Journal Homepage: - www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI: 10.21474/IJAR01/16984
DOI URL: http://dx.doi.org/10.21474/IJAR01/16984

RESEARCH ARTICLE

THE AETIOLOGY OF ADOLESCENT IDIOPATHIC SCOLIOSIS: IS SLEEP POSITION THE MISSING LINK? THE NIGHTTIME PERFECT STORM HYPOTHESIS

Jarrett B. Grunstein D.C[1] and Theodoros B. Grivas MD PhD[2]

1. Research conducted at: Grunstein Family Chiropractic Center 340 East Northfield Road, Suite 2E Livingston, New Jersey 07039, USA.
2. Former Head of the Department of Orthopaedics and Traumatology, "Tzaneio" General Hospital of Piraeus, Zanni and Afendouli 1, Piraeus, 18536, Greece.

Manuscript Info

Manuscript History
Received: 23 March 2023
Final Accepted: 27 April 2023
Published: May 2023

Key words:-
Adolescent Idiopathic Scoliosis, AIS, Sleep Position, Scoliosis/Aetiology, Scoliosis/Genetics, Scoliosis/Epigenetics

Abstract

A review of the literature on adolescent idiopathic scoliosis (AIS) reveals that the cause remains unknown. Further, scientific investigation by researchers around the globe has determined that neither the nervous or endocrine systems, nor the muscular, connective, or osseous tissues are the primary causative factors which lead to the development of spinal curvatures as seen in AIS. This report will serve to introduce a new hypothetical model that we have termed, "The Nighttime Perfect Storm Hypothesis." The model serves to explain why peripubescent children who have a particular genetic predisposition may be at heightened risk of developing a curvature in their spine if their body is habitually positioned while asleep in what we refer to as the "Provocative Sleep Position (PSP)." The concept of spinal stabilization is explored with respect to a landmark theoretical model by Panjabi in 1992. In the case of AIS, the child's spinal stabilization has gone completely awry. Through the lens of our hypothesis, this loss of stabilization is due to four interdependent components that may conspire and lead to the perfect storm. These components include 1) a genetic predisposition, 2) sleeping in the Provocative Sleep Position, 3) while in the REM stage of sleep, 4) during the child's peripubescent growth spurt. Included is a complete biomechanical analysis of the child's spine while lying in either the Prone or Lateral PSP, and how this may lead to the development of a thoracic or lumbar curvature, respectively. Finally, we propose a path forward that will make clear the need for subsequent scientific investigation to determine whether or not the "The Nighttime Perfect Storm Hypothesis" is a viable theory.

Introduction:-

Adolescent Idiopathic Scoliosis (AIS) is defined as a spinal curvature that measures at least 10 degrees with curve onset between 10 years of age and skeletal maturity [1]. Both the prevalence and severity of scoliosis is elevated in girls as compared to boys, with the female-to-male ratio increasing from 1.4:1 in mild curves (10-20 degrees) up to 7.2:1 in severe curves (over 40 degrees) [2]. The overall prevalence rate of AIS ranges from 0.47-5.2% [2].

Corresponding Author:- Jarrett B. Grunstein D.C
Address**:-** Research conducted at: Grunstein Family Chiropractic Center 340 East Northfield Road, Suite 2E Livingston, New Jersey 07039, USA.

According to the current literature, muscles [3, 4, 5, 6], connective tissues [7], osseous tissues, nor hormonal levels are believed to be the primary causative factor in the development of AIS [8]. Rather, the noted changes in the spine and associated connective tissues that have been observed in children with AIS are considered to be secondary to an underlying pathophysiology of the disorder [9]. An effective preventive method for the management of AIS will be elusive as long as the primary cause of scoliosis remains unknown [10].

The subject of sleep position and its potential involvement in the development of orthopaedic conditions such as AIS has yet to be thoroughly examined by the scientific community. A review of the literature on the topic of sleep position revealed that the majority of studies are primarily focused on sleep pathologies such as obstructive sleep apnea, sudden infant death syndrome, insomnia, ulcer prevention, and sleep system designs [11].

While AIS patients have not been found to suffer from sleep disturbances [12], the scientific community has never proven that sleep position is not the underlying environmental factor that participates in the development and progression of the scoliotic curvature. The scientific method relies quite heavily on visual observation. Unfortunately, the sleep positions of a child are inherently ill suited to observation due to the fact that sleeping is typically performed in darkness and while under a blanket. Darkness is key because the production and release of melatonin, the hormone that induces sleep, is heavily effected by the light-dark cycle, with increased production in darkness and reduced production with light exposure [13]. Universal blanket use for warmth may be due to the effects of the circadian rhythm on temperature regulation, which results in higher body temperatures during the day and dropping temperatures during the first few hours of sleep [14].

In a historical overview on spinal deformities and the discoveries made by the great doctors of Ancient Greece, Vasiliadis et al. reported that Hippocrates revealed in his writings what he believed to be the cause of scoliosis (as we use the term today). He reportedly postulated two possible causes of the disease: "due to 'gatherings' (probably tuberculous abscesses) on the inner side of the spine and postural - while in some cases the positions the patients are accustomed to take in bed are accessory to the malady [15]."

A perfect storm is a meteorological event aggravated by a rare combination of circumstances. Similarly, AIS may be considered a perfect storm that only develops in peripubescent children that have a particular genetic mutational burden and regularly sleep in one of two positions during the REM stage of sleep each night. Consequently, we decided to coin our model "The Nighttime Perfect Storm Hypothesis." The hypothetical model presented herein will propel the AIS research community forward in exploring the potential relationship between sleep position and the development of the structural spinal curvatures as seen in AIS.

Genetics And Epigenetics

Genetic studies of those with AIS have demonstrated linkage to a multitude of different loci throughout the genome. However, despite the variety of association studies, linkage studies, and evaluation of candidate genes, no single gene has yet to be determined to be the cause of AIS [16]. Burwell et al. have noted that while genetic factors may indeed play an important etiological role in the development of AIS, the discordant findings in monozygotic twins with AIS suggests that environmental factors must also contribute to the aetiology of this disease [17]. Kesling et al. discovered only a 73% concordance among monozygotic twins and a 36% concordance of dizygous twins [18]. In a study by Del Curto et al., a pair of monozygotic twins with AIS were evaluated, each with differing curve type, side of convexity, and severity [19]. These phenotypic differences among monozygotic twins point to the participation of the environment in the development of AIS [20].

In perhaps the first study of sufficient size to make heritability estimates of scoliosis, Grauers et al. gathered and analyzed self-reported data on scoliosis from 64,578 twins in the Swedish Twin Registry. In their analysis, they estimated that 38% of the variance in the liability to develop scoliosis is due to additive genetic effects and 62% is due to environmental factors [21]. Oliazadeh et al. pointed out that it is likely that AIS phenotypic heterogeneity is a result of the combination of genetic variations and biomechanical forces that are influenced by an individual's behavior patterns [22]. Davies et al. adeptly described the role biomechanics might play in altering gene expression via epigenetic pathways [23]. In summary, while genetics undoubtedly play a crucial role in the initiation and development of AIS, it seems evident that there is an environmental factor that will provide the key to unlocking the mystery of the underlying aetiology of AIS.

Environmental Factors

Numerous studies have investigated, yet have failed to find, the environmental component that may participate in the underlying aetiology of AIS. Lifestyle factors [24], dietary factors [25], environmental factors such as industrialization [26], nor exercises [27] can account for why a spinal curvature develops and progresses in an otherwise perfectly healthy child. The notable exceptions are studies that have found a potential correlation between AIS and early life exposure to chlorinated pools [28, 29] and a Vitamin D deficiency [30, 31, 32, 33]. However, when accounting for racial differences, Kiebzak et al. recently discovered that the percentage deficiency in Vitamin D was no greater in girls with AIS as compared with race-matched cohorts without AIS [34].

Sleeping in a Hammock

One study found in the literature does briefly touch upon the potential participation of sleep position in the development of AIS. Baroni et al. in Santa Cruz, Brazil tested randomly selected public school children for AIS and proceeded to evaluate a variety of demographic and lifestyle factors to determine their potential participation in the development of the scoliotic curve. They accounted for socioeconomic characteristics, anthropometry, lifestyle habits, sexual maturation, and even the ergonomics of the children's school furniture. In the 212 pupils that participated in the study, 123 of which who had AIS, of all the lifestyle factors investigated, there was only one that directly related to the variability of developing AIS. The researchers concluded that sleeping in a hammock was inversely associated with scoliosis [35]. In other words, the greater the proportion of time the child slept in a hammock, the less likely she was to develop AIS. The significance here is that a hammock is primarily used for lying in the supine position, and less commonly, in the lateral decubitus position. However, when children are sleeping in a hammock, most likely they are NOT sleeping prone, and thus would be protected from the deleterious effects of the Prone PSP. Therefore, if the only negative correlation with AIS that investigators found was with those who slept more in hammocks each night, we might be able to infer that those who slept primarily in the supine position had less incidence of AIS, which is what The Nighttime Perfect Storm Hypothesis would predict.

Panjabi's Spinal Stabilization Model

In 1992, Panjabi published a paper describing a hypothetical spinal stabilization model. His model encompasses three functionally interdependent physiological systems within the body that serve to ensure the stability of the spine. A spine is said to be stable if it can withstand varying mechanical demands due to changes in spinal posture, and also adapt to static and dynamic loads. Spinal instability leads to abnormally large intervertebral motion resulting in deformations of ligaments, joint capsules, annular fibers, and end-plates [36].

In the case of AIS, the stability of the spine has gone completely awry. Seemingly, out of nowhere, the child's spine becomes misaligned in the coronal, sagittal, and axial planes [37]. Given these dynamics, it may be instructive to turn to Panjabi's landmark theoretical model on spinal stabilization in order to discern what faulty mechanism may reasonably account for the development of the spinal curvatures seen in AIS.

The 3 physiological subsystems in Panjabi's model include the passive musculoskeletal subsystem, the active musculoskeletal subsystem, and the neural and feedback subsystem. The passive musculoskeletal subsystem is encompassed by the vertebrae, intervertebral discs, facet articulations, spinal ligaments, and joint capsules. The active musculoskeletal subsystem includes the muscles and tendons that surround and support the spinal column. Finally, the neural and feedback subsystem is comprised of different force and motion transducers located in ligaments, tendons (GTO's), muscles (muscle spindles), as well as the neural control centers of the central nervous system [36].

In order to maintain spinal stability, the body utilizes the neural and feedback subsystem to continuously monitor proprioceptive input from the various transducers located in the ligaments, tendons, and muscles. These signals are relayed to the brain for processing. Once processed by the brain, stimulation of efferent neural pathways ultimately lead to contractions in the appropriate musculature surrounding the spinal column, enabling the active musculoskeletal system to stabilize the spine [36].

Under normal circumstances, within physiological ranges of spinal movements and against normal spinal loads, the three subsystems function in a highly coordinated manner. Further, if dysfunction in a subsystem does develop, compensation may be provided by the system, within certain limits. However, damage to even one of these three subsystems due to disease, injury, or degeneration may deleteriously effect the stability of the spine [36].

The Nighttime Perfect Storm Hypothesis
The Nighttime Perfect Storm Hypotheses proposes that there is a window of time during each 24 hour cycle of a child's life when all three of the subsystems in Panjabi's model are dysfunctional simultaneously. During REM sleep, accompanied by muscle atonia, the child's body may be situated in one of two possible Provocative Sleep Positions (PSP), initiating a pattern of biomechanical forces that affect the child's recumbent body, potentially leading to the development of either a thoracic or lumbar scoliotic curvature.

During the Nighttime Perfect Storm, four circumstances occur simultaneously, resulting in the initiation and development of the spinal deformities seen in children with AIS. These 4 pillars include:

Pillar #1:REM Atonia:
During the REM stage of sleep, there is a disturbance in the operational interchange between the neural feedback and control subsystem and the active musculoskeletal subsystem.

Pillar #2: Genetics:
The child has a genetic constitution that leads to dysfunction in the structural integrity of the spinal vertebrae, intervertebral discs, and/or surrounding soft tissues of the passive musculoskeletal subsystem.

Pillar #3: Sleep position:
The child sleeps in either, or both, the Lateral and/or Prone Provocative Sleep Position (PSP).

Pillar #4: Adolescent growth spurt:
The child is going through her peripubescent growth spurt.

