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ORIGINAL ARTICLE

The role of pineal gland volume in the development of scoliosis

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Abstract

Purpose Adolescent idiopathic scoliosis (AIS) is believed to be caused by genetic, neurological, osseous growth anomalies, histological variables including muscle fiber percentage and core structure changes, metabolic and hormonal dysfunction, vestibular dysfunction, and platelet microarchitecture. The objective of this study was to contribute to the determination of the cause of AIS by analyzing the changes in pineal gland volume in AIS cases.

Methods Study (AIS) and control group were each comprised of 26 patients who met the inclusion requirements. Scoliosis radiograph and MRI of the pineal glands were used for radiological examinations. The distribution of age, gender, Risser grading for skeletal radiological development, and sexual maturation according to Tanner categorization were uniform and statistically insignificant between groups.

Results When the pineal gland volumes of the cases were evaluated according to age, the AIS group was found to have significantly reduced pineal gland volumes in all age groups. The pineal gland volume was found to be 38.1% lower in the AIS group compared to the control group ($p<0.001$). In the AIS group, patients aged 13 years had the lowest pineal gland volume (77.2 ± 13.86 mm^3), while patients aged 15 years had the highest volume (97.9 ± 16.47 mm^3).

Conclusion Changes in pineal gland volume support the role of the pineal gland in the etiopathogenesis of AIS.

Keywords Pineal gland · Pineal gland volume · Scoliosis · Adolescent · AIS

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Introduction

The stability of the entire spine depends on the vertebrae, thoracic and lumbar muscles, and ligaments, as well as intervertebral discs. Imbalance in any of these components impairs stability. This imbalance results in deformity in the rapid growth adolescence period [1].

Adolescent idiopathic scoliosis (AIS) is a three-dimensional spinal deformity involving one or more segments of the spine, characterized by vertebral rotation in the transverse plane, lateral curvature in the frontal plane, and also often abnormal alignment in the sagittal plane [2, 3]. It is known that this phenomenon is seen at a higher rate in girls between the ages of 11 and 18 [3]. Although the etiopathogenesis of AIS is still unknown exactly, it is thought to be caused by genetic, neurological, osseous growth anomalies, histological factors including muscle fiber percentage and core structure changes, metabolic and hormonal dysfunction, vestibular dysfunction, and platelet microstructure [1, 4–6].

Experimental animal models in the literature focus on many hypotheses regarding the pathogenesis of AIS. An important part of these hypotheses is deficiency of the hormone melatonin, which is necessary for the symmetrical development of paraspinal muscles and straight spine growth, and melatonin signal dysfunction [3, 7, 8]. Melatonin, also known as N-acetyl-5-methoxytryptamine, is the main hormone secreted by the pineal gland [3]. The pineal gland is a neuroendocrine gland located in the posterior wall of the third ventricle in the center of the brain. It can be easily said that there is a direct proportion between melatonin secretion and pineal gland volume [9].

Some experimental studies show that scoliosis develops in rats and chickens undergoing pinealectomy, and there is a close relationship between the pineal gland and the hormones it secretes and scoliosis [10, 11]. In some studies, it has been reported that melatonin levels in individuals with scoliosis are significantly reduced compared to healthy individuals [7, 12–14]. The role of the pineal gland in the pathogenesis of human AIS therefore necessitates further research.

The fact that the several animal subjects used in the experimental studies do not adequately reflect the characteristics of the human spine is perhaps the most influential factor in the research results. Since human experiments are limited in number, studies on patients with AIS make important and indispensable. By analyzing the volume changes in the pineal gland in AIS cases, this study hoped to contribute to the understanding and determination of the causes of AIS.

