.0000000000002167.
32. **Fadzan M, Bettany-Saltikov J.** Etiological theories of adolescent idiopathic scoliosis: past and present. Open Orthop J. 2017;11:1466–1489. DOI: 10.2174/1874325001711011466.
33. **Fendri K, Patten SA, Kaufman GN, Zaouter C, Parent S, Grimard G, Edery P, Moldovan F.** Microarray expression profiling identifies genes with altered expression in Adolescent Idiopathic Scoliosis. Eur Spine J. 2013;22:1300–1311. DOI: 10.1007/s00586-013-2728-2.
34. **Burwell RG, Dangerfield PH, Moulton A, Grivas TB.** Adolescent idiopathic scoliosis (AIS), environment, exposome and epigenetics: a molecular perspective of postnatal normal spinal growth and the etiopathogenesis of AIS with consideration of a network approach and possible implications for medical therapy. Scoliosis. 2011;6:26. DOI: 10.1186/1748-7161-6-26.
35. **Mao SH, Qian BP, Shi B, Zhu ZZ, Qiu Y.** Quantitative evaluation of the relationship between COMP promoter methylation and the susceptibility and curve progression of adolescent idiopathic scoliosis. Eur Spine J. 2018;27:272–277. DOI: 10.1007/s00586-017-5309-y.
36. **Meng Y, Lin T, Liang S, Gao R, Jiang H, Shao W, Yang F, Zhou X.** Value of DNA methylation in predicting curve progression in patients with adolescent idiopathic scoliosis. EBioMedicine. 2018;36:489–496. DOI: 10.1016/j.ebiom.2018.09.014.
37. **Liang G, Gao W, Liang A, Ye W, Peng Y, Zhang L, Sharma S, Su P, Huang D.** Normal leptin expression, lower adipogenic ability, decreased leptin receptor and hyposensitivity to Leptin in Adolescent Idiopathic Scoliosis. PLoS One. 2012;7:e36648. DOI: 10.1371/journal.pone.0036648.
38. **Park WW, Suh KT, Kim JI, Kim SJ, Lee JS.** Decreased osteogenic differentiation of mesenchymal stem cells and reduced bone mineral density in patients with adolescent idiopathic scoliosis. Eur Spine J. 2009;18:1920–1926. DOI: 10.1007/s00586-009-1129-z.
39. **Tahvildari BP, Erfani MA, Nouraei H, Sadeghian M.** Evaluation of bone mineral status in adolescent idiopathic scoliosis. Clin Orthop Surg. 2014;6:180–184. DOI: 10.4055/cios.2014.6.2.180.
40. **Cheng JC, Qin L, Cheung CS, Sher AH, Lee KM, Ng SW, Guo X.** Generalized low areal and volumetric bone mineral density in adolescent idiopathic scoliosis. J Bone Miner Res. 2000;15:1587–1595. DOI: 10.1359/jbmr.2000.15.8.1587.
41. **Zhuang Q, Li J, Wu Z, Zhang J, Sun W, Li T, Yan Y, Jiang Y, Zhao RC, Qui G.** Differential proteome analysis of bone marrow mesenchymal stem cells from adolescent idiopathic scoliosis patients. PLoS One. 2011;6:e18834. DOI: 10.1371/journal.pone.0018834.
42. **Zhuang Q, Mao W, Xu P, Li H, Sun Z, Li S, Qiu G, Li J, Zhang J.** Identification of differential genes expression profiles and pathways of bone marrow mesenchymal stem cells of adolescent idiopathic scoliosis patients by microarray and integrated gene network analysis. Spine. 2016;41:840–855. DOI: 10.1097/BRS.0000000000001394.
43. **Chen C, Xu C, Zhou T, Gao B, Zhou H, Chen C, Zhang C, Huang D, Su P.** Abnormal osteogenic and chondrogenic differentiation of human mesenchymal stem cells from patients with adolescent idiopathic scoliosis in response to melatonin. Mol Med Rep. 2016;14:1201–1209. DOI: 10.3892/mmr.2016.5384.
44. **Wang Q, Yang J, Lin X, Huang Z, Xie C, Fan H.** Spot14/Spot14R expression may be involved in MSC adipogenic differentiation in patients with adolescent idiopathic scoliosis. Mol Med Rep. 2016;13:4636–4642. DOI: 10.3892/mmr.2016.5109.
45. **Zhou T, Chen C, Xu C, Zhou H, Gao B, Su D, Liao Z, Li Y, Yang S, Su P.** Mutant MAPK7-induced idiopathic scoliosis is linked to impaired osteogenesis. Cell Physiol Biochem. 2018;48:880–890. DOI: 10.1159/000491956.
46. **Xu E, Lin T, Jiang H, Ji Z, Shao W, Meng Y, Gao R, Zhou X.** Asymmetric expression of GPR126 in the convex/concave side of the spine is associated with spinal skeletal malformation in adolescent idiopathic scoliosis population. Eur Spine J. 2019;28:1977–1986. DOI: 10.1007/s00586-019-06001-5.
47. **Zhuang Q, Ye B, Hui S, Du Y, Zhao RC, Li J, Wu Z, Li N, Zhang Y, Li H, Wang S, Yang Y, Li S, Zhao H, Fan Z, Qiu G, Zhang J.** Long noncoding RNA lncAIS downregulation in mesenchymal stem cells is implicated in the pathogenesis of adolescent idiopathic scoliosis. Cell Death Differ. 2019;26:1700–1715. DOI: 10.1038/s41418-018-0240-2.