Pillar #1- REM Atonia
REM sleep is characterized by rapid eye movement, desynchronized rhythms in the electroencephalogram (EEG), hippocampal theta activity, and a loss of postural muscle tone [38]. The neural control subsystem and the active musculoskeletal subsystem cannot coordinate spinal stabilization while the child is in the REM stage of sleep. The neuronal pathways governing REM sleep are located in the pontine and medullary brainstem. To summarize, muscle atonia occurs when the glutamatergic neurons of the sublaterodorsal nucleus (SLD) activate glycinergic pre-motor neurons in the spinal cord and/or ventromedial medulla which ultimately inhibits motor neurons [38]. Therefore, during REM sleep, even though the sensory elements of the neural feedback and control subsystem are functional, the brain is incapable of responding to the stabilization demands of the spine because the motor neurons are inhibited from stimulating the stabilizing musculature.

A great deal of AIS research has focused on neurological deficits in children suffering with this condition. Scientists have studied the neurofunctional and neuroanatomical changes seen in the cerebellum, brain stem, and cerebrum of children with AIS [39]. While abnormalities in the cerebrum and brain stem have been found in those with AIS, no solid evidence has proven that these alterations are primary and not a consequence of the curvature [72]. Numerous researchers who have discovered abnormalities in the CNS of AIS patients have posed that these changes are not the cause, but instead are secondary responses to the scoliotic curve [40, 41, 42, 43, 44].

PIllar #2 - Genetics
Bone
Low bone mineral density (BMD) is a consistent finding in those with AIS [45, 46, 47, 48]. Further, it has been shown that the diminished BMD found in the bones of children with AIS may lead to a reduction in bone quality [49, 50]. Due to the high prevalence of low BMD in those with AIS, a number of investigators have concluded that BMD may serve as an independent risk factor for curve progression [51, 52, 53].

Genetic mutations associated with the metabolism of bone have been found in children with AIS, including OPG [54], Runx2 [55, 56, 57], and MAPK7 [58]. Epigenetic abnormalities of the bone have also been discovered, such as miR-145 and β-catenin [59].

In addition to the progress that has been made on the genetic front, researchers have also investigated a number of hormones that may play a potential role in the metabolic dysfunction of bone in children with AIS. Hormonal abnormalities that might be involved include the leptin signaling pathway [60, 61], the melatonin signaling pathway

[62, 63], as well as estrogen involvement [64, 65]. Additionally, other metabolic abnormalities have been discovered in the bones of children with AIS, such as higher levels of the membrane protein RANKL and RANKL to OPG ratio [66, 67]. Finally, mesenchymal stem cells in children with AIS have demonstrated a diminished propensity for osteogenic differentiation [68, 69, 70].

Intervertebral Disc

Intervertebral discs display at least three times more deformation in the true sagittal, transverse, and coronal planes as compared to the deformation of the vertebral bodies in those with AIS [71, 72]. Recently, this finding was confirmed by Brink et al., who found that while the absolute height of the vertebrae did not differ between AIS and controls in the midsagittal plane, the intervertebral structures significantly contributed to the anterior-posterior length discrepancies due to lengthening of the anterior aspect of the disc [73].

Burger et al. performed a histological analysis of the intervertebral discs in children with AIS. They discovered abnormalities such as increased synthetic and decreased proliferative cell activity, as well as increased protein synthesis. Based on these findings, the authors concluded that initial genetic determinants are probably responsible for these IVD elements. They claim that these histological abnormalities may be affected by the mechanical environment [74].

Numerous genetic mutations associated with the intervertebral discs in those with AIS have been discovered, such as the COMP gene [75], MMP-3 [76], IL-6 [77], and the Type X Collagen Gene [78].

Facet Joint

Shea et al. analyzed the micro-architecture of the vertebral facets in the thoracic spine of children with AIS. They found that the bone of the facet on the convex side was more porous and had a thinner cortex as compared to the concave side [79]. Bisson et al. recently investigated the facet joints of those with AIS and found clear signs of facet joint degeneration with substantial proteoglycan loss. On the genetic front, they found a higher expression of MMP-3, MMP-13, and IL-1β [80].

Ligaments

Elastic fiber abnormalities in the spinal ligaments of those with AIS have been reported [81]. There may be a genetic link in children with AIS that can account for these spinal ligament abnormalities. For example, Sheng et al. discovered that a common variant of the FBN1 gene is significantly associated with AIS susceptibility. Further, they noted that decreased expression of FBN1 is correlated with curve severity in AIS [82].

Finally, as mentioned in the "Bone" section above, low BMD is a common finding in AIS. A notable study by Neuman et al. showed that low bone mineral content may negatively impact the structural integrity of spinal ligaments [83]. Thus, the low bone mineral density commonly found in children with AIS may effect the mechanical properties of not only the bones themselves, but also the ligamentous attachments.

Pillar #3 - The Provocative Sleep Positions (PSP)

While the child is lying in either the Prone or Lateral Provocative Sleep Position (PSP), her spine will be effected by gravitational forces that run transverse to her`` recumbent body. These forces will have a biomechanical impact on the vertebrae, intervertebral discs, and surrounding soft tissues. The Nighttime Perfect Storm Hypothesis asserts that the spine of the sleeping child will deform in patterned ways that model the familiar structural curvatures seen in AIS.

As mentioned, there are two distinct PSPs. The Prone PSP leaves the body vulnerable to developing a structural curve in the thoracic spine, while the Lateral PSP leaves the body vulnerable to the development of a lumbar curve. In the discussion of the two Provocative Sleep Positions below, we will focus on the development of a right thoracic curvature and a left lumbar curvature.

Figure 1:- The Prone Provocative Sleep Position (PSP): with right leg elevated & head turned to the right, will lead to a right thoracic curvature (dextroscoliosis).

The Prone PSP

The prone PSP is often adopted as an alternative to lying flat prone. When a child lies flat prone, the entire abdomen and thorax will be flush with the mattress, both legs will be fully outstretched, and the pelvic section, being the heaviest part of the body, will sink deeper into the mattress [84]. Ultimately, this sleep position leads to an increased lumbar lordosis, and consequently, increased pressure on the lumbar facet joints [85]. In addition, the cervical spine will be forced into maximal rotation when the head is turned to the side while in this flat prone sleeping position, causing increased spinal loading due to compression of the facet joints in the upper cervical vertebrae on the side the child's head is turned to [84]. Hypothetically, the increased pressure in the facets of both the lumbar and cervical spine while in this flat prone position leads the child to adopt a slightly modified prone sleeping position. This altered position is what we refer to as the Prone PSP.

While in the Prone PSP (See Figure 1), one will flex the hip and the knee on the side to which the head is turned. In the case of a right thoracic scoliosis, one would expect the child to have her right leg elevated and head turned to the right with either the left arm or both arms elevated above the head. The right leg acts like a kickstand on a bicycle, allowing for the entire torso to lean at an angle relative to the mattress. Consequently, the left anterior rib cage presses directly into the mattress, while the right anterior rib cage does not make meaningful contact with the mattress.

While the child is sleeping in the Prone PSP, two primary forces are simultaneously effecting the thoracic spine: rotation and extension.

Rotation of the Thoracic Vertebrae

According to The Nighttime Perfect Storm Hypothesis, the rotation of the thoracic vertebrae may be a direct consequence of the constant pressure being applied by the ribs at the costovertebral articulations. This dynamic is initiated as gravitational forces bear down on the rib cage. While in the Prone PSP, the left anterior aspect of the rib cage will be compressed into the mattress. As these left anterior ribs meet the resistance of the mattress, a rotational force is initiated. This force will first be transmitted across the body of the sternum into the right anterior rib cage. From there, the forces are transmitted from the right anterior rib cage around the thorax and thru to the right posterior rib cage. Lastly, these involved ribs in the right posterior rib cage apply pressure directly upon the vertebrae they articulate with at the juncture with the thoracic spine.

A fundamental question that has confounded the AIS researcher community thru the years is whether the ribs follow the rotational torque applied by the spine or if the opposite is true, whereby the ribs cause the vertebrae to rotate. While very recent literature reviews on AIS purport that it is the vertebrae that dictate the motion of the ribs [86, 87], a number of researchers have suggested that the opposite is true and that, in fact, it is the ribs that hold dominion

over the vertebrae. For example, thoracoplasty was performed in multiple studies, each showing that a progressive thoracic scoliosis curvature developed with the convexity directed toward the side of rib resection [88, 90].

As early as 1958, Roaf pointed out that the pressure the ribs impose upon the vertebrae cause these vertebrae to rotate. He also observed that the pressure the ribs apply on the convex side of the curve is posterior to the axis of rotation, while the pressure on the concave side is anterior to the axis of rotation [90]. Consequently, it is predictable that when the right posterior ribs apply pressure to the right aspect of the vertebrae, the vertebrae will rotate to the right (ie towards the convexity).

Sevastik et al. postulated that asymmetric growth of the ribs may be the primary cause of the thoracospinal deformity in the case of right convex, thoracic, idiopathic scoliosis [91]. In what he referred to as "The Thoracospinal Concept," he postulated that adolescent girls with a right thoracic curvature had a sympathetic nervous system disorder that directly impacted the thorax. Further, he wrote that this sympathetic nervous system imbalance may lead to 1) a side to side disparity in blood supply within the thorax and 2) unequal activation of the associated musculature. Both of these factors could conceivably lead to asymmetric rib growth and consequently disturb the equilibrium of the forces determining the normal alignment of the thoracic spine, thus triggering the development of a spinal curvature in all three cardinal planes [92]. Korovessis et al. subsequently showed that female adolescents with progressive right-convex thoracic scoliosis displayed abnormalities in the evolution of the anterior chest wall blood supply [93].

If the rotation of the vertebrae dictate the motion and the deformity of the ribs, then one would expect to always find a curvature in the thoracic spine when there is rib humping. Yet, in a group of children referred to their clinic via a scoliosis school-screening program, Grivas et al. found that out of the 83 children referred, 14 (16.9%) had scoliometer readings that were equal to or greater than 7 degrees, yet their spines were completely straight [94]. Logically, this lends evidence to the argument that it is in fact the ribs that are rotating the vertebrae and not the other way around.

As mentioned earlier, there is a loss of postural muscle tone due to the atonic state during the REM stage of sleep. Notably, this includes marked muscle tone loss of postural muscles such as the intercostal muscles [95, 96] which may leave the rib cage less stable [97], a factor particularly important when considering the development of thoracic spine curvatures. Notably, in an animal model, Sevastik et al. showed that resecting three intercostal nerves on the right side of growing rabbits elicits a moderate left-convex thoracic scoliosis as well as a reduction in the sagittal curvature within 1 to 3 months [98].

Vertebral Extension (Hypokyphosis)

According to the Nighttime Perfect Storm Hypothesis, there are two possible mechanisms that may account for the sagittal plane flattening in the thoracic spine, as well as the relative anterior spinal overgrowth so commonly seen in thoracic curvatures of AIS [99]. The first is the gravitational force running transverse to the prone and horizontally oriented thoracic spine. Also, extension of the thoracic spine may be enhanced further as the child places one or both arms above their head while in the Prone PSP. [100, 101, 102].

Extension First, Rotation Second

Hypothetically, the rotational force applied by the right ribs on the right aspect of the vertebrae initially does not cause the vertebrae to rotate. Instead, it is possible that the thoracic kyphosis must decrease below a certain threshold before the rotational forces applied by the ribs can initiate rotation of the vertebrae. Therefore, in the initial phases of AIS, the ribs are applying pressure upon the thoracic vertebrae while the child is asleep in the Prone PSP as mentioned in the previous section. However, since the kyphosis of the thoracic spine has not decreased enough to achieve rotational instability, the right posterior ribs will be compelled to reabsorb these biomechanical forces, resulting in gradual bone remodeling of the involved ribs via mechanotransduction pathways leading to subsequent rib humping. In addition, this dynamic may also lead to increased pressure placed upon the epiphyseal growth plates within the right ribs and consequently stunt the growth consistent with the Heuter-Volkmann Law. This may explain the rib length discrepancy found in children with AIS [103].

Figure 2:- The Lateral Provocative Sleep Position (PSP)- leads to a left lumbar curvature (levoscoliosis) while lying on left side.