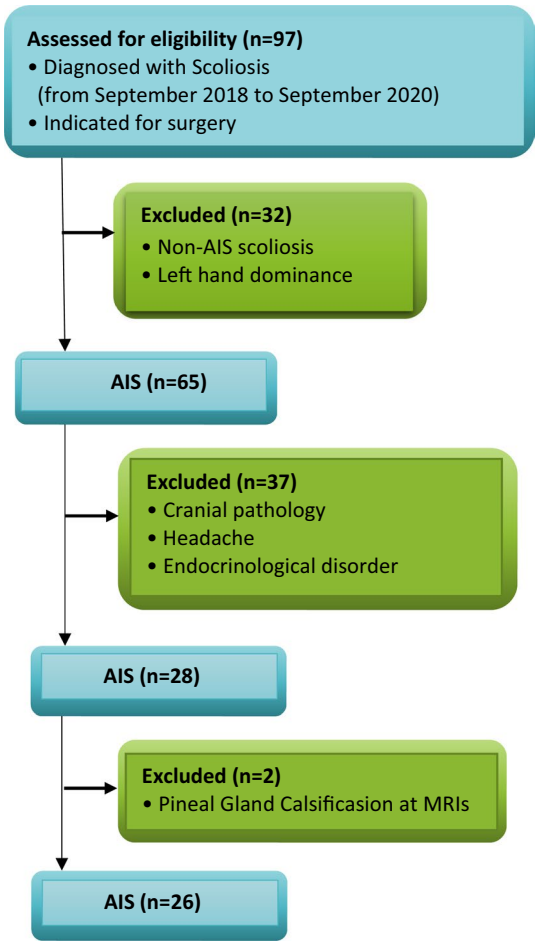
Methods

This single-center, randomized control, prospective and cross-sectional cohort study was conducted at Kayseri City Education and Research Hospital, Department of Orthopedics and Traumatology, in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from each patient and/or his/her legal guardian. And also, this study was approved by the Local Ethics Committee with decision # 2021/538.

Determination of sample size and study groups

The sample of this study was determined by power analysis with G power 3.1.9.4. program as $\alpha = 0.05$, $\beta = 0.10$, effect size = 0.80; each study and control group should consist of at least 21 patients. Between September 2018 and September 2020, study (AIS) and control group were formed from 26 patients in each group, meeting the inclusion criteria for both (Table 1). Since the incidence of AIS is significantly higher

Table 1 Flow diagram of study according to inclusion and exclusion criteria.



in favor the female gender, only female cases were included in the study and control groups for optimal homogenization. In this study, the control group was selected by block randomization from the social pediatrics outpatient clinic of the center where the study was conducted, considering gender, age, race, and sociocultural similarities with the study group between the dates of the study. Clinical sexual maturity rating was evaluated for both group patients with Tanner classification.

AIS group inclusion criteria were diagnosed with AIS and indicated for surgery (Cobb angle > 45°-55°), 10–18 years old, and right hand dominance. *Control group inclusion criteria* were according to clinical scoliometric examination, postural analysis, and radiological evaluation; there is no postural deformity, 10–18 years old, and right-hand dominance.

Exclusion criteria for both groups were the story of head injury, headache, back injury, weakness or numbness in any extremity, a history of cranial surgery for any reason, a history of endocrinologically diagnosed disease and/or related syndrome, and pineal gland calcifications at magnetic resonance images (MRIs) (Table 1).

Radiological evaluation

A two-way mixed-effects model and intra-class correlation coefficients (ICC) were used to evaluate agreement and differences between intra- and inter-observer measurements for radiological evaluations of scoliosis. ICC values less than 0.5 are considered to have poor reliability, values between 0.5 and 0.75 have moderate reliability, values between 0.75 and 0.9 have good reliability, and values greater than 0.90 have excellent reliability.

Intra- and inter-observer reliability was evaluated based on scoliosis measurements from all subjects repeated twice with an interval of one month by two orthopedic surgeons with at least 10 years of professional experience and one radiology specialist with 10 years of professional experience in a double-blind manner.

Intra- and inter-observer reliability was evaluated based on pineal gland measurements from all subjects repeated twice with an interval of one month by one clinical neuroanatomist with at least 10 years of professional experience and one radiology specialist with 10 years of professional experience in a double-blind manner. Intra- and inter-observer reliability was determined to be excellent (ICC:0.985–0.992) and good (ICC: 0.870–0.965), respectively.