48. **Hui S, Yang Y, Li J, Li N, Xu P, Li H, Zhang Y, Wang S, Lin G, Li S, Qiu G, Zhao RC, Zhang J, Zhuang Q.** Differential miRNAs profile and bioinformatics analyses in bone marrow mesenchymal stem cells from adolescent idiopathic scoliosis patients. Spine J. 2019;19:1584–1596. DOI: 10.1016/j.spinee.2019.05.003.
49. **Shi L, Wang D, Chu WC, Burwell RG, Freeman BJ, Heng PA, Cheng JC.** Volume-based morphometry of brain MR images in adolescent idiopathic scoliosis and healthy control subjects. AJNR Am J Neuroradiol. 2009;30:1302–1307. DOI: 10.3174/ajnr.A1577.
50. **Wang D, Shi L, Chu WC, Burwell RG, Cheng JC, Ahuja AT.** Abnormal cerebral cortical thinning pattern in adolescent girls with idiopathic scoliosis. Neuroimage. 2012;59:935–942. DOI: 10.1016/j.neuroimage.2011.07.097.
51. **Liu T, Chu WC, Young G, Li K, Yeung BH, Guo L, Man GC, Lam WW, Wong ST, Cheng JC.** MR analysis of regional brain volume in adolescent idiopathic scoliosis: neurological manifestation of a systemic disease. J Magn Reson Imaging. 2008;27:732–736. DOI: 10.1002/jmri.21321.
52. Dudin MG, Pinchuk DYu, Bekshaev SS, Svyatogor IA, Pinchuk OD, Bumakova SA, Pavlova VB, Rybka DO. On etiopathogenesis of idiopathic scoliosis. Hir. Pozvonoc. 2006;(4):18–25. DOI: 10.14531/ss2006.4.18-25.
53. **Geissele AE, Kransdorf MJ, Geyer CA, Jelinek JS, Van Dam BE.** Magnetic resonance imaging of the brain stem in adolescent idiopathic scoliosis. Spine. 1991;16:761–763. DOI: 10.1097/00007632-199107000-00013.
54. **Chu WC, Man GC, Lam WW, Yeung BH, Chau WW, Ng BK, Lam TP, Lee KM, Cheng JC.** A detailed morphologic and functional magnetic resonance imaging study of the craniocervical junction in adolescent idiopathic scoliosis. Spine. 2007;32:1667–1674. DOI: 10.1097/BRS.0b013e318074d539.
55. **Lee RK, Griffith JF, Leung JH, Chu WC, Lam TP, Ng BK, Cheng JC.** Effect of upright position on tonsillar level in adolescent idiopathic scoliosis. Eur Radiol. 2015;25:2397–2402. DOI: 10.1007/s00330-015-3597-3.
56. **Shi L, Wang D, Hui SC, Tong MC, Cheng JC, Chu WC.** Volumetric changes in cerebellar regions in adolescent idiopathic scoliosis compared with healthy controls. Spine J. 2013;13:1904–1911. DOI: 10.1016/j.spinee.2013.06.045.
57. **Chau WW, Chu WC, Lam TP, Ng BK, Fu LL, Cheng JC.** Anatomical origin of abnormal somatosensory-evoked potential (SEP) in adolescent idiopathic scoliosis with different curve severity and correlation with cerebellar tonsillar level determined by MRI. Spine. 2016;41:E598–E604. DOI: 10.1097/brs.0000000000001345.
58. **Lee JS, Kim SJ, Suh KT, Kim IJ, Kim YK.** Adolescent idiopathic scoliosis may not be associated with brain abnormalities. Acta Radiol. 2009;50:941–946. DOI: 10.1080/02841850903104161.
59. **Sun X, Chu WC, Cheng JC, Zhu F, Zhu Z, Yu Y, Wang B, Qiu Y.** Do adolescents with a severe idiopathic scoliosis have higher locations of the conus medullaris than healthy adolescents? J Pediatr Orthop. 2008;28:669–673. DOI: 10.1097/BPO.0b013e3181834afa.
60. **Chu WC, Lam WW, Chan YL, Ng BK, Lam TP, Lee KM, Guo X, Cheng JC.** Relative shortening and functional tethering of spinal cord in adolescent idiopathic scoliosis?: study with multiplanar reformat magnetic resonance imaging and somatosensory evoked potential. Spine. 2006;31:E19–E25. DOI: 10.1097/01.brs.0000193892.20764.51.
61. **Byl NN, Holland S, Jurek A, Hu SS.** Postural imbalance and vibratory sensitivity in patients with idiopathic scoliosis: implications for treatment. J Orthop Sports Phys Ther. 1997;26:60–68. DOI: 10.2519/jospt.1997.26.2.60.

62. **Lambert FM, Malinvaud D, Glaunes J, Bergot C, Straka H, Vidal PP.** Vestibular asymmetry as the cause of idiopathic scoliosis: a possible answer from Xenopus. J Neurosci. 2009;29:12477–12483. DOI: 10.1523/jneurosci.2583-09.2009.