The Lateral PSP

A neutral lateral sleeping position is inherently unstable due to the decreased amount of contact between the body and the mattress surface as well as the body's more elevated center of gravity. Consequently, by bending the arms and legs, a greater surface area of the body makes contact with the mattress, thus improving the overall stability of the body [84]. This may explain why many sleep in a modified lateral sleeping position, which we refer to as the Lateral PSP (Figure 2). Cary et al. also identified this sleep position in their study, calling it "3/4 side lying." They point out that while in this modified side sleeping position, the top femur (thigh) that is furthest from the mattress does not rest directly on the lower thigh that is adjacent to the mattress. Instead, the top thigh is flexed further at the hip, allowing for the top knee to lower to and rest upon the mattress. The authors note that this obliquity between the upper and lower thighs force the lumbar vertebrae into rotation and extension [1]. Further, while sleeping on one's side in a non-neutral manner, lateral bending as well as unbalanced loading of the intervertebral discs and facet joints may occur [104].

Perhaps, the transverse dimensions of the pelvis will have a direct effect on the biomechanics of the thoracolumbar and lumbar spine regions while in the lateral PSP. Conceivably, the pelvic width is a direct determinant of how far the upper femur will be positioned away from the mattress surface. The broader the child's pelvis, the stronger moment due to a longer moment arm, resulting in potentially more lumbar rotation and extension, leading to either a lumbar (or thoracolumbar scoliotic curvature).

To summarize, if the child were lying on her left side while in the Lateral PSP, her right thigh would fold forward in front of the left thigh, allowing the right knee and lower leg to rest directly upon the mattress. One would expect the spine to laterally bend towards the mattress due to gravitational forces leading to a global lateral curvature in the lumbar spine that is convex to the left. Additionally, the lumbar vertebrae will rotate due to the obliquity of the thighs as discussed above.

With regard to pelvic and lumbar kinematics, the Lateral PSP is biomechanically very similar to the body positioning during gait. In the Lateral PSP, the upper leg furthest from the mattress is flexed forward at the hip joint, which is analogous to the moment just prior to heel strike during gait. Further, during normal gait, when one takes a step, the opposite arm reflexively is flexed forward simultaneously. Similarly, when one is in the Lateral PSP, the arm that is adjacent to the mattress tends to be flexed forward. The authors acknowledges that turning to gait as a model to study the biomechanics of the Lateral PSP has its limitations due the fact that one's body is oriented vertically during gait, yet horizontally while asleep.

A number of studies have focused on the positioning of the lumbar vertebrae during gait. Gombatto et al. evaluated the kinematics of the lumbar spine during gait of individuals with and without low back pain. They determined that both axial rotation and lateral bending occur in the upper and lower lumbar vertebrae [105]. In other words, while walking, when one leg is fully flexed forward, similar to when the body is in the Lateral PSP, the lumbar vertebrae demonstrate rotation as well as lateral deviations in the frontal plane, allowing a temporary scoliotic curvature to develop globally throughout the lumbar spine. In a separate study, Crosbie et al. investigated the patterns and ranges of movement of not only the lumbar spine, but the lower thoracic spine as well. They noted that during gait, lateral flexion of the vertebrae occurred in both the lower thoracic and lumbar spinal regions. Significantly, they pointed out that while the patterns of motion in the lower thoracic spine and lumbar spine were similar, they occurred in opposite directions [106].

To summarize, if the child were lying on her left side while in the Lateral PSP, her right thigh would fold forward in front of the left thigh, allowing the right knee, tibia and foot to rest directly upon the mattress. One would expect the spine to laterally bend towards the mattress due to gravitational forces leading to a global lateral curvature in the lumbar spine that is convex to the left. While positioned in the lateral PSP, this lumbar convexity on the left could conceivably lead to a perpetual tension placed upon the left quadratus lumborum due to the progressive separation of the 12th rib from the iliac crest. This would in effect lead to a chronic tension placed on the 12th rib with potential overgrowth consequences, as tension leads to enhanced bone growth per the Heuter-Volkmann Law. In one study, 14 AIS children with lateral lumbar curves with Cobb angles ranging from 5-22 degrees were analyzed, and it was discovered that in 12 of the 14 children, the 12 rib was longer on the side of the curve convexity[107].

Pillar #4 - Adolescent Growth Spurt

In AIS, the spine is most vulnerable to curve development during the adolescent growth spurt [108], with the most rapid rate of curve progression occurring during the beginning of puberty [109, 110]. The relationship between the growth spurt and curve progression centers around the vertebral growth plate, the central player in longitudinal vertebral growth during the pubertal phase of growth [111]. To that end, melatonin may participate in AIS in relation to it's role in the timing of menarche, a factor that potentially leaves girls more vulnerable to developing AIS due to the expanded time window of bones that have not yet fully matured, and thus may more easily deform [112].

In order to explain how gravitational forces might effect the tissues of the thoracic spine and account for findings such as relative anterior spine overgrowth seen in thoracic curvatures, we will turn to an explanation by Haex. He does not write on the mechanics of the thoracic spine while in a completely prone sleeping position with outstretched legs. However, he writes the following in regard to the lumbar spine while sleeping in a prone position. He states, "Gravity causes the heaviest middle part of the human body to sink deeper into the mattress while legs remain stretched. Consequently, lumbar lordosis will increase significantly and will augment the pressure on the facet joints at the posterior side [85], while soft tissues (e.g., ligaments) will be under tension at the anterior side [84]." The Nighttime Perfect Storm Hypothesis predicts that a similar biomechanical event occurs in the thoracic spine that is being driven into extension while in the Prone PSP, as detailed in a previous section. Based on the "Hueter-Volkmann Law", this dynamic should lead to gradual overgrowth of the anterior aspect of the involved thoracic vertebrae and diminished growth in the posterior aspects of these same vertebrae [113]. Ultimately, these growth patterns may be responsible for the relative lengthening of the anterior aspect of the disc seen first [73] and the eventual relative anterior spinal overgrowth [99] leading to the consequent vertebral wedging seen in the sagittal plane of the thoracic spines of children with AIS.

Curvature Development: Upright Or Recumbent?

One fundamental question is whether the scoliotic curve is more likely to develop while the child's body is upright or while recumbent. It is thought that the compressive load due to gravity and muscle contraction is likely to be much greater while the spine is vertically positioned as compared to horizontally. [114, 115]. Further, it has been discovered that spinal movements decrease under a superimposed compressive load [116, 117]. On the contrary, while lying down, there is a reduced gravitational load in the craniocaudal direction, creating a low compression environment which potentially allows for an increased range of spinal movement [118].

The Intervertebral Disc And Recumbency

It has been found that torsion loads applied to the body while in a weight bearing position are primarily resisted by the zygopophyseal joints of the spine. However, while recumbent, torsion loads are mostly absorbed by the annulus fibrosis of the intervertebral discs [119]. Thus, whether the child's body is positioned in either the Prone or Lateral

PSP, the intervertebral discs may be the most vulnerable tissues. It was discovered by Grivas et al. that the scoliotic spine first deforms at the level of the intervertebral disc (IVD), not the vertebrae, due to the increased plasticity of the IVD [120]. Later, these findings were confirmed by Will et al. [121]. Notably, many researchers that have discovered histological abnormalities in the intervertebral discs of children with AIS have concluded that these abnormalities are secondary to an altered mechanical environment [122, 123, 124, 125].

Utilizing CT technology, Brink et al.discovered that the intervertebral discs contribute more to anterior length of the spine compared to the contribution by the vertebrae [126]. They suggest that this finding implies that the curve progresses due to altered mechanical loading and NOT a primary growth disturbance.

While in the Prone PSP, the thoracic spine will be exposed to extension and rotation forces, potentially leading to wedging and torsion in the intervertebral disc, respectively. Separately, while in the Lateral PSP, torsion forces will be applied to the IVD of the lumbar spine. Hypothetically, throughout the night, and as the intervertebral discs are deranged due to the deleterious biomechanical effects of sleeping in one of the PSPs, the asymmetrically positioned proteoglycans macromolecules within an asymmetrically positioned nucleus pulposus within the disc will imbibe water, and then expel water throughout the day while the child is upright. This process of imbibing and expelling of water by the GAGs of intervertebral disc is referred to as the Gibbs Donnan effect [127].

In a paper very recently published by Grivas, he proposed that the cyclical diurnal variation in the water content of the discs which are wedged may directly effect the adjacent secondary growth centers of the vertebrae in what the author refers to as the "accordian-like phenomenon"[128]. It must be pointed out that his concept that the stage of REM sleep is highly significant for scoliogenesis due to the atonic state of the musculature during this sleep stage is totally consistent with The Nighttime Perfect Storm Hypothesis. He explained that since the scoliotic disc is wedged and the GAGs are asymmetrically positioned, with greater concentrations located on the convex side of the disc, there will be more water imbibed and expelled throughout the 24 hour cycle on this convex side as compared to the concave side. Furthermore, this intermittent loading on the convex side of the disc, which falls within the normal limits of stress and strain, will result in stimulation of the adjacent vertebral growth plate, as suggested by Pauwel's law. However, the concave aspect of the wedged disc, with decreased concentration of GAGs as compared to the convex side, is not subject to the cyclic loading process throughout the 24 hour cycle. Instead, compressive forces that will be translated to the adjacent growth plate will lead to a net decrease in the rate of chondrocyte proliferation, consistent with the Heuter-Volkmann Law. The net effect of this pattern may be asymmetrical growth of the vertebral body, as well as the posterior elements of the vertebrae.

Are Bone Growth Changes Most Likely To Occur At Night?

In reference to the skeletal system, it has been known for some time that metabolic functions of chondrocytes [129, 130, 131], osteoclasts [132], osteoblasts [133], and osteocytes [134] display intrinsic circadian rhythms [135, 136]. In fact, if defined by circadian variation in bone turnover markers, according to Hettiarachchi et al., bone remodeling exhibits a unimodal diurnal rhythm that crests during nocturnal hours while reaching its nadir during daytime hours [137].

Pillar #4 of The Nighttime Perfect Storm Hypothesis stresses the importance of the adolescent growth spurt in the development of AIS, a process in which bone growth is integral. Noonan et al. set out to determine the timing of bone growth in lambs, studying four growthplates (proximal and distal radial; proximal and distal tibial) to document bone growth every 167 seconds for 21 to 25 days. They discovered that 90% of bone elongation occurred during recumbency and almost no growth occurred during standing or locomotion. The authors hypothesized that the same pattern of nocturnal growth may also occur in children during rest or sleep, thus supporting the concept of nocturnal growth and perhaps a relationship to growing pains [138]. If vertebral growth in children is indeed a nighttime event that occurs during the hours of recumbency, it is all the more plausible that the child with a genetic predisposition to AIS will be vulnerable to developing a spinal curve while positioned in one of the two PSPs.

REM And Time Spent In The Provocative Sleep Position

Hypothetically, increased time spent in one of the PSPs only increases the window of time that the spine will be vulnerable to curvature development in those children with genetic vulnerabilities to AIS. However, it may be that the effects of the PSP are most damaging while the child is in the REM stage of sleep, given that REM sleep is accompanied by full body muscular atonia [139]. If this were the case, children with a genetic vulnerability for AIS

may be at greater risk if they are also physiologically programmed to spend more time in the REM stage of sleep while asleep at night.

Leptin And REM Sleep

Currently, it is thought that hormonal disturbances may contribute to bone mass abnormalities in the spinal vertebrae, contributing to the progression of spinal deformities in those with AIS [140]. One of the suspected hormones that may participate in the development of AIS is leptin. Qiu et al. found that blood leptin levels are significantly lower in girls with AIS compared with healthy controls [141]. They determined that this correlation may mean that leptin plays a role in the lower BMI and bone mass found in girls with AIS. Other researchers have also found an association between AIS and low leptin levels [142, 143]. In a population- based prospective study conducted by Clark et al., it was discovered that low fat mass, low lean mass, low circulating leptin and high circulating adiponectin levels in 10-year olds was associated with scoliosis by 15 years of age [144].

While leptin's role in AIS has been explored within the context of osteology and BMI, there may be an alternative explanation of leptin's participation in the development of AIS. In a study designed to examine the relationship between serum leptin and REM sleep in a sample of healthy adults, Olson et al. found that a greater percentage of REM sleep was accompanied by marked reductions in leptin [145]. Might it be that low leptin levels found in children with AIS is related to the amount of time they are spending in a PSP while in the REM stage of sleep?

BMI And REM Sleep

Low BMI has been found to be associated with AIS [146, 147, 148]. Separately, there also may be an association between BMI and REM sleep. In a study of 319 Caucasian and Hispanic children between ages 10 and 17 years designed to determine if there was a relationship between sleep architecture and BMI, nutrition, and physical activity, Karim et al. discovered that in girls, total fat intake was associated with a reduction in REM sleep [149]. It may be that there is also a relationship between BMI and total sleep time. Benefice E et al. discovered that while puberty status did not influence sleep habits of the girls in their study, there was a significant relationship between BMI and sleep habits. Girls who were thinner slept a longer time and more quietly than those who were overweight [150].