Anteroposterior, lateral standing, and side (left/rightward)-bending radiographs were taken by *Philips C57, Germany* scoliometric X-ray device by the same radiological technician. For the standardization of the plain radiographs, the patient is positioned 72 inch (183 cm) from the radiation source with the feet a shoulder-width apart and the knees extended. On the lateral images, the patient looks straight ahead with elbows flexed and hands placed over the clavicles. This keeps the upper extremities from being superimposed over the spine on the lateral view. Cobb angle, sagittal and coronal balance, and Risser grading for skeletal radiological maturity were measured.

Pineal gland radiological evaluations were performed with a *Siemens Magnetom Skyra, Netherlands* 3 T (Tesla) MRI device. T1-weighted magnetization prepared rapid acquisition with gradient echo (MPRAGE) sequence was used to visualize the anatomical structures of the brain. The corpus callosum and the upper colliculus, the posterior part of the third ventricle, and the quadrigeminal cistern were stated as the anatomical landmarks to define the pineal gland (Fig. 1). T1-weighted MPRAGE sequence: sagittal, repetition time (TR) = 2300 ms, echo time (TE) = 3.4 ms, flip angle = 9°, FOV = 250 × 250 mm2, voxel size = 1 x 1 x 1, matrix = 256 × 256, slice thickness = 1 mm. In this study, the Insight Segmentation and Registration Tool Kit (ITK -SNAP) program was used for the segmentation of the pineal. In the ITK-SNAP program, there are two different modes for segmentation, manual and semi-automatic (Fig. 2). In our study, pineal gland volume was calculated using a semi-automatic segmentation algorithm in ITK-SNAP. The segmentation process was performed by loading the MRI data obtained in Digital Imaging and Communications in Medicine (DICOM) format into the ITK-SNAP toolkit. After the ITK-SNAP program application, "Active Label" and "Draw-Over" settings were made in the "Quick Label Picker" tab, the "interpolate Labels" option under the "Tool" tab was selected and the pineal gland volume was calculated in the sagittal plane. The algorithm classifies pixels corresponding to pineal gland volume in all MRI data slices and calculates the volume in mm^3 (Fig. 3).

Statistical analysis

In this study, the normal distribution analysis of data was performed using 5 parameters (Skewness-Kurtosis, Histogram, mean ± Standard deviation (SD), Q-Q plots, Shapiro Wilk Test). Since the data got a score above 3, it was accepted that they met the normal distribution condition and the parameters were shown as mean ± SD. Independent samples t test was used for comparisons between two groups. The comparison of the results among different groups was carried out by one-way ANOVA, followed by Tukey multiple comparisons test, and a value of $p < 0.05$ was accepted as significant. Statistical analysis of this study was done with IBM SPSS 23.0 software.