63. **Zeng W, Lui LM, Shi L, Wang D, Chu WC, Cheng JC, Hua J, Yau ST, Gu X.** Shape analysis of vestibular systems in adolescent idiopathic scoliosis using geodesic spectra. In: Medical Image Computing and Computer-Assisted Intervention – MICCAI 2010. Springer, Berlin, Heidelberg, 2010;13(Pt 3):538–546. DOI: 10.1007/978-3-642-15711-0_67.
64. **Hitier M, Hamon M, Denise P, Lacoudre J, Thenint MA, Mallet JF, Moreau S, Quarck G.** Lateral semicircular canal asymmetry in idiopathic scoliosis: an early link between biomechanical, hormonal and neurosensory theories? PLoS One. 2015;10:e0131120. DOI: 10.1371/journal.pone.0131120.
65. **Antoniadou N, Hatzitaki V, Stavridis S, Samoladas E.** Verticality perception reveals a vestibular deficit in adolescents with idiopathic scoliosis. Exp Brain Res. 2018;236:1725–1734. DOI: 10.1007/s00221-018-5256-9.
66. **Catanzariti JF, Agnani O, Guyot MA, Wlodyka-Demaille S, Khenioui H, Donze C.** Does adolescent idiopathic scoliosis relate to vestibular disorders? A systematic review. Ann Phys Rehabil Med. 2014;57:465–479. DOI: 10.1016/j.rehab.2014.04.003.
67. **Wang ZW, Lee WY, Lam TP, Yip BH, Yu FW, Yu WS, Zhu F, Ng BK, Qiu Y, Cheng JC.** Defining the bone morphometry, micro-architecture and volumetric density profile in osteopenic vs non-osteopenic adolescent idiopathic scoliosis. Eur Spine J. 2017;26:1586–1594. DOI: 10.1007/s00586-016-4422-7.
68. **Burner WL 3rd, Badger VM, Sherman FC.** Osteoporosis and acquired back deformities. J Pediatr Orthop. 1982;2:383–385. DOI: 10.1097/01241398-198210000-00006.
69. **Hung VWY, Qin L, Cheung CSK, Lam TP, Ng BKW, Tse YK, Guo X, Lee KM, Cheng JCY.** Osteopenia: a new prognostic factor of curve progression in adolescent idiopathic scoliosis. J Bone Joint Surg Am. 2005;87:2709–2716. DOI: 10.2106/jbjs.D.02782.
70. **Sarioglu O, Gezer S, Sarioglu FC, Koremezli N, Kara T, Akcali O, Ozaksoy D, Balci A.** Evaluation of vertebral bone mineral density in scoliosis by using quantitative computed tomography. Pol J Radiol. 2019;84:e131–e135. DOI: 10.5114/pjr.2019.84060.
71. **Kopylov VS, Potapov VE, Gorbunov AV, Sorokovikov VA.** Structural changes in spine at the apparent forms of scoliosis. Bulletin of the East Siberian Scientific Center SBRAMS. M2011;(4–1):99–102.
72. **Khotim O, Sychevsky L, Anosob V.** Osteopenia as a risk factor of development and progression of scoliosis in children. Journal of the Grodno State Medical University. 2017;15(2):176–180.
73. **Tanabe H, Aota Y, Nakamura N, Saito T.** A histomorphometric study of the cancellous spinal process bone in adolescent idiopathic scoliosis. Eur Spine J. 2017;26:1600–1609. DOI: 10.1007/s00586-017-4974-1.
74. Zaydman AM, Sadovoy MA, Strokova EL. Scoliosis; a 50-year experience of research. Siberian Scientific Medical Journal. 2017;37(6):76–85.
75. **Zaidman AM, Strokova EL, Kiselyova EV, Ageeva TA, Suldina LA, Strunov AA, Shevchenko AI.** Ectopic localization of neural crest cells: etiological factor of scoliosis. Hir. Pozvonoc. 2015;12(4):88–97. DOI: 10.14531/ss2015.4.88-97.
76. **Wajchenberg M, Martins DE, Luciano RP, Puertas EB, Del Curto D, Schmidt B, Oliveira ABS, Faloppa F.** Histochemical analysis of paraspinal rotator muscles from patients with adolescent idiopathic scoliosis: a cross-sectional study. Medicine. 2015;94:e598. DOI: 10.1097/md.0000000000000598.
77. **Shchurova E, Filimonova G, Ryabykh S.** Magnitude of thoracic spine deformity affecting morphological characteristics of paraspinal muscles in patients with severe idiopathic scoliosis. Genij Ortopedii. 2021;27(1):68–73. DOI: 10.18019/1028-4427-2021-27-1-68-73.
78. **Cheung J, Veldhuizen AG, Halberts JP, Sluiter WJ, Van Horn JR.** Geometric and electromyographic assessments in the evaluation of curve progression in idiopathic scoliosis. Spine. 2006;31:322–329. DOI: 10.1097/01.brs.0000197155.68983.d8.
79. **Chwal a W, Koziana A, Kasperczyk T, Walaszek R, Plaszewski M.** Electromyographic assessment of functional symmetry of paraspinal muscles during static exercises in adolescents with idiopathic scoliosis. Biomed Res Int. 2014;2014:573276. DOI: 10.1155/2014/573276.