Latitude And Total Sleep Time

Brockmann, et al. discussed the possibility of there being a correlation between latitudinal levels and sleeping patterns. In their findings, they discovered that those who lived in higher latitudes tended to sleep more. [151] If the PSP indeed participates in the development of the scoliotic curve, we would expect a higher incidence of AIS in higher latitudes where people sleep progressively for longer periods.

Grivas et al. conducted a literature review examining whether there were differing prevalences of AIS at different latitudes. They evaluated seventeen peer-reviewed published papers, reporting that there was a definitive positive association between prevalence of AIS and geographic latitude. They found this pattern particularly for girls in their study. Further, they concluded that this positive association implicates the possible role of environmental factors in the pathogenesis of AIS [110].

Gender: Breast And Hip Involvement In AIS

As mentioned, the prevalence and severity of the spinal curvatures seen in AIS are higher in females than males [152]. Likely, there are a multitude of reasons for the noted gender discrepancy. However, within the context of The Nighttime Perfect Storm Hypothesis, the development of breasts and hips in girls during puberty may serve to exacerbate the thoracic and lumbar curvatures, respectively, ultimately accounting for the sexual dimorphism seen in AIS.

Breast Development and the Prone PSP

AIS most commonly manifests during the peripubital period, a phase of growth that generally occurs at 11-14 years of age [153, 154]. Further, the fastest rate of development of the spinal curvatures is seen during the beginning of puberty [155, 156]. This period of time corresponds to Stage 2 according to the Tanner Scale [157], an objective classification used by providers in order to document and track the development of secondary sex characteristics during puberty [158]. Stage 2 marks the period of thelarche, the onset of breast development, where the breast bud is palpable under the areola (1st pubertal sign in females) [158]. Girls achieve peak height velocity during sexual maturity ratings 2 and 3 (mean: 8.3 cm per year, age 11 or 12 years) [159].

Breast development may play an integral role in the development of thoracic curvatures seen in AIS. In reference to the Prone PSP, the reader will remember that the left anterior ribsare compressed into the mattress and this starts a chain of reactive forces that ultimately lead to the right posterior ribs pressing into the vertebrae, resulting in the development of a right thoracic curvature. Perhaps, the developing breasts during the early stages of puberty lead the female child to develop slight adaptations while in the Prone PSP. Developing breast buds are often accompanied by soreness [160] which may prompt the child to unconsciously position her thorax at a slightly greater angle with respect to the mattress in order to avoid direct pressure in the pain sensitive region, resulting in more rotational torque on the entire rib cage in a clockwise direction (when viewing from above) as the left anterior ribs press into the mattress.

As the child enters Stage 3 on the Tanner Scale and the breasts continue to grow larger, she may consciously (or unconsciously) position the left breast towards the midline of the body so she is not sleeping directly on the breast itself. Positioning the breast towards the midline may serve to increase the rotational torque in the ribcage (clockwise if looking at the body from above) while in the Prone PSP due to an increase in tension of the soft tissues, potentially exacerbating curvature development.

Alternatively, it may be that as the breasts develop, instead of the left breast being positioned towards the midline, the child sleeps directly on the left breast while in the Prone PSP with right leg elevated and head turned to the right. Possibly, the additional mass of breast tissue between the left anterior ribs and the mattress serves to create even more pressure on the rib cage, ultimately leading to more torque on the thorax and consequent pressure on the associated thoracic vertebrae.

Hip Development and the Lateral PSP

While breast development may be a contributing factor in the thoracic curvature while the female child is in the Prone PSP, the broadening of the hips may contribute to the development of the lumbar curve while the female child is in the Lateral PSP. The pubertal stage of growth in girls is partly characterized by broadening and rounding of the hips, a result of increased width between iliac crests [161]. The increased width of the hips may change the biomechanics in such a way that may generate more torque throughout the lumbar spine while the child is positioned in the Lateral PSP.

Further, in another finding that highlights the sexual dimorphism with respect to the morphology of the skeletal system, it has also been discovered that the lower ribs tend to droop more in girls than boys. The authors of this finding suggested that the increased transverse diameter of the pelvis in females, a harbinger of the childbearing years approaching, necessitates a decreased transverse diameter in the lower thorax as a way of maintaining the economy of energy expenditure during gait. They posed that a broad lower thorax plus a broad pelvis would create far too much inertia during gait. Thus, if the lower thorax is reduced in transverse diameter (by the drooping of the ribs), then the proper amount of inertia may be established [162, 163].

Also, the hip widening would be accompanied by an increase in the overall mass of the pelvis. Conceivably, this increased mass may lead to the pelvis sinking deeper into the mattress, possibly leading to increased lateral flexion throughout the lumbar spine. In summary, the increased dimensions and mass of the pelvis in females going through puberty may participate to curve development in the lumbar spine due to rotary and lateral flexion forces.

The Thoracolumbar Curve

The reader may be wondering why thoracolumbar curvesare absent from the discussion thus far. In an attempt to minimize the amount of conjecture, the focus of The Nighttime Perfect Storm Hypotheses has been on the development of thoracic and lumbar curvatures due to the effects of the Prone and Lateral PSPs, respectively. The thoracolumbar curve is a distinct curvature pattern, categorized as a Type 5 Lenke curve, with apex located between the cephalad border of the twelfth thoracic vertebra and the caudad border of the first lumbar vertebra [164].

It may be that the apical location of the scoliotic curvature that develops in the lumbar spine is determined by how much the child flexes her thigh that is furthest from the mattress while in the Lateral PSP. As the thigh is flexed more, possibly the apex of the curve will shift steadily in a superior direction. Thus, the greatest degree of thigh flexion while in the Lateral PSP might be expected to cause a thoracolumbar curvature to develop. However, when there is less flexion in the thigh furthest from the mattress, a curvature may more likely develop between the first or

second lumbar disc and the caudad border of the fourth lumbar vertebra, what Lenke et al. defines as a lumbar curvature [164].

Handedness And Side Of Curvature

While in the prone PSP, one leg is elevated. The elevated leg in our example is on the right (See Figure 1). Importantly, 90% of the general public are known to be right side dominant [165]. The vast majority of stomach sleepers sleep in the Prone PSP with right leg elevated. While no research is currently available to verify this claim, the primary author has interviewed thousands of patients in clinical practice regarding their sleeping positions and found this to be the case. There may be a number of reasons why someone who is right side dominant would instinctively prefer to raise their dominant right leg while in the Prone PSP. Barut et al. explored the relationship between hand and foot preference and found that right-handed men preferred their right foot 75.5% of the time, while right-handed women preferred their right foot 89.9% of the time [166]. The side preference would support the findings of Goldberg et al, who discovered a correlation between scoliosis configuration and handedness [167].

A further association between handedness and side of the curve was discovered by Grivas et al., who explored the possible correlation of trunk asymmetry, as assessed by scoliometer evaluation, and lateralization of the brain, as expressed by handedness in a population of school aged children. Their findings showed a significant statistical correlation of trunk asymmetry and handedness in both girls and boys with a mid-thoracic asymmetry, but not in those with a thoracolumbar or lumbar asymmetries [168]. This finding may serve as a clue, where handedness may turn out to be a factor in lateralization preferences in only one of the two PSPs. Simply put, since they discovered lateralization to be statistically significant in the boys and girls with mid-thoracic asymmetry, but not in those with a thoracolumbar or lumbar asymmetry, this could possibly mean that children who assume the prone PSP do tend to flex their dominant thigh and turn their head to their dominant side which would lead to a thoracic scoliotic curvature with convexity to the dominant side as well. However, it may be that the laterality of thoracolumbar and lumbar curves do not correlate with handedness because perhaps lateral recumbent preferences (ie sleeping on one's left or right side) are guided by factors other than handedness.

The Path Forward

In order to determine whether or not The Nighttime Perfect Storm Hypothesis can account for the initiation and development of the spinal curvatures seen in children with AIS, the first question that needs to be investigated is whether or not a child with a developing structural thoracic curvature customarily sleeps in the Prone PSP and whether a child with a developing lumbar curve regularly sleeps in the Lateral PSP. Video recording is the proposed method to investigate this question. A self-report survey to find out the child's nightly sleep positions would be expedient. In fact, some studies have reported moderate to high correlation between self-reporting by the sleep subject and their sleep position determined by video recordings in a lab setting [169, 170]. However, more recent studies have demonstrated a high inaccuracy rate of self-reporting [171], with one study reporting a 42.3% misreporting rate for the second laboratory self-report [172]. Another advantage of video recording the sleeping child throughout the night is that it would allow investigators to study the exact positioning of the child's body as well as the time spent in each sleep position [118].

If the first study demonstrates a high correlation between the children's sleep positions and their developing spinal curvatures as predicted by The Nighttime Perfect Storm Hypothesis, the next proposed step would be to develop an orthopaedic device that will prevent the child with AIS from lying in either the Lateral PSP or Prone PSP. The individuals in the study groups should have curves between 10-25 degrees, the period when they would be under observation according to the current SOSORT Guidelines [173]. One sample group of AIS patients (thoracic curves, lumbar curves) will get their sleep orthotic device, while the other sample group of AIS patients (thoracic curves, lumbar curves, with roughly the same average curvature magnitude as the other group) will NOT use the sleep orthotic. X-rays should be compared over a reasonable time period to determine if there is any difference in the progression of the curve between the two groups. Results will determine whether or not preventing the child from sleeping in the PSP either completely or partially halts curvature progression, and whether the Nighttime Perfect Storm Hypothesis will become a new theoretical model that can guide clinicians in a new era of treatment for AIS.

Acknowledgments:

None.

Funding:
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Consent statement/Ethical approval:
The woman who is photographed in both the pictures in our paper was not being treated for Adolescent Idiopathic Scoliosis and strictly served as a model and consent was also obtained from her.