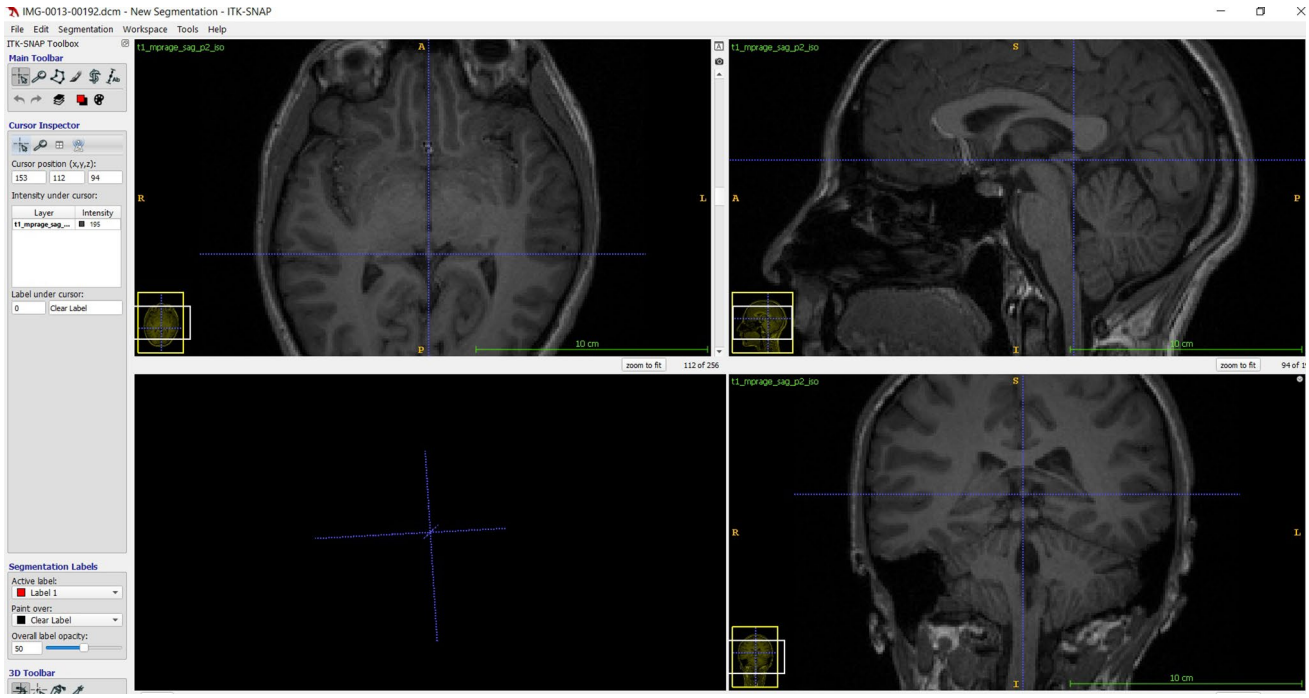


Fig. 1 Determination of the pineal gland according to the anatomical landmarks at T1-weighted magnetization prepared with MPRAGE sequence

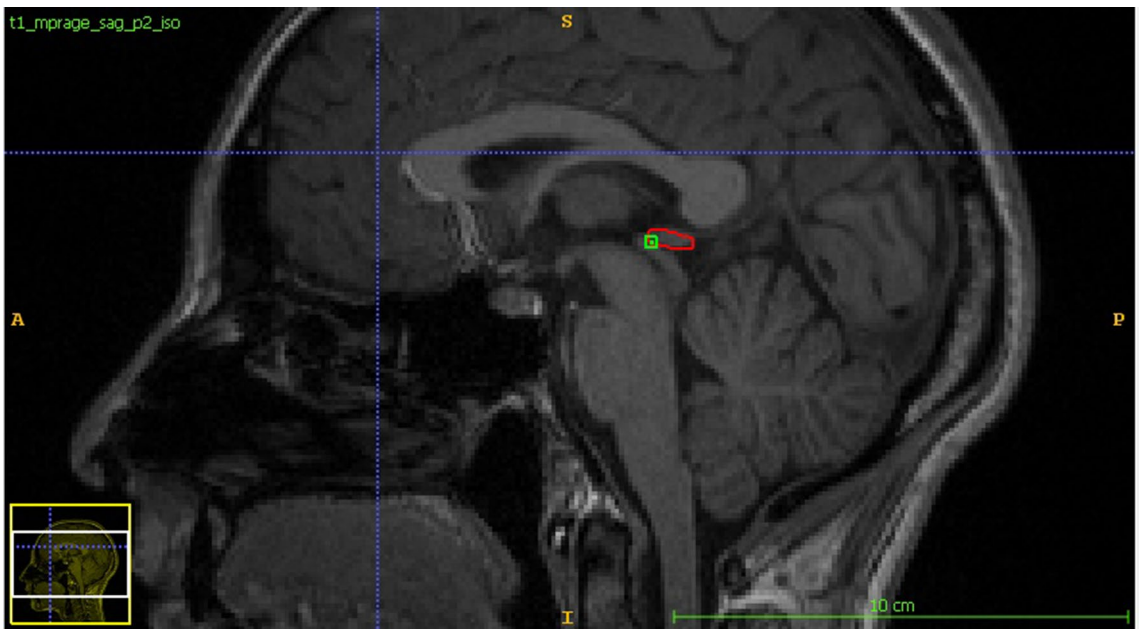


Fig. 2 The segmentation of the pineal gland with ITK-SNAP program

Results

The age, gender, Risser grading for skeletal radiological maturity, and sexual maturation with Tanner classification were homogeneously distributed, and statistically insignificant between groups ($p = 0.214$) (Table 2). The average Cobb angle in the AIS group was 50.1 ± 2.95 degrees. The mean pineal gland volume of the AIS group was 86.5 ± 22.02 mm^3, while it was 144.6 ± 41.46 mm^3 in the