80. **Acaroglu E, Akel I, Alanay A, Yazici M, Marcucio R.** Comparison of the melatonin and calmodulin in paravertebral muscle and platelets of patients with or without adolescent idiopathic scoliosis. Spine. 2009;34:E659–E663. DOI: 10.1097/BRS.0b013e3181a3c7a2.
81. **Wilson JM, Loenneke JP, Jo E, Wilson GJ, Zourdos MC, Kim JS.** The effects of endurance, strength, and power training on muscle fiber type shifting. J Strength Cond Res. 2012;26:1724–1729. DOI: 10.1519/JSC.0b013e318234eb6f.
82. **Buchan JG, Alvarado DM, Haller GE, Cruchaga C, Harms MB, Zhang T, Willing MC, Grange DK, Braverman AC, Miller NH, Morcuende JA, Tang NL, Lam TP, Ng BK, Cheng JC, Dobbs MB, Gurnett CA.** Rare variants in FBN1 and FBN2 are associated with severe adolescent idiopathic scoliosis. Hum Mol Genet. 2014;23:5271–5282. DOI: 10.1093/hmg/ddu224.
83. **Nowak R, Kwiecien M, Tkacz M, Mazurek U.** Transforming growth factor-beta (TGF-β) signaling in paravertebral muscles in juvenile and adolescent idiopathic scoliosis. Biomed Res Int. 2014;2014:594287. DOI: 10.1155/2014/594287.
84. **Sharma S, Londono D, Eckalbar WL, Gao X, Zhang D, Mauldin K, Ku I, Takahashi A, Matsumoto M, Kamiya N, Murphy KK, Cornelia R, Herring JA, Burns D, Ahituv N, Ikegawa S, Gordon D, Wise CA.** A PAX1 enhancer locus is associated with susceptibility to idiopathic scoliosis in females. Nat Commun. 2015;6:6452. DOI: 10.1038/ncomms7452.
85. **Zhu Z, Tang NL, Xu L, Qin X, Mao S, Song Y, Liu L, Li F, Liu P, Yi L, Chang J, Jiang L, Ng BK, Shi B, Zhang W, Qiao J, Sun X, Qiu X, Wang Z, Wang F, Xie D, Chen L, Chen Z, Jin M, Han X, Hu Z, Zhang Z, Liu Z, Zhu F, Qian BP, Yu Y, Wang B, Lee KM, Lee WYW, Lam TP, Qiu Y, Cheng JC.** Genome-wide association study identifies new susceptibility loci for adolescent idiopathic scoliosis in Chinese girls. Nat Commun. 2015;6:8355. DOI: 10.1038/ncomms9355.
86. **Chernozemov VG, Dudin MG.** Results of complex examination of children with grade I–II scoliosis living in European North of Russia. Hir. Pozvonoc. 2006;(1):39–43.
87. **Murray DW, Bulstrode CJ.** The development of adolescent idiopathic scoliosis. Eur Spine J. 1996;5:251–257. DOI: 10.1007/bf00301328.
88. **Stokes IA.** Stature and growth compensation for spinal curvature. Stud Health Technol Inform. 2008;140:48–51.
89. **Shi L, Wang D, Driscoll M, Villemure I, Chu WC, Cheng JC, Aubin CE.** Biomechanical analysis and modeling of different vertebral growth patterns in adolescent idiopathic scoliosis and healthy subjects. Scoliosis. 2011;6:11. DOI: 10.1186/1748-7161-6-11.
90. **Crijns TJ, Stadhouder A, Smit TH.** Restrained differential growth: the initiating event of adolescent idiopathic scoliosis? Spine. 2017;42:E726–E732. DOI: 10.1097/brs.0000000000001946.
91. **Guo X, Chau WW, Chan YL, Cheng JC, Burwell RG, Dangerfield PH.** Relative anterior spinal overgrowth in adolescent idiopathic scoliosis--result of disproportionate endochondral-membranous bone growth? Summary of an electronic focus group debate of the IBSE. Eur Spine J. 2005;14:862–873. DOI: 10.1007/s00586-005-1002-7.
92. **Will RE, Stokes IA, Qiu X, Walker MR, Sanders JO.** Cobb angle progression in adolescent scoliosis begins at the intervertebral disc. Spine. 2009;34:2782–2786. DOI: 10.1097/BRS.0b013e3181c11853.
93. **Brink RC, Schlosser TPC, Colo D, Vavruch L, van Stralen M, Vincken KL, Malmqvist M, Kruyt MC, Tropp H, Castelein RM.** Anterior spinal overgrowth is the result of the scoliotic mechanism and is located in the disc. Spine. 2017;42:818–822. DOI: 10.1097/brs.0000000000001919.

94. **Zhu F, Chu WC, Sun G, Zhu ZZ, Wang WJ, Cheng JC, Qiu Y.** Rib length asymmetry in thoracic adolescent idiopathic scoliosis: is it primary or secondary? Eur Spine J. 2011;20:254–259. DOI: 10.1007/s00586-010-1637-x.
95. **Chen B, Tan Q, Chen H, Luo F, Xu M, Zhao J, Liu P, Sun X, Su N, Zhang D, Fan W, Liu M, Huang H, Wang Z, Huang J, Zhang R, Li C, Li F, Ni Z, Du X, Jin M, Yang J, Xie Y, Chen L.** Imbalanced development of anterior and posterior thorax is a causative factor triggering scoliosis. J Orthop Translat. 2019;17:103–111. DOI: 10.1016/j.jot.2018.12.001.