References:-

[1] M.N. Choudry, Z. Ahmad, R. Verma, Adolescent idiopathic scoliosis, Open Orthop. J. 10 (2016) 143-154. doi: 10.2174/1874325001610010143.
[2] M.R. Konieczny, H. Senyurt, R. Krauspe, Epidemiology of adolescent idiopathic scoliosis, J. Child Orthop. 7 (1) (2013) 3-9. doi: 10.1007/s11832-012-0457-4.
[3] J. Cheung, J.P. Halbertsma, A.G. Veldhuizen, W.J. Sluiter, N.M. Maurits, J.C. Cool, J.R. van Horn, A preliminary study on electromyographic analysis of the paraspinal musculature in idiopathic scoliosis, Eur. Spine J. 14 (2) (2005) 130-137. doi: 10.1007/s00586-004-0780-7.
[4] K.H. Yeung, G.C.W. Man, L. Shi, S.C.N. Hui, C. Chiyanika, T.P. Lam, B.K.W. Ng, J.C.Y. Cheng, W.C.W. Chu, Magnetic resonance imaging-based morphological change of paraspinal muscles in girls with adolescent idiopathic scoliosis, Spine (Phila Pa 1976). 44 (19) (2019) 1356-1363. doi: 10.1097/BRS.0000000000003078.
[5] M. Reuber, A. Schultz, T. McNeill, D. Spencer, Trunk muscle myoelectric activities in idiopathic scoliosis, Spine (Phila Pa 1976). 8 (5) (1983) 447-456. doi: 10.1097/00007632-198307000-00002.
[6] U.T. Slager, J.D. Hsu, Morphology and pathology of the paraspinous muscles in idiopathic scoliosis, Dev. Med. Child Neurol. 28 (6) (1986) 749-756. doi: 10.1111/ j.1469-8749.1986.tb03928.x.
[7] T.G. Lowe, M. Edgar, J.Y. Margulies, N.H. Miller, V.J. Raso, K.A. Reinker, C.H. Rivard, Etiology of idiopathic scoliosis: current trends in research, J. Bone Joint Surg. Am. 82 (8) (2000) 1157-1168. doi: 10.2106/00004623-200008000-00014.
[8] M. Fadzan, J. Bettany-Saltikov, Etiological theories of adolescent idiopathic scoliosis: past and present, 11 (2017) 1466-1489. doi: 10.2174/1874325001711011466.
[9] J. Zadeh, M. Gleiber, Adolescent idiopathic scoliosis: an in depth analysis and historical review, MOJ Orthop. & Rheum. 3 (4) (2015). doi: 10.15406/mojor/2015.03.00105.
[10] S. Pasha, 2019. 3D deformation patterns of S shaped elastic rods as a pathogenesis model for spinal deformity in adolescent idiopathic scoliosis, Sci. Rep. 9, 16485. doi: https://doi.org/ 10.1038/s41598-019-53068-7.
[11] D. Cary, R. Collinson, M. Sterling, N.K. Briffa, Examining the relationship between sleep posture and morning spinal symptoms in the habitual environment using infrared cameras, J. Sleep Disor. Treat. Care. 5 (2) (2016) 1-7. http://dx.doi.org/10.4172/2325-9639.1000173.
[12] T.B. Grivas, O.D. Savvidou, Melatonin the "light of night' in human biology and adolescent idiopathic scoliosis, Scoliosis 2 (2007) 6. doi: 10.1186/1748-7161-2-6.
[13] E.S. Vasiliadis, T.B. Grivas, A. Kaspiris, Historical overview of spinal deformities in ancient Greece, Scoliosis 4 (6) (2009). doi: 10.1186-1748-7161-4-6. doi: 10.1186-1748-7161-4-6.
[14] K.P. Parker, S.B. Dunbar, Cardiac Nursing, in: S.L. Woods, E.S.S. Froelicher, S.U. Motzer, E. Bridges (Eds.), Sleep, fifth ed, Lippincott Williams and Wilkins, Philadelphia, 2005, pp. 197-219.
[15] H.R. Colten, B.M. Altevogt (Eds.), Institute of Medicine (US) Committee on Sleep Medicine and Research. Sleep disorders and sleep deprivation: an unmet public health problem, National Academic Press (US), Washington (DC), 2006. PMID: 20669438.
[16] L.M. Kruse, J.G. Buchan, C.A. Gurnett, M.B. Dobbs, Polygenic threshold model with sex dimorphism in adolescent idiopathic scoliosis: The Carter effect, The J. of Bone and Joint Surg. 94 (16) (2012) 1485-149. https://digitalcommons.wustl.edu/open_access_pubs/1190. doi: 10.2106/JBJS.K.01450.
[17] R.J. Burwell, P.H. Dangerfield, A. Moulton, T.B. Grivas, 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. 6 (1) (2011) 26. doi: 10.1186/1748-7161-6-26.
[18] K. Kesling, K. Reinker, Scoliosis in twins: A meta-analysis of the literature and report of six cases, Spine. 22 (1997) 2009-2014. doi: 10.109 DOI: 10.1097/00007632-199709010-00014. [19] D. Del Curto, R.H.S. Ueta, M. Wajchenberg, F.D.E. Martin, E.B. Puertas, Variacoes Variacoes na aprentacao fenotipica da escoliose idiopatica do adoscente, Couna. 201: 2(1): (2010) 12-23. doi: 10.1590/S1808-18512010000100005.

[20] M. Wajchenberg, N. Astur, M. Kanas, D.E. Martins, Adolescent idiopathic scoliosis: current concepts on neurological and muscular etiologies, Scoliosis Spinal Discord. 11: 4 (2016). doi: 10.1186/s13013-016-0066-y.
[21] A. Grauers, I. Rahman, P. Gerdhem, Heritability of scoliosis, Eur. Spine J. 21 (6) (2012) 1069-1074. doi: 10.1007/s00586-011-2074-1.
[22] N. Oliazadeh, K.F. Gorman, R. Eveleigh, G. Bourque, A. Moreaua, Identification of elongated primary cilia with impaired mechanotransduction in idiopathic scoliosis patients, Sci. Rep. 7: 44260 (2017). https://doi.org/10.1038/srep44260.
[23] P.F. Davies, E. Manduchi, J.M. Jimenez, Biofluids, cell mechanics and epigenetics: Flow- induced epigenetic mechanisms of endothelial gene expression, J. Biomech. 50 (2017) 3-10. doi: 10.1016/j.jbiomech.2016.11.017.
[24] K. Watanabe, T. Michikawa, I. Yonezawa, M. Takaso, S. Minami, S. Soshi, T. Tsuji, E. Okada, K. Abe, M. Takahashi, K. Asakura, Y. Nishiwaki, M. Matsumoto, Physical activities and lifestyle factors related to adolescent idiopathic scoliosis, J. Bone Joint Surg. Am. 99 (4) (2017) 284-294. doi: 10.2106/JBJS.16.00459.
[25] K. Asakura, T. Michikawa, M. Takaso, S. Minami, S. Soshi, T. Tsuji, E. Okada, K. Abe, M. Takahashi, M. Matsumoto, Y. Nishiwak, K. Watanabe, Dietary habits had no relationship with adolescent idiopathic scoliosis: analysis utilizing quantitative data about dietary intakes, Nutrients. 11 (10) (2019) 2327. doi: http://doi.org/10.3390/nu11102327.
[26] T.B. Grivas, P. Samelis, B.D. Polyzois, B. Giourelis, D. Polyzois, School screen in the heavily industrialized area-Is there any role of industrial environmental factors in idiopathic adolescent scoliosis prevalence? Stud. Health Technol. Inform. 91 (2002) 76-80. PMID: 15457698.
[27] E. Kenanidis, M.E. Potoupnis, K.A. Papavasiious, F.E. Sayegh, G.A. Kapetanos, Adolescent idiopathic scoliosis and exercising: is there truly a liaison? Spine (Phila Pa 1976) 33 (20) (2008) 2160-2165. doi: 10.1097/BRS.0b013e31817d6db3.
[28] M.E. McMaster, A.J. Lee, R.G. Burwell, Indoor heated swimming pools: the vulnerability of some infants to develop spinal asymmetries years later, Stud. Health Technol. Inform. 123 (2006) 151-155. PMID: 17108419.
[29] M.E. McMaster, Heated indoor swimming pools, infants, and the pathogenesis of adolescent idiopathic scoliosis: a neurogenic hypothesis, Enviorn. Health. 10 (2011) 86. doi: https://doi.org/ 10.1186/1476-069X-10-86.
[30] M.B. Balioglu, C. Aydin, D. Kargin, A. Albayrak, Y. Atici, S.K. Tas, M.A. Kaygusuz, Vitamin-D measurement in patients with adolescent idiopathic scoliosis, J Pediatr. Orthop. B. 26 (1) (2017) 48-52. doi: 10.1097/BPB.0000000000000320.
[31] Q. Zhu, J. Chen, C. Chen, H. Wang, S. Yang, Association between calcium-phosphorus balance and adolescent idiopathic scoliosis: a meta-analysis. Acta Orthop. Traumatol. Turc. 53 (6) (2019) 468-473. doi: 10.1016/j.aott.2019.08.012.
[32] A. Goździalska, M. Knapik-Czajka, J. Drag, M. Gawlik, M. Cieśla, A. Kulis, D. Zarzycki, E. Lipik, Association of calcium and phosphate balance, vitamin D, PTH, and calcitonin in patients with adolescent idiopathic scoliosis, Spine (Phila Pa 1976) 41 (8) (2016) 693-697. doi: 10.1097/BRS.0000000000001286.
[33] S.Y. Ng, J. Bettany-Saltikov, I.Y.K. Cheung, K.K.Y. Chan, The role of vitamin D in the pathogenesis of adolescent idiopathic scoliosis, Asian Spine J. 12 (6) (2018) 1127-1145. doi: 10.31616/asj.2018.12.6.1127.
[34] G.M. Kiebzak, K.M. Neal, Impact of race subgroups on the assessment of vitamin D status in adolescent idiopathic scoliosis, Orthop. 42 (3) (2019) 158-162. doi: 10.3928/0147447-20190424-07.
[35] M. Baroni, G.J.B. Sanchis, S.J.C. de Assis, R.G. dos Santos, S.A. Pereira, K.G. Sousa, J.M. Lopes, Factors associated with scoliosis in schoolchildren: a cross-sectional population-based study, J. of Epid., Japan Epid. Assoc. 25 (3) (2015) 212-220. doi: 10.2188/jea.JE20140061.
[36] M.M. Panjabi, The stabilizing system of the spine. Part 1: Function, dysfunction, adaptation, and enhancement, J Spinal Disord. & Tech. 5 (4) (1992) 383-389. doi: 10.1097/00002517-199212000-00001.
[37] T.B. Sullivan, F.G. Reighard, E.J. Osborn, K.C. Parvaresh, P.O. Newton, 2017. Thoracic idiopathic scoliosis severity is highly correlated with 3D measures of thoracic kyphosis, J Bone Joint Surg. Am. 99 (11), e54. doi: 10.2106/JBJS.16.01324.
[38] E. Arrigoni, M.C. Chen, P.M. Fuller, The anatomical, cellular and synaptic basis of motor atonia during rapid eye movement sleep, J Physiol. 594 (19) (2016) 5391-5414. doi: 10.1113/ JP271324.
[39] Y. Peng, S. Wang, G. Qiu, Research progress on the etiology an pathogenesis of adolescent idiopathic scoliosis, Chin. Med. J. (Engl). 133 (4) (2020) 483-493. doi: 10.1097/ CM9.0000000000000652.
[40] D. Wang, L. Shi, W.C. Chu, R.G. Burwell, J.C. Cheng, Abnormal cerebral cortical thinning pattern in adolescent girls with idiopathic scoliosis, Neuroimage. 59 (2012) 935-942. doi: 10.1016/j.neuroimage.2011.07.097.
[41] J.W.M. Kouwenhoven, R.M. Castelein, The pathogenesis of adolescent idiopathic scoliosis: review of the literature, Spine (Phila Pa 1976). 33 (26) (2008) 2898-2908. doi: 10.1097/ BRS.0b013e3181891751.