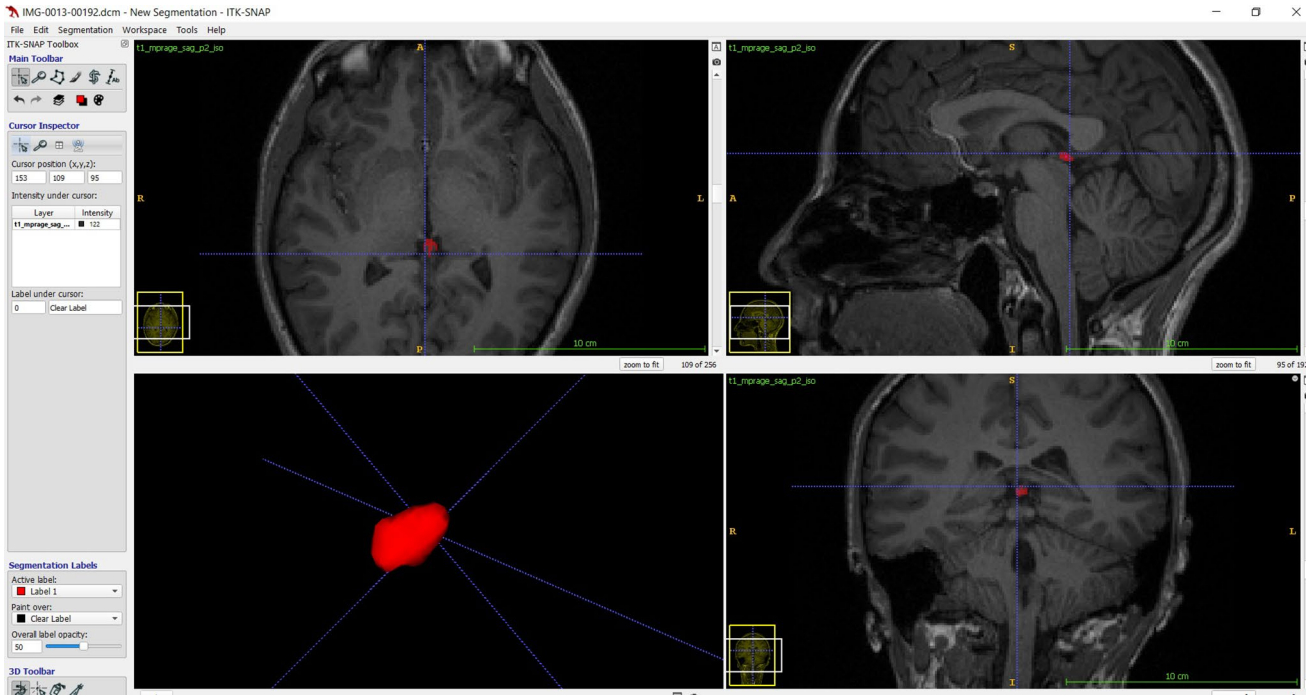


Fig. 3 The calculation of pineal gland volume in mm.[3]

Table 2 Demographic data of the cases in both groups

	AIS Group (mean ± SD, $n = 26$)	Control Group (mean ± SD, $n = 26$)	p
Gender	26 F	26 F	
Age (years)	14.4 ± 2.15	14.7 ± 2.45	0.124
Cobb Angle (°)	50.1 ± 2.95		
BMI (kg/m^2)	20.2 ± 2.45	20.4 ± 1.67	0.093
PGV (mm^3)	86.5 ± 22.02	144.6 ± 41.44	0.0003*

SD, standard deviation; F, female; BMI, body mass index; PGV, pineal gland volume

*Statistically significant

control group. The pineal gland volume was found to be 38.1% lower in the AIS group compared to the control group, and this difference between the groups was statistically significant (p = 0.0003) (Table 2).