96. **Yang ZD, Li M.** There may be a same mechanism of the left-right handedness and left-right convex curve pattern of adolescent idiopathic scoliosis. Med Hypotheses. 2011;76:274–276. DOI: 10.1016/j.mehy.2010.10.021.
97. **Sanchez-Barcelo EJ, Mediavilla MD, Tan DX, Reiter RJ.** Scientific basis for the potential use of melatonin in bone diseases: osteoporosis and adolescent idiopathic scoliosis. J Osteoporos. 2010;2010:830231. DOI: 10.4061/2010/830231.
98. **Yim AP, Yeung HY, Sun G, Lee KM, Ng TB, Lam TP, Ng BK, Qiu Y, Moreau A, Cheng JC.** Abnormal skeletal growth in adolescent idiopathic scoliosis is associated with abnormal quantitative expression of melatonin receptor, MT2. Int J Mol Sci. 2013;14:6345–6358. DOI: 10.3390/ijms14036345.
99. **Man GC, Wong JH, Wang WW, Sun GQ, Yeung BH, Ng TB, Lee SK, Ng BK, Qiu Y, Cheng JC.** Abnormal melatonin receptor 1B expression in osteoblasts from girls with adolescent idiopathic scoliosis. J Pineal Res. 2011;50:395–402. DOI: 10.1111/j.1600-079X.2011.00857.x.
100. **Yang P, Liu H, Lin J, Yang H.** The association of rs4753426 polymorphism in the melatonin receptor 1B (MTNR1B) gene and susceptibility to adolescent idiopathic scoliosis: a systematic review and meta-analysis. Pain Physician. 2015;18:419–431.
101. **Wang WW, Man GC, Wong JH, Ng TB, Lee KM, Ng BK, Yeung HY, Qiu Y, Cheng JC.** Abnormal response of the proliferation and differentiation of growth plate chondrocytes to melatonin in adolescent idiopathic scoliosis. Int J Mol Sci. 2014;15:17100–71114. DOI: 10.3390/ijms150917100.
102. **Sadat-Ali M, al-Habdan I, al-Othman A.** Adolescent idiopathic scoliosis. Is low melatonin a cause? Joint Bone Spine. 2000;67:62–64.
103. **Hilibrand AS, Blakemore LC, Loder RT, Greenfield ML, Farley FA, Hensinger RN, Hariharan M.** The role of melatonin in the pathogenesis of adolescent idiopathic scoliosis. Spine. 1996;21:1140–1146. DOI: 10.1097/00007632-199605150-00004.
104. **Machida M, Dubousset J, Imamura Y, Iwaya T, Yamada T, Kimura J.** Role of melatonin deficiency in the development of scoliosis in pinealectomised chickens. J Bone Joint Surg Br. 1995;77:134–138.
105. **Kono H, Machida M, Saito M, Nishiwaki Y, Kato H, Hosogane N, Chiba K, Miyamoto T, Matsumoto M, Toyama Y.** Mechanism of osteoporosis in adolescent idiopathic scoliosis: experimental scoliosis in pinealectomized chickens. J Pineal Res. 2011;51:387–393. DOI; 10.1111/j.1600-079X.2011.00901.x.
106. **Wu JZ, Wu WH, He LJ, Ke QF, Huang L, Dai ZS, Chen Y.** Effect of melatonin and calmodulin in an idiopathic scoliosis model. Biomed Res Int. 2016;2016:8460291. DOI: 10.1155/2016/8460291.
107. **Man GC, Wang WW, Yim AP, Wong JH, Ng TB, Lam TP, Lee SK, Ng BK, Wang CC, Qiu Y, Cheng CY.** A review of pinealectomy-induced melatonin-deficient animal models for the study of etiopathogenesis of adolescent idiopathic scoliosis. Int J Mol Sci. 2014;15:16484–16499. DOI: 10.3390/ijms150916484.
108. **Pinchuk DY, Bekshaev SS, Bumakova SA, Dudin MG, Pinchuk OD.** Bioelectric activity in the suprachiasmatic nucleus-pineal gland system in children with adolescent idiopathic scoliosis. ISRN Orthop. 2012;2012:987095. DOI: 10.5402/2012/987095.
109. **Moreau A, Forget S, Azeddine B, Angeloni D, Fraschini F, Labelle H, Poitras B, Rivard CH, Grimard G.** Melatonin signaling dysfunction in adolescent idiopathic scoliosis. Spine. 2004;29:1772–1781. DOI; 10.1097/01.brs.0000134567.52303.1a.
110. **Girardo M, Bettini N, Dema E, Cervellati S.** The role of melatonin in the pathogenesis of adolescent idiopathic scoliosis (AIS). Eur Spine J. 2011;20 Suppl 1:S68–S74. DOI: 10.1007/s00586-011-1750-5.
111. **Fagan AB, Kennaway DJ, Sutherland AD.** Total 24-hour melatonin secretion in adolescent idiopathic scoliosis. A case-control study. Spine. 1998;23:41–46. DOI: 10.1097/00007632-199801010-00009.
112. **Machida M, Dubousset J, Yamada T, Kimura J.** Serum melatonin levels in adolescent idiopathic scoliosis prediction and prevention for curve progression – a prospective study. J Pineal Res. 2009;46:344–348. DOI: 10.1111/j.1600-079X.2009.00669.x.