[42] K.M. Cheung, T. Wang, G.X. Qiu, K.D. Luk, Recent advances in the aetiology of adolescent idiopathic scoliosis, Int. Orthop. 32 (2008) 729-734. doi: 10.1007/s00264-007-0393-y.
[43] L. Shi, D. Wang, S.C.N. Hui, M.C.F. Tong, J.C.Y. Cheng, W. C.W. Chu, Volumetric changes in cerebellar regions in adolescent idiopathic scoliosis compared with healthy controls, Spine J. 13 (12) (2013) 1904-1911. doi: 10.1016/j.spinee.2013.06.045.
[44] N.N. Byl, S. Holland, A. Jurek, S.S. Hu, Postural imbalance and vibratory sensitivity in patients with idiopathic scoliosis: implications for treatment, J. Orthop. Sports Phys. Ther. 26 (2) (1997) 60-68. doi: 10.2519/jospt.1997.26.2.60.
[45] F. Zhu, Y. Qiu, H.Y Yeung, K.M. Lee, C.Y. Cheng, Trabecular bone micro-architecture and bone mineral density in adolescent idiopathic and congenital scoliosis, Orthop. Surg. 1 (1) (2009) 78-83. doi: 10.1111/j.1757-7861.2008.00014.x.
[46] K. Ishida, Y. Aota, N. Mitsugi, M. Kono, T. Higashi, T. Kawai, et al, Relationship between bone density and bone metabolism in adolescent idiopathic scoliosis, Scoliosis. 10 (2015) 9. doi: 10.1186/s13013-015-0033-z.
[47] T.P. Lam, V.W. Hung, H.Y. Yeung, Abnormal bone quality in adolescent idiopathic scoliosis: a case-control study on 635 subjects and 269 normal controls with bone densitometry and quantitative ultrasound, Spine (Phila Pa 1976). 36 (15) (2011) 1211-1217. doi: 10.1097/ BRS.0b013e3181ebab39.
[48] M. Chiru, Adolescent idiopathic scoliosis and osteopenia, Maedica (Buchar). 6 (1) (2011) 17-22. Chinese. PMID: 21977185.
[49] W.S. Yu, K.Y. Chan, F.W. Yu, B.K. Ng, K.M. Lee, L. Qin, T.P. Lam, J.C. Cheng, Bone structural and mechanical indices in adolescent idiopathic scoliosis evaluated by high-resolution peripheral quantitative computed tomography (HR-pQCT), Bone. 61 (2014) 109-115. doi: 10.1016/j.bone.2013.12.033.
[50] H. Chen, J. Zhang, Y. Wang, K.Y. Cheuk, A.L.H. Hung, T.P, Lam, Y. Qiu, J.Q. Feng, W.Y.W. Lee, J.C.Y. Cheng, Abnormal lacuno-canalicular network and negative correlation between serum osteocalcin and Cobb angle indicate abnormal osteocyte function in adolescent idiopathic scoliosis, FASEB J. 33 (12) (2019) 13882-13892. doi: 10.1096/fj.201901227R.
[51] X. Sun, T. Wu, Z. Liu, Z. Zhu, B. Qian, F. Zhu, W. Ma, Y. Yu, B. Wang, Y. Qiu, Osteopenia predicts curve progression of adolescent idiopathic scoliosis in girls treated with brace treatment, J Pediatr. Orthop. 33 (4) (2013) 366-371. doi: 10.1097/bpo.0b013e31827b7b5f.
[52] V.W.Y. Hung, L. Qin, C.S.K. Cheung, T.P. Lam, B.K.W. Ng, Y.K. Tse, X. Guo, K.M. Lee, J.C.Y. Cheng, Osteopenia: a new prognostic factor of curve progression in adolescent idiopathic scoliosis, J Bone Joint Surg. Am. 87 (12) (2005) 2709-2716. doi: 10.2106/JBJS.D.02782.
[53] W.T. Lee, C.S. Cheung, Y.K. Tse, Association of osteopneia with curve severity in adolescent idiopathic scoliosis: a study of 919 girls, Oseoporos. Int. 16 (12) (2005) 1924-1932. doi: 10.1007/s00198-005-1964-7.
[54] I.S. Eun, W.W. Park, K.T. Suh, J.I. Kim, J.S. Lee, Association between osteoprotegerin gene polymorphism and bone mineral density in patients with adolescent idiopathic scoliosis, Eur. Spine J. 18 (12) (2009) 1936-1940. doi: 10.1007/s00586-009-1145-z.
[55] P.G. Ziros, E.K. Basdra, A.G. Papavassiliou, Runx2: of bone and stretch, Int. J Biochem. Cell Biol. 40 (9) (2008) 1659-1663. doi: 10.1016/j.biocel.2007.05.024.
[56] W.J. Wang, C. Sun, Z. Liu, X. Sun, F. Zhu, Z.Z. Zhu, Y. Qiu, Transcription factor Runx2 in the low bone mineral density of girls with adolescent idiopathic scolioisis, Orthop. Surg. 6 (1) (2014) 8-14. doi: 10.1111/os.12087.
[57] C. Sun, Y. Qiu, G. Yin, H. Shu, Z. Liu, X.H. Wang, W.J. Liu, H.B. Li. Abnormal expression and significance of Runx2 in osteoblasts of adolescent idiopathic scoliosis patients, Zhonghua Wai Ke Za Zhi. 47 (19) (2009) 1495-1498. Chinese. PMID: 20092765.
[58] T. Zhou, C. Chen, C. Xu, H. Zhou, B. Gao, D. Su, Z. Liao, Y. Li, S. Yang, P. Su, Mutant MAPK7-induced idiopathic scoliosis is linked to impaired osteogenesis, Cell Physiol. Biochem. 48 (3) (2018) 880-890. http://doi.org/10.1159/000491956.
[59] J. Zhang, H. Chen, R.K.K. Leung, K.W. Choy, T.P. Lam, B.K.W. Ng, Y. Qiu, J.Q. Fenq, J.C.Y. Cheng, W.Y.W. Lee, Aberrant miR-14-5p/beta-catenin signal impairs osteocyte function in adolescent idiopathic scoliosis, FASEB J. (2018) fj201800281. doi: 10.1096/fj.201800281.
[60] E.M.S. Tam, F.W.P. Yu, V.W.Y. Hung, Z. Liu, K.L. Liu, B.K.W. Ng, S.K.M. Lee, Y. Qiu, J.C.Y. Cheng, T-P. Lam. 2014. Are volumetric bone mineral density and bone micro-architecture associated with leptin and soluble leptin receptor levels in adolescent idiopathic scoliosis?--A case-control study, PLoS One. 9 (2), e87939. doi: 10.1371/journal.pone.0087939.
[61] G.C. Man, E.M. Tam, Y.S. Wong, V.W. Hung, Z. Hu, T.P. Lam, Z. Liu, W.H. Cheung, T.B. Ng, Z. Zhu, Y. Qiu, J.C. Cheng, Abnormal osteoblastic response to leptin in patients with adolescent idiopathic scoliosis, Sci. Rep.

9 (1) (2019) 17128. doi: 10.1038/s41598-019-53857-3. [62] G.C. Man, W.W. Wang, B.H. Yeung, S.K. Lee, B.K. Ng, W.Y. Hung, J.H. Wong, T.B. Ng, Y. Qiu, J.C. Cheng, Abnormal proliferation and differentiation of osteoblasts from girls with adolescent idiopathic scoliosis to melatonin, J Pineal Res. 49 (1) (2010) 69-77. doi: 10.111/ j.1600-079X.2010.00768.x.
[63] A. Moreau, D.S. Wang, S. Forget, B. Azeddine, D. Angeloni, F. Fraschini, H. Labelle, B. Poitras, C.H. Rivard, G. Grimand., Melatonin signaling dysfunction in adolescent idiopathic scoliosis, Spinej (Phila PA 1976). 29 (16) (2004) 1772-1781. doi: 10.1097/01.brs.0000134567.52303.1a.
[64] D. Leboeuf, K. Letellier, N. Alos, P. Edery, F. Moldovan, Do estrogens impact adolescent idiopathic scoliosis? Trends Endocrinol. Metab. 20 (4) (2009) 147-152. doi: 10.1016/ j.tem..2008.12.004.
[65] K. Letellier, B. Azeddine, S. Parent, H. Labelle, P.H. Rompre, A. Moreau, F. Moldovan, Estrogen cross-talk with the melatonin signaling pathway in human osteoblasts derived from adolescent idiopathic scoliosis patients, J Pineal. Res. 45 (4) (2008) 383-393. doi: 10.1111/ j.1600-079x.2008.00603.x.
[66] K.T. Suh, S.S. Lee, S.H. Hwang, S.J. Kim, J.S. Lee, Elevated soluble receptor activator of nuclear factor-kappa B ligand and reduced bone mineral density in patients with adolescent idiopathic scoliosis, Eur. Spine J. 16 (10) (2007) 1563-1569. doi: 10.1007/s00586-007-0390-2. [67] S. Zhou, W. Wang, Z. Zhu, X. Sun, F. Zhu, Y. Yu, B. Qian, B. Wang, G. Yin, Y. Qiu, Increased expression of receptor activator of nuclear factor-kB ligand in osteoblasts from adolescent idiopathic scoliosis patients with low bone mineral density, J Huazhong Univ. Sci. Tehnolog. Med. Sci. 32 (5) (2012) 686-690. https://doi.org/10.1007/s11596-012-1018-2.
[68] W.W. Park, K.T. Suh, J.I. Kim, S.J. Kim, J.S. Lee, Decreased osteogenic differentiation of mesenchymal stem cells and reduced bone mineral dnesity in patients with adolescent idiopathic scoliosis, Eur. Spine J. 18 (12) (2009) 1920-1926. doi: 10.1007/s00586-009-1129-z.
[69] Q. Zhuang, J. Li, Z. Wu, J. Zhang, W. Sun, T. Li, Y. Yan, Y. Jiang, R.C. Zhao, G. Qiu, 2011. Differential proteome analysis of bone marrow mesenchymal stem cells from adolescent idiopathic scoliosis patients, PLoS One. 6 (4), e18834. doi: 10.1371/journal.pone.0018834.
[70] Q. Zhuang, B. Ye, S. Hui, Y. Du, R.C. Zhao, J. Li, Z. Wu, N. Li, Y. Zhang, H. Li, S. Wang, Y. Yang, S. Li, H. Zhao, Z. Fan, G. Qiu, J. Zhang, Long noncoding RNA lncAIS downregulation in mesenchymal stem cells is implicated in the pathogenesis of adolescent idiopathic scoliosis, Cell Death Differ. 26 (9) (2019) 1700-1715. doi: 10.1038/s41418-018-0240-2.
[71] I.A. Stokes, D.D. Aronsson, Disc and vertebral wedging in patients with progressive scoliosis, J Spinal Disord. 14 (4) (2001) 317-322. doi: 10.1097/00002517-200108000-00006. [72] H.N. Modi, S.W. Suh, H.R. Song, J.H. Yang, H.J. Kim, C.H. Modi, Differential wedging of vertebral body and intervertebral disc in thoracic and lumbar spine in adolescent idiopathic scoliosis: a cross sectional study in 150 patients, Scoliosis. 3 (2008) 11. doi: 10.1186/1748-7161-3-11.
[73] R.C. Brink, T.P.C. Schlösser, M. van Stralen, K.L. Vincken, M.C. Kruyt, S.C.N. Hui, M.A. Viergever, W.C.W. Chu, J.C.Y. Cheng, R.M. Castelein. Anterior-posterior length discrepancy of the spinal column in adolescent idiopathic scolisosis-a 3D CT study, Spine J. 18 (12) (2018) 2259-2265. doi: 10.1016/j.spinee.2018.05.005.
[74] E.L. Burger, A. Noshchenko, V.V. Patel, E.M. Lindley, A.P. Bradford, Ultrastructure of intervertebral disc and vertebra-disc junctions zones as a link in etiopathogenesis of idiopathic scoliosis, Advances in Orthop. Surg. 850594 (2014). http://dx.doi.org/10.1155/2014/850594. [75] S. Mao, B. Qian, B. Shi, Z. Zhu, Y. Qiu, Quantitative evaluation of the relationship between COMP promoter methylation and the susceptibility of the relationship between COMP promoter methylation and the susceptibility and curve progression of adolescent idiopathic scoliosis, Eur. Spine J. 27 (2) (2018) 272-277. doi: 10.1007/s00586-017-5309-y.
[76] L. Aulisa, P. Papaleo, E. Pola, F. Angelini, A.G. Aulisa, F.C. Tamburrelli, P. Pola, C.A. Longroscino, Association between IL-6 and MMP-3 gene polymorphisms and adolescent idiopathic scoliosis: a case-control study, Spine (Phila Pa 1976) 32 (24) (2007) 2700-2702. doi: 10.1097/BRS.0b013e31815a5943.
[77] S. Nikolova, M. Dikova, D. Dikov, A. Djerov, G. Dzhebir, V. Atanasov, A. Savov, I. Kremensky, Role of the IL-6 gene in the etiopathogenesis of idiopathic scoliosis, Anal. Cell Pathol. (Amst). (2015) 621893. doi: 10.1155/205/621893.
[78] Q. Lin, Z.H. Wu, Y. Liu, Y.P. Wang, X.S. Weng, J. Lin, Y. Tian, J.X. Shen, H. Zhao, J.G. Zhang, G.X. Qiu, Gene expression of type X collagen in the intervertebral disc of idiopathic scoliosis patients, Zhongguo Yi Xue Ke Xue Yuan Xue Bao. 26 (6) (2004) 696-699. PMID: 15663235.
[79] K.G. Shea, T. Ford, R.D. Bloebaum, J. D'Astous, H. King, A comparison of the micro architectural bone adaptations of the concave and convex thoracic spinal facets in idiopathic scoliosis, J Bone Joint Surg. Am. 86 (5) (2004) 1000-1006. doi: 10.2106/00004623-200405000-00017.
[80] D.G. Bission, P. Lama, F, 2018. Abduljabbar, D.H. Rosenzweig, N. Saran, J.A. Oueliet, L. Haglund, Facet joint degeneration in adolescent idiopathic scoliosis, JOR Spine. 1 (2), e1016. doi: 10.1002/jsp2.1016.

[81] N. Hadley-Miller, B. Mims, D.M. Milewicz, The potential role of the elastic fiber system in adolescent AIS, J Bone Jt. Surg. [Am]. 76 (8) (1994) 1193-1206. doi: 10.2106/00004623-199408000-00010.
[82] F. Sheng, C. Xia, L. Xu, New evidence supporting the role of FBN1 in the development of adolescent idiopathic scoliosis, Spine (Phila Pa 1976). 44 (4) (2019) E225-E232. doi: 10.1097/ BRS.0000000000002809.
[83] P. Neumann, T. Keller, L. Ekstrom, E. Hult, T. Hansson, Structural properties of the anterior longitudinal ligament. Correlation with lumbar bone mineral content, Spine (Phila Pa 1976). 18 (5) (1993) 637-645. doi: 10.1097/00007632-199304000-00017.
[84] B. Haex, Back and bed: ergonomic aspects of sleeping, Boca Raton Press, 2005.
[85] L.T. Twomey, J.R. Taylor, Sagittal movements of the human lumbar vertebral column: a quantitative study of the role of the posterior vertebral elements, Arch. Phys. Med. Rehabil. 64 (7) (1983) 322-325. PMID: 6860110.
[86]: M. Fadzan, J. Bettany-Saltikov, Etiological Theories of Adolescent Idiopathic Scoliosis: Past and Present, Open Orthop J. 11 (2017) 1466–1489. doi: 10.2174/1874325001711011466. [87]: J.R. Zadeh, M.M.A. Gleiber, Adolescent Idiopathic Scoliosis: An in Depth Analysis and Historical Review, Orthoped. and Rheum. 3 (4) (2015). doi: 10.15406/jojor.2015.03.00105. [88]: R.D. Loynes, Scoliosis after thoracoplasty, J Bone Joint Surg Br. 54 (3) (1972) 484-98. PMID: 5053892.
[89]: N. Kawakami, R.B. Winter, J.E. Lonstein, F. Denis, Scoliosis secondary to rib resection. J Spinal Disord. 7 (6) (1994) 522-527. PMID: 7873852.
[90] R. Roaf, Rotation movements of the spine with special reference to scoliosis. The J of Bone and Joint Surg. 40-B (2) (1958) 312-332. doi: 10.1302./0301-620X40B2.312.
[91] J.A. Sevastik, S. Aaro, H. Normelli, Scoliosis. Experimental and clinical studies, Clin. Orthop. Relat. Res. 191 (1984) 27-34. PMID: 6499319
[92] J.A. Sevastik, R.G. Burwell, P.H. Dangerfield, A new concept for the etiopathogenesis of the thoraco-spinal deformity of idiopathic scoliosis: summary of an electronic focus group debate of the IBSE. Eur Spine J. 12 (4) (2003) 440–450. doi: 10.1007/s00586-002-0489-4.
[93] P.G. Korovessis, P. Iliopoulos, G. Koureas, S. Zacharatos, P. Stergiou, Evolution of anterior chest wall blood supply in female adolescents with progressive right-convex thoracic idiopathic scoliosis, J. Spinal Disord. Tech. 20 (3) (2007) 190-194. doi: 10.1097/01.bsd.0000211267.66615.ac.
[94] T.B. Grivas, E. Vasiliadis, C. Mihas, The effect of growth on the correlation between the spinal and rib cage deformity: implications on idiopathic scoliosis pathogenesis, Scoliosis. 2 (2007) 11. https://doi.org/10.1186/1748-7161-2-11.
[95] W.T. McNicholas, Impact of sleep on respiratory muscle function, Monaldi Arch. Chest Dis. 57 (5-6) (2002) 277-280. PMID: 12814041.
[96] E. Tabachnik, N.L. Muller, A.C. Bryan, H. Levison, Changes in ventilation and chest wall mechanics during sleep in normal adolescents, J Appl. Physiol. Respir. Environ. Exerc. Physiol. 51 (3) (1981) 557-564. doi: 10.1152/jappl.1981.513.557.
[97] A.C. Bryan, N.L. Muller, Lung mechanics and gas exchange during sleep, Sleep. 3 (3-4) (1980) 401-406. doi: 10.1093/sleep/3.3-4.401.
[98]: (76). J.A. Sevastik, M. Agadir, B. Sevastik, Effects of rib elongation on the spine. II. Correction of scoliosis in the rabbit. Spine. 15 (8) (1990) 826–829. doi: 10.1097/00007632-199008010-00016.
[99] T.P. Schlösser, M. van Stralen, W.C.W. Chu, T.P. Lam, B.K.W. Ng, K.L. Vincken, J.C.Y. Yeung, R.M. Castelein, 2016. Anterior overgrowth in primary curves, compensatory curves and junctional segments in adolescent idiopathic scoliosis, PLoS One. 11(7), e0160267. doi: 10.1371/ fournal.pone.0160267
[100] H.J. Crawford, G.A. Jull, The influence of thoracic posture and movement on range of arm elevation, Physiother. Theory and Pract. 9 (1993) 143-148. doi: 10.3109/09593989309047453.
[101] S.J. Edmondston, A. Ferguson, P. Ippersiel, L. Ronningen, S. Sodeland, L. Barclay, Clinical and radiological investigation of thoracic spine extension motion during bilateral arm elevation, J of Orthop.& Sports Phys. Ther. 42 (10) (2012) 861-869. doi: 10.2519/ jospt.2012.4164.
[102] D. Theodoridis, S. Ruston, The effect of shoulder movements on thoracic spine 3D motion, Clin. Biomech. (Briston, Avon). 17 (2002) 418-421. doi: 10.1016/s0268-0033(02)00026-8.
[103] F. Zhu, W.C. Chu, G. Sun, Z.Z. Zhu, W.J. Wang, J.C. Cheng, Y. Qiu, Rib length asymmetry in thoracic adolescent idiopathic scoliosis: Is it primary or secondary? Eur. Spine J. 20 (2) (2011) 254–259. doi: 10.1007/s00586-010-1637-x.
[104] T. Huysmans, B. Haex, T. De Wilde, R. Van Audekercke, J. Vander Sloten, G. Van Der Perre, A 3D active shape model for the evaluation of the alignment of the spine during sleeping, Gait & Posture. 25 (2004) 54-61. doi: 10.1016/j.gaitpost.2005.07.002.

[105] T.B. Grivas, R.G. Burwell, V. Kechagias, C. Mazioti, A. Fountas, D. Kolovou, Idiopathic and normal lateral lumbar curves: muscle effects interpreted by 12th rib length asymmetry with pathomechanic implications for lumbar idiopathic scoliois, Scoliosis Spinal Disord. 11 (Suppl 2) (2016) 35. http://doi.org/10.1186/s13013-016-0093-8.
[106] S.P. Gombatto, T. Brock, A. DeLork, J. Glynis, E. Madden, C. Rinere, Lumbar spine kinematics during walking in people with and people without low back pain, Gait & Posture. 42 (2015) 539-544. doi: 10.1016/j.gaitpost.2015.08.010.
[107] J. Crosbie, R. Vachalathiti, R. Smith, Age, gender and speed effects on spinal kinematics during walking. Gait & Posture. 5 (1997) 13-20. http://doi.org/10.1016/S0966-6362(96)01068-5.
[108] M. Latalski, A. Danielewicz-Bromberek, M. Fatyga, M. Latalska, M. Kröber, P. Zwolak, Current insights into the aetiology of adolescent idiopathic scoliosis, Archives of Orthop. and Trauma Surg. 137 (2017) 1327-1333. doi: 10.1007/s00402-017-2756-1.
[109] H-K. Wong, J.H.P. Hui, U. Rajan, H-P. Chia, Idiopathic scoliosis in Singapore schoolchildren: a prevalence study 15 years into the screening program, Spine. 30 (10) (2005) 1188-1196. doi: 10.1097/01.brs.0000162280.95076.bb.
[110] T.B. Grivas, E. Vasiliadis, V. Mouzakis, C. Mihas, G. Koufopoulos, Association between adolescent idiopathic scoliosis prevalence and age at menarche in different geographic latitudes, Scoliosis. 1 (2006) 9. doi: 10.1186/1748-7161-1-9.
[111] I.A.F. Stokes, H. Spence, D.D. Aronsson, N. Kilmer, Mechanical effects on skeletal growth, Musculoskel. Neuron. Interact. 2 (3) (2002) 277-280. PMID: 15758453.
[112] T.B. Grivas, O.D. Savvidou, Melatonin the "light of night" in human biology and adolescent idiopathic scoliosis, 2 (2007) 6. doi: 10.1186/1748-7161-2-6.
[113] I.A.F. Stokes, H. Spence, D.D. Aronsson, N. Kilmer, Mechanical modulation of vertebral body growth: implications for scoliosis progression, Spine. 21 (10) (1996) 1162-1167. doi: 10.1097/00007632-199605150-00007.
[114] P. Dolan, M. Earley, M.A. Adams, Bending and compressive stresses acting on the lumbar spine during lifting activities, J. Biomech. 27 (10) (1994) 1237-1248. doi: 10.1016/0021-9290(94)90277-1.
[115] L. Kingma, C.T. Baten, P. Dolan, H.M. Toussaint, J.H. van Dieen, M.P. de Looze, Lumbar loading during lifting: a comparative study of three measurement techniques, J. Electromyogr. Kinesio. 11 (5) (2001) 337-345. doi: 10.1016/s1050-6411(01)00011-6.
[116] T.R. Oxland, Fundamental biomechanics of the spine--what we have learned in the past 25 years and future directions, J. Biomech. 49 (2016) 817-832. doi:10.1016/j.jbiomech.2015.10.035. [117] M.M. Panjabi, R.A. Brand, A.A. White, Mechanical properties of the human thoracic spine as shown by three-dimensional load-displacemtn curves, J. Bone Joint Surg. Am. 58 (5) (1976) 642-652. PMID: 932062.
[118] D. Cary, K. Briffa, L. McKenna. (2019) Identifying relationships between sleep posture and non-specific spinal symptoms in adults: a scoping review, BMJ Open. 9 (6), e027633.
[119] M. Krismer, C. Haid, W. Rabl, The contribution of anulus fibers to torque resistance, Spine (Phila Pa 1976) 21 (1996) 2551-2557. doi: 10.1136/bmjopen-2018-027633.
[120] T.B. Grivas, E. Vasiliadis, M. Malakasis, V. Mouzakis, D. Segos, Intervertebral disc biomechanis in the pathogenesis of idiopathic scoliosis, Stud. Health Technol. Inform. 123 (2006) 80-83. doi: 10.3233/978-1-60750-935-6-25.
[121] R.E. Will, I.A. Stokes, X. Qiu, M.R. Walker, J.O. Sanders, Cobb angle progression in adolescent scoliosis begins at the intervertebral disc, Spine (Phila Pa 1976). 34 (25) (2009) 2782-2786. doi: 10.1097/BRS.0b013e3181c11853.
[122] E.L. Burger, A. Noshchenko, V.V. Patel, E.M. Lindley, A.P. Bradford, Ultrastructure of intervertebral disc and vertebra-disc junctions zones as a link in etiopathogenesis of idiopathic scoliosis, Advan. in Orthop. Surg. 4 (2014) 23. https://doi.org/10.1155/2014/850594.
[123] C.C. Shu, J. Melrose, The adolescent idiopathic scoliotic IVD displays advanced aggrecanolysis and a glycosaminoglycan composition similar to that of aged human and ovine (sheep) IVDs, Eur. Spine J. 27 (9) (2018) 2102-2113. doi: 10.1007/s00586-018-5515-2.
[124] J. Antoniou, V. Arlet, T. Goswami, M. Aebi, M. Alini, Elevated synthetic activity in the convex side of scoliotic intervertebral discs and endplates compared with normal tissues, Spine (Phila Pa 1976) 26 (10) (2001) E198-E206. doi: 10.1097/00007632-200105150-00002.
[125] S. Roberts, J. Menage, S.M. Eisenstein, The cartilage end-plate and intervertebral disc in scoliosis: calcification and other sequelae, J. Orthop. Res. 11 (1993) 747-757. doi: 10.1002/ jor.1100110517.
[126] R.C. Brink, T.P.C. Schlosser, D. Colo, Anterior spinal overhgrowth is the result of the scoliotic mechanism and is located in the disc, Spine (Phila Pa 1976) 42 (11) (2017) 818-822. doi: 10.1097/BRS.0000000000001919.