113. **Li J, Li N, Chen Y, Hui S, Fan J, Ye B, Fan Z, Zhang J, Zhao RC, Zhuang Q.** SPRY4 is responsible for pathogenesis of adolescent idiopathic scoliosis by contributing to osteogenic differentiation and melatonin response of bone marrow-derived mesenchymal stem cells. Cell Death Dis. 2019;10:805. DOI: 10.1038/s41419-019-1949-7.
114. **Yang M, Wei X, Yang W, Li Y, Ni H, Zhao Y, Chen Z, Bai Y, Li M.** The polymorphisms of melatonin receptor 1B gene (MTNR1B) (rs4753426 and rs10830963) and susceptibility to adolescent idiopathic scoliosis: a meta-analysis. J Orthop Sci. 2015;20:593–600. DOI: 10.1007/s00776-015-0725-5.
115. **Shyy W, Wang K, Gurnett CA, Dobbs MB, Miller NH, Wise C, Sheffield VC, Morcuende JA.** Evaluation of GPR50, hMel-1B, and ROR-alpha melatonin-related receptors and the etiology of adolescent idiopathic scoliosis. J Pediatr Orthop. 2010;30:539–543. DOI: 10.1097/BPO.0b013e3181e7902c.
116. **Koyama H, Nakade O, Takada Y, Kaku T, Lau KHW**. Melatonin at pharmacologic doses increases bone mass by suppressing resorption through down regulation of the RANKL mediated osteoclast formation and activation. J Bone Miner Res. 2002;17:1219–1229. DOI: 10.1359/jbmr.2002.17.7.1219.
117. **Lowe TG, Burwell RG, Dangerfield PH.** Platelet calmodulin levels in adolescent idiopathic scoliosis (AIS): can they predict curve progression and severity? Summary of an electronic focus group debate of the IBSE. Eur Spine J. 2004;13:257–265. DOI: 10.1007/s00586-003-0655-3.
118. **Acaroglu E, Akel I, Alanay A, Yazici M, Marcucio R.** Comparison of the melatonin and calmodulin in paravertebral muscle and platelets of patients with or without adolescent idiopathic scoliosis. Spine. 2009;34:E659–E63. DOI: 10.1097/BRS.0b013e3181a3c7a2.
119. **Lowe T, Lawellin D, Smith D, Price C, Haher T, Merola A, O'Brien M.** Platelet calmodulin levels in adolescent idiopathic scoliosis: do the levels correlate with curve progression and severity? Spine. 2002;27:768–775. DOI: 10.1097/00007632-200204010-00016.
120. **Burwell RG, Aujla RK, Grevitt MP, Dangerfield PH, Moulton A, Randell TL, Anderson SI.** 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. DOI: 10.1186/1748-7161-4-24.
121. **Wang YJ, Yu HG, Zhou ZH, Guo Q, Wang LJ, Zhang HQ.** Leptin receptor metabolism disorder in primary chondrocytes from adolescent idiopathic scoliosis girls. Int J Mol Sci. 2016;17:1160. DOI: 10.3390/ijms17071160.
122. **Qiu Y, Sun X, Qiu X, Li W, Zhu Z, Zhu F, Wang B, Yu Y, Qian B.** Decreased circulating leptin level and its association with body and bone mass in girls with adolescent idiopathic scoliosis. Spine. 2007;32:2703–2710. DOI: 10.1097/BRS.0b013e31815a59e5.
123. **Tam EM, Liu Z, Lam T-P, Ting T, Cheung G, Ng BK, Lee SK, Qiu Y, Cheng JC.** Lower muscle mass and body fat in adolescent idiopathic scoliosis are associated with abnormal leptin bioavailability. Spine. 2016;41:940–946. DOI: 10.1097/BRS.0000000000001376.
124. **Man GC, Tam EM, Wong YS, Hung VW, Hu Z, Lam TP, Liu Z, Cheng WH, Ng TB, Zhu Z, Qiu Y, Cheng JC.** Abnormal osteoblastic response to leptin in patients with adolescent idiopathic scoliosis. Scientific Reports. 2019;9:1–7.

125. **Kulis A, Gozdzialska A, Drag J, Jaskiewicz J, Knapik-Czajka M, Lipik E, Zarzycki D.** Participation of sex hormones in multifactorial pathogenesis of adolescent idiopathic scoliosis. Int Orthop. 2015;39:1227–1236. DOI: 10.1007/s00264-015-2742-6.
126. **Zhou C, Wang H, Zou Y, Fang H.** [Research progress of role of estrogen and estrogen receptor on onset and progression of adolescent idiopathic scoliosis]. Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi. 2015;29:1441–1445.
127. **Leboeuf D, Letellier K, Alos N, Edery P, Moldovan F.** Do estrogens impact adolescent idiopathic scoliosis? Trends Endocrinol Metab. 2009;20:147–152. DOI: 10.1016/j.tem.2008.12.004.
128. **Willner S, Nilsson K, Kastrup K, Bergstrand C.** Growth hormone and somatomedin A in girls with adolescent idiopathic scoliosis. Acta Paediatr Scand. 1976;65:547–552. DOI: 10.1111/j.1651-2227.1976.tb04930.x.