[127] A. Maroudas, H. Evans, (1972) Study of Ionic Equilibria in Cartilage. Connective Tissue Res. 1 (1) (1972) 69-77. doi: 10.3109/0300820709152058.
[128] T.B. Grivas, The diurnal variation "accordion"-like phenomenon of wedged intervertebral discs: a progression factor in idiopathic scoliosis, Ann Pediatr. Child Health. 9 (5) (2021) 1241.
[129] T. Takarada, A. Kodama, S. Hotta, Clock genes influence gene expression in growth plate and endochondral ossification in mice, J. Biol. Chem. 287 (43) (2012) 36081-36095. doi: 10.1074/jbc.M112.408963.
[130] S. Onuora, Chondrocyte clock maintains cartilage tissue, Nature Reviews Rheum. 12 (2016) 71. https://doi.org/10.1038/nrrheum.2015.183.
[131] Z. Ma, X. Jin, Z. Qian, F. Li, M. Xu, Y. Zhang, X. Kang, H. Li, X. Gao, L. Zhao, Z. Zhang, Y. Zhang, S. Wu, H. Sun, Deletion of clock gene Bmal1 impaired the chrondrocyte function due to disruption of the HIF1α-VEGF signaling pathway, Cell Cycle. 18 (13) (2019) 1473-1489. doi: 10.1080/15384101.2019.1620572.
[132] Y. Fujihara, H. Kondo, T. Noguchi, A. Togari, Glucocorticoids mediate circadian timing in peripheral osteoclasts resulting in the circadian expression rhythm of osteoclast-related genes, Bone. 61 (2014) 1-9. doi: 10.1016/j.bone.2013.12.026.
[133] S. Komoto, H. Kondo, O. Fukuta, A. Togari, Comparison of beta-adrenergic and glucocorticoid signaling on clock gene and osteoblast-related gene expressions in human osteoblast, Chronobiology Int. 29 (2012) 66-74. https://doi.org/10.3109/074205.28.2011.636496. [134] T. Takarada, C. Xu, H. Ochi, R. Nakazato, D. Yamada, S. Nakamura, A. Kodama, S. Shimba, M. Mieda, K. Fukasawa, K. Ozaki, T. Iezaki, K. Fujikawa, Y. Yoneda, R. Numano, A. Hida, H. Tei, S. Takeda, E. Hinoi, Bone resorption is regulated by circadian clock in osteoblasts, J. of Bone and Min. Res. 32 (2017) 872-881. doi: 10.1002/jbmr.305.3.
[135] C.F. Goncalves, Q.J. Meng, Timing metabolism in cartilage and bone: links between circadian clocks and tissue homeostasis. J Endocrinol, 243 (3) (2019) R29-R46. doi: 10.1530/ JOE-19-0256.
[136] C.M. Swanson, W.M. Kohrt, O.M. Buxton, C.A. Everson, K.P. Wright Jr., E.S. Orwoll, S.A. Shea, The importance of the circadian system & sleep for bone health, Metabolism. 84 (2018) 28-43. doi: 10.1016/j.metabol.2017.12.002.
[137] M. Hettiarachchi, R. Cooke, C. Norton, P. Jakeman, Temporal change in biomarkers of bone turnover following late evening ingestion of a calcium-fortified, milk-based protein matrix in postmenopausal women with osteopenia. Nutrients. 11 (6) (2019) 1413. doi: 10.3390/ nu11061413.
[138] K.J. Noonan, C.E. Farnum, E. Leiferman, M. Laml, M.D. Markel, N.J. Wilsman, Growing pains: are they due to increased growth during recumbency as documented in a lamb model? J. of Ped. Orthop. 24 (6) (2004) 726-731. doi: 10.1097/00004694-200411000-00024.
[139] E. Arrigoni, M.C. Chen, P.M. Fuller, The anatomical, cellular and synaptic basis of motor atonia during rapid eye movement sleep. J. Physiol. 594 (19) (2016) 5391-5414. doi: 10.1113/ JP271324.
[140] R.G. Burwell, E.M. Clark, P.H.Dangerfield, A. Moulton, Adolescent idiopathic scoliosis (AIS): a multifactorial cascade concept for pathogenesis and embryonic origin. Scoliosis Spinal Disord. 11 (2016) 8. http://doi.org/10.1186/s13013-016-0063-1.
[141] X. Qiu, X. Sun, X. Qiu, W. Li, Z. Zhu, F. Zhu, B. Wang, Y. Yu, B. Qian, Decreased circulating leptin level and its association with body and bone mass in girls with adolescent idiopathic scoliosis, Spine (Phila Pa 1976). 32 (24) (2007) 2703-2710. doi: 10.1097/ BRS.0b013e31815a59e5.
[142] T.B. Grivas, R.G. Burwell, C. Mihas, E.S. Vasiliadis, G. Triandaffylopoulos, A. Kaspiris, Relatively lower body mass index is associated with an excess of severe truncal asymmetry in healthy adolescents. Do body fat, leptin, hypothalamus and sympathetic nervous system influence truncal growth asymmetry? Scoliosi 4 (1) (2009) 13. doi: 10.1186/1748-7161-4-13. [143] E.M. Tam, Z. Liu, T.P. Lam, T. Ting, G. Cheung, B.K.Ng, S.K. Lee, Y. Qiu, J.C. Cheng, Lower muscle mass and body fat in adolescent idiopathic scoliosis are associated with abnormal leptin bioavailability, Spine. 41 (11) (2016) 940-946. doi: 10.1097/BRS.0000000000001376. [144] E.M. Clark, H.J. Taylor, I. Harding, J. Hutchinson, I. Nelson, J.E. Deanfield, A.R. Ness, J.H. Tobias, Association between components of body composition and scoliosis: a prospective cohort study reporting differences identifiable before the onset of scoliosis, J. Bone Miner. Res. 29 (8) (2014) 1729-1736. doi: 10.1002/jbmr.2207.
[145] C.A. Olson, N.A. Hamilton, V.K. Somers, Percentage of REM sleep is associated with overnight change in leptin, J. Sleep Res. 25 (4) (2016) 419-425. doi: 10.1111/jsr.12394.
[146] C. Barrios, S. Cortes, C. Perez-encinas, M.D. Escriva, I. Benet, J. Burgos, E. Hevia, G. Piza, Anthropometry and body composition profile of girls with non surgically treated adolescent idiopathic scoliosis, Spine (Phila Pa 1976). 36 (18) (2011) 1470-1477. doi: 10.1097/ BRS.0b013e3181f55083.
[147] Y. Qui, X.S. Qiu, X. Sun, B. Wang, Y. Yu, Z.Z. Zhu, B.P. Qian, F. Zhu, Z. Liu, [Body mass index in girls with adolescent idiopathic scoliosis]. [Article in Chinese] Zhonghua Wai Ke Za Zhi 46 (8) (2008) 588-591. PMID 18844053.

[148] O. Hershkovich, A. Friedlander, B. Gordon, H Arzi, E. Derazne, D. Tzur, A. Shamiss, A. Afek, Association between body mass index, body height, and the prevalence of spinal deformities, Spine J. 14 (2014) 1581-1587. doi: 10.1016/j.spinee.2013.09.034.
[149] K.M. Awad, A.A. Drescher, A. Malhotra, S.F. Quan, Effects of exercise and nutritional intake on sleep architecture in adolescents, Sleep and Breathing, 17 (1) (2013) 117-124. doi: 10.1007/s11325-012-0658-6.
[150] E. Benefice, D. Garnier, G. Ndiaye, Nutritional status, growth and sleep habits among Senegalese adolescent girls, Eur. J. of Clin. Nutr. 58 (2004) 292-301. https://doi.org/10.1038/ sj.ejcn.1601781.
[151] P.E. Brockmann, D. Gozal, L. Villarroel, F. Damiani, F. Nunez, C. Cajochen, Geographic latitude and sleep duration: A population-based survey from the Tropic of Capricorn to the Antarctic Circle, Chronobiol.Int. 34 (3) (2017) 373-381. doi: 10.1080/07420528.2016.1277735. [152] S.L. Weinstein, Natural history, Spine (Phila Pa 1976) 24 (24) (1999) 2592-2600. doi: 10.1097/00007632-199912150-00006.
[153] S. Negrini, L. Aulisa, C. Ferraro, P. Fraschini, S. Masiero, P. Simonazzi, C. Tedeschi, A. Venturin, Italian guidelines on rehabilitation treatment of adolescents with scoliosis or other spinal deformities, Eura Medicophys. 41 (2) (2005) 183-201. PMID: 16200035.
[154] S. Negrini, A.G. Aulisa, L. Aulisa, A.B. Circo, J.C. de Mauroy, J. Durmala, et al, SOSORT guidelines: orthopaedic and rehabilitation treatment of idiopathic scoliosis during growth, Scoliosis. 7 (1) (2011) 3. doi: 10.1186/1748-7161-7-3.
[155] H-K. Wong, J.H.P. Hui, U. Rajan, H-P. Chia, Idiopathic scoliosis in Singapore schoolchildren: a prevalence study 15 years into the screening program, Spine. 30 (10) (2005) 1188-1196. doi: 10.1097/01.brs.0000162280.95076.bb.
[156] T.B. Grivas, E. Vasiliadis, V. Mouzakis, C. Mihas, G. Koufopoulos, Association between adolescent idiopathic scoliosis prevalence and age at menarche in different geographic latitudes, Scoliosis. 1 (2006) 9. doi: 10.1186/1748-7161-1-9.
[157] R.A. Dickson, Scoliosis in the community, Br. Med. J.Clin. Res. Ed. 286 (6379) (1983) 1745. doi: 10.1136/bmj.286.6379.1745-b.
[158] M. Emmanuel, B.R. Bokor. (2021) Tanner Stages, StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing.
[159] D.A. Klein, J.E. Emerick, J.E. Sylvester, K.S. Vogt, Disorders of puberty: an approach to diagnosis and management, Am. Fam. Phys. 96 (9) (2017) 590-599. PMI: 29094880.
[160] L. Ameryckx, M. Leunen, P. Wylock, J.J. Amy, Breast problems in children and adolescents, Eur. Clinics Obstet. Gynaecol. 1 (2005) 151-163. doi: 10.1007/s11296-005-0009-2. [161] D.J.P. Parker, C. Osmond, K.L. Thornburg, E. Kajantie, G. Eriksson, A possible link between the pubertal growth of girls and ovarian cancer in their daughters, Am. J. Hum. Biol. 20 (6) (2008) 659-662. doi: 10.1002/ajhb.20789.
[162] T. B. Grivas, R.G. Burwell, M. Purdue, J.K. Webb, A. Moulton, Segmental patterns of rib- vertebra angles in chest radiographs of children: changes related to rib level, age, sex, side and significance for scoliosis, Clinical Anatomy. 5 (4) (1992) 272-288. https://doi.org/10.1002/ ca.980050404.
[163] T.B. Grivas, R.G. Burwell, M. Purdue, J.K. Webb, A. Moulton, A segmental analysis of thoracic shape in chest radiographs of children. Changes related to spinal level, age, sex, side and significance for lung growth and scoliosis, J. Anat. 178 (1991) 21-38. PMID: 1810928. PMCID:PMC1260532.
[164] L.G. Lenke, R.R. Betz, J. Harms, K.H. Bridwell, D.H. Clements, T. G. Lowe, et al, Adolescent idiopathic scoliosis: a new classification to determine extent of spinal arthrodesis, J. Bone Joint Surg. Am. 83-A (8) (2001) 1169-1181. PMID: 11507125.
[165] S.M. Scharoun, P.J. Bryden, Hand preference, performance abilities, and hand selection in children, Front. Psychol. 5 (2014) 82. doi: 10.3389/fpsyg.2014.00082.
[166] C. Barut, O. Sevine, M. Gumus, C. Ozer, Relationships between hand and foot preferences, Int. J. of Neuroscience. 117 (2) (2007) 177-185. doi: 10.1080/00207450600582033. [167] C. Goldberg, F.E. Dowling, Handedness and scoliosis convexity: a reappraisal, Spine 15 (2) (1990) 61-64. doi: 10.1097/00007632-199002000-00001.
[168] T.B. Grivas, E.S. Vasiliadis, V.D. Polyzois, V. Mouzakis. Trunk asymmetry and handedness in 8245 school children. Pediatric. Rehab. 9 (3) (2006) 259-266. https://doi.org/ 10.1080/10428190500343027
[169] J. Warland, J. Dorrian, 2014. Accuracy of self-reported sleep position in late pregnancy, PLoS ONE. 9, e115760. doi: 10.1371/journal.pone.0115760.
[170] S.J. Gordon, K.A. Grimmer, P. Trott, Self-reported versus recorded sleep position an observational study, Internet J of Allied Health Sciences and Practice. 2 (1) (2004). http:// nsuworks.nova.edu//ijahsp/vol2/iss1/7/.
[171] K. Russo, M.T. Bianchi, How reliable is self-reported body position during sleep?, J of Clin. Sleep Med. 12 (2016) 127-128. https://doi.org/10.5664/jcsm.5410.

[172] C. Kai-Ching Yu, Why is self-report of sleep position sometimes unreliable? Sleep and Hypnosis: A J of Clin. Neuroscience and Psychopathology. 20 (2) (2018) 105-113. http:// dx.doi.org/10.5350/Sleep.Hypn.2017.19.0140.
[173] S. Negrini, S. Donzelli, A.G. Aulisa, 2016 SOSORT guidelines: orthopaedic and rehabilitation treatment of idiopathic scoliosis during growth, Scoliosis Spinal Disord. 13 (3) (2018) 3. https://doi.org/10.1186/s13013-017-0145-8.