129. **Yang Y, Wu Z, Zhao T, Wang H, Zhao D, Zhang J, Wang Y, Ding Y, Qiu G.** Adolescent idiopathic scoliosis and the single-nucleotide polymorphism of the growth hormone receptor and IGF-1 genes. Orthopedics. 2009;32:411. DOI: 10.3928/01477447-20090511-08.
130. **Zhuang QY, Wu ZH, Qiu GX.** [Is polymorphism of CALM1 gene or growth hormone receptor gene associated with susceptibility to adolescent idiopathic scoliosis?]. Zhonghua Yi Xue Za Zhi. 2007;87:2198–2202.
131. **Park SJ, Lee KH, Lee CS, Kim KT, Jang JH, Shin DH, Kim MS, Kim J, Cho SY, Jin DK.** Impact of growth hormone treatment on scoliosis development and progression: analysis of 1128 patients with idiopathic short stature. J Pediatr Endocrinol Metab. 2021;34:243–250. DOI: 10.1515/jpem-2020-0393.
132. **Day GA, McPhee IB, Batch J, Tomlinson FH.** Growth rates and the prevalence and progression of scoliosis in short-statured children on Australian growth hormone treatment programmes. Scoliosis. 2007;2:3. DOI: 10.1186/1748-7161-2-3.
133. **Suh KT, Lee SS, Hwang SH, Kim SJ, Lee JS.** Elevated soluble receptor activator of nuclear factor-kappaB ligand and reduced bone mineral density in patients with adolescent idiopathic scoliosis. Eur Spine J. 2007;16:1563–1569. DOI: 10.1007/s00586-007-0390-2.
134. **Zhou S, Wang W, Zhu Z, Sun X, Zhu F, Yu Y, Qian B, Wang B, Yin G, Qiu Y.** Increased expression of receptor activator of nuclear factor- B ligand in osteoblasts from adolescent idiopathic scoliosis patients with low bone mineral density. J Huazhong Univ Sci Technolog Med Sci. 2012;32:686–690. DOI: 10.1007/s11596-012-1018-2.
135. **Eun IS, Park WW, Suh KT, Kim JI, Lee JS.** Association between osteoprotegerin gene polymorphism and bone mineral density in patients with adolescent idiopathic scoliosis. Eur Spine J. 2009;18:1936–1940. DOI: 10.1007/s00586-009-1145-z.
136. **Wang Wj, Sun C, Liu Z, Sun X, Zhu F, Zhu ZZ, Qiu Y.** Transcription factor Runx2 in the low bone mineral density of girls with adolescent idiopathic scoliosis. Orthop Surg. 2014;6:8–14. DOI: 10.1111/os.12087.
137. **Song XX, Jin LY, Li XF, Qian L, Shen HX, Liu ZD, Yu BW.** Effects of low bone mineral status on biomechanical characteristics in idiopathic scoliotic spinal deformity. World Neurosurg. 2018;110:e321–e329. DOI: 10.1016/j.wneu.2017.10.177.
138. **Sun ZJ, Jia HM, Qiu GX, Zhou C, Guo S, Zhang JG, Shen JX, Zhao Y, Zou ZM.** Identification of candidate diagnostic biomarkers for adolescent idiopathic scoliosis using UPLC/QTOF-MS analysis: a first report of lipid metabolism profiles. Sci Rep. 2016;6:22274. DOI: 10.1038/srep22274.
139. **Ghosh P, Bushell GR, Taylor TK, Pearce RH, Grimmer BJ.** Distribution of glycosaminoglycans across the normal and the scoliotic disc. Spine. 1980;5:310–317. DOI: 10.1097/00007632-198007000-00004.
140. **He Y, Qiu Y, Zhu F, Zhu Z.** Quantitative analysis of types I and II collagen in the disc annulus in adolescent idiopathic scoliosis. Stud Health Technol Inform. 2006;123:123–128.
141. **Lowe TG, Edgar M, Margulies JY, Miller NH, Raso VJ, Reinker KA, Rivard CH.** Etiology of idiopathic scoliosis: current trends in research. J Bone Joint Surg Am. 2000;82:1157–1168. DOI: 10.2106/00004623-200008000-00014.
142. **Golding J.** Observations on idiopathic scoliosis aetiology and natural history in Jamaica: A food and growth connection. Cajanus. 1991;24:31–38.
143. **Kikanloo SR, Tarpada SP, Cho W.** Etiology of adolescent idiopathic scoliosis: a literature review. Asian Spine J. 2019;13:519-526. DOI: 10.31616/asj.2018.0096.
144. **Yang Z, Xie Y, Chen J, Zhang D, Yang C, Li M.** High selenium may be a risk factor of adolescent idiopathic scoliosis. Med Hypotheses. 2010;75:126–127. DOI: 10.1016/j.mehy.2010.02.006.
145. **Ji XR, Yang ZD, Yang XH, Liu DD, Ni HJ, Li M.** Change of selenium in environment and risk of adolescent idiopathic scoliosis: a retrospective cohort study. Eur Rev Med Pharmacol Sci. 2013;17:2499–2503.
146. **Shen N, Chen N, Zhou X, Zhao B, Huang R, Liang J, Yang X, Chen M, Song Y, Du Q.** Alterations of the gut microbiome and plasma proteome in Chinese patients with adolescent idiopathic scoliosis. Bone. 2019;120:364–370. DOI: 10.1016/j.bone.2018.11.017.
147. **Ng SY, Bettany-Saltikov J, Cheung IYK, Chan KKY.** The role of vitamin D in the pathogenesis of adolescent idiopathic scoliosis. Asian Spine J. 2018;12:1127–1145. DOI: 10.31616/asj.2018.12.6.1127.
148. **Herdea A, Charkaoui A, Ulici A.** Prevalence of 25-OH-vitamin D and calcium deficiency in adolescent idiopathic scoliosis. J Med Life. 2020;13:260–264. DOI: 10.25122/jml-2020-0101.
149. **Mithal A, Wahl DA, Bonjour JP, Burckhardt P, Dawson-Hughes B, Eisman JA, El-Hajj Fuleihan G, Josse RG, Lips P, Morales-Torres J.** Global vitamin D status and determinants of hypovitaminosis D. Osteoporos Int. 2009;20:1807–1820. DOI: 10.1007/s00198-009-0954-6.
150. **Balioglu MB, Aydin C, Kargin D, Albayrak A, Atici Y, Tas SK, Kaygusuz MA.** Vitamin-D measurement in patients with adolescent idiopathic scoliosis. J Pediatr Orthop B. 2017;26:48–52. DOI: 10.1097/bpb.0000000000000320.
151. **Kalueff AV, Lou YR, Laaksi I, Tuohimaa P.** Increased anxiety in mice lacking vitamin D receptor gene. Neuroreport. 2004;15:1271–1274. DOI: 10.1097/01.wnr.0000129370.04248.92.
152. **Minasyan A, Keisala T, Zou J, Zhang Y, Toppila E, Syvala H, Lou YR, Kalueff AV, Pyykko I, Tuohimaa P.** Vestibular dysfunction in vitamin D receptor mutant mice. J Steroid Biochem Mol Biol. 2009;114:161–166. DOI: 10.1016/j.jsbmb.2009.01.020.
153. **Yin X, Wang H, Guo J, Zhang L, Zhang Y, Li L, Hou S.** Association of vitamin D receptor BsmI rs1544410 and ApaI rs7975232 polymorphisms with susceptibility to adolescent idiopathic scoliosis: A systematic review and meta-analysis. Medicine (Baltimore). 2018;97:e9627. DOI: 10.1097/md.0000000000009627.
154. **Chen WJ, Qiu Y, Zhu F, Zhu ZZ, Sun X, Liu Z, Chen ZJ.** [Vitamin D receptor gene polymorphisms: no association with low bone mineral density in adolescent idiopathic scoliosis girls]. Zhonghua Wai Ke Za Zhi. 2008;46:1183–1186.
155. **McMaster ME.** Heated indoor swimming pools, infants, and the pathogenesis of adolescent idiopathic scoliosis: a neurogenic hypothesis. Environ Health. 2011;10:86. DOI: 10.1186/1476-069x-10-86.
156. **McMaster ME, Lee AJ, Burwell RG.** Indoor heated swimming pools: the vulnerability of some infants to develop spinal asymmetries years later. Stud Health Technol Inform. 2006;123:151–155.
157. **McMaster ME, Lee AJ, Burwell RG.** Physical activities of patients with adolescent idiopathic scoliosis (AIS): preliminary longitudinal case–control study historical evaluation of possible risk factors. Scoliosis. 2015;10:6. DOI: 10.1186/s13013-015-0029-8.
158. **Watanabe K, Michikawa T, Yonezawa I, Takaso M, Minami S, Soshi S, Tsuji T, Okada E, Abe K, Takahashi M, Asakura K, Nishiwaki Y, Matsumoto M.** Physical activities and lifestyle factors related to adolescent idiopathic scoliosis. J Bone Joint Surg Am. 2017;99:284–294. DOI: 10.2106/jbjs.16.00459.

Address correspondence to:
Sergeenko Olga Mikhailovna
National Ilizarov Medical Research Centre for Orthopaedics and Traumatology,
6 Marii Ulyanovoy str., Kurgan, 640014, Russia,
pavlova.neuro@mail.ru

Received 25.04.2022
Review completed 26.05.2022
Passed for printing 31.05.2022

Alina Pavlovna Gorbach, postgraduate student, National Ilizarov Medical Research Centre for Orthopaedics and Traumatology, 6 Marii Ulyanovoy str., Kurgan, 640014, Russia, ORCID: 0000-0001-7788-2687, alinatomilova@mail.ru;
Olga Mikhailovna Sergeenko, MD, PhD, trauma orthopedist, neurosurgeon, head of the laboratory of the Clinic of Spine Pathology and Rare Diseases, National Ilizarov Medical Research Centre for Orthopaedics and Traumatology, 6 Marii Ulyanovoy str., Kurgan, 640014, Russia, ORCID: 0000-0003-2905-0215, pavlova.neuro@mail.ru;
Elena Nikolayevna Shchurova, DSci in Biology, leading researcher, Clinical Laboratory of the Clinic of Spine Pathology and Rare Diseases, National Ilizarov Medical Research Centre for Orthopaedics and Traumatology, 6 Marii Ulyanovoy str., Kurgan, 640014, Russia, ORCID: 0000-0003-0816-1004, elena.shurova@mail.ru.