The pineal gland volumes of the cases were analyzed according to age, and the pineal gland volumes of the patients in the AIS group were found to be significantly lower in all age groups ($p < 0.05$) (Fig. 4). Pineal gland volume was measured as the lowest in the AIS group. In patients aged 13 years old, the pineal volume was 77.2 ± 13.86 mm3; on the other hand, the pineal volume was 97.9 ± 16.47 mm^3 which was highest in patients aged 15 years old. In the control group, the pineal gland volume was measured in 16-year-old cases as 113.3 ± 13.75 mm^3 and the lowest pineal gland volume was 197.9 ± 16.47 mm^3-12-years-old cases (Fig. 5).

BMI of the AIS and control groups was statistically similar (20.2 ± 2.45 kg/m^2 and 20.4 ± 1.67 kg/m^2, respectively; $p > 0.05$). When the BMI of the cases was examined according to age, similar measurements were taken in the cases aged 16 years, while it was measured that the AIS group cases at the ages of 13, 14, and 17 years, and the cases in the control group at other ages had higher values (Fig. 6). However, this value was not statistically significant ($p = 0.124$).

Discussion

In addition to the unknowns in the etiopathogenesis of AIS, the decrease in the volume of the pineal gland makes the role of the pineal gland indisputable in the development of scoliosis.

The role of the pineal gland in the development of scoliosis began with the development of spinal curvature in 65% of chickens from which the pineal gland was removed [15]. The observation of 10% scoliosis in all chickens undergoing pinealectomy and 10% in those with autografted pineal glands in the trunk muscle led to the hypothesis that neurotransmitter or neurohormonal system play a role in scoliosis [3]. Machida et al., in their experiment study using chickens by adding melatonin and serotonin, reported that serotonin supplementation could not prevent the development

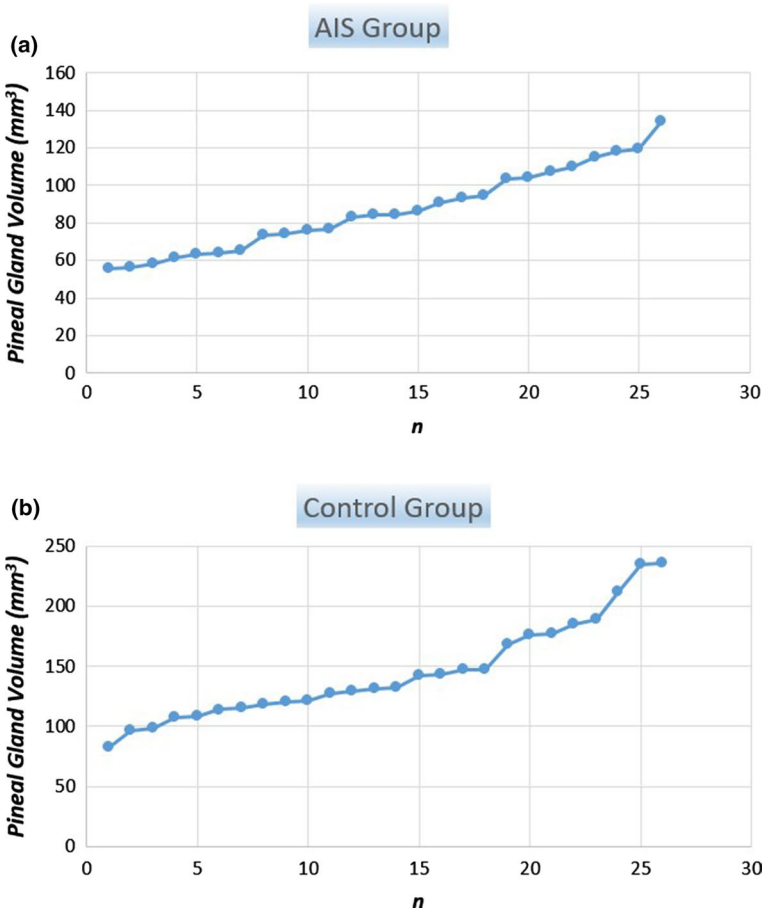


Fig. 4 Distribution of the pineal gland volumes of the all cases in both groups (a and b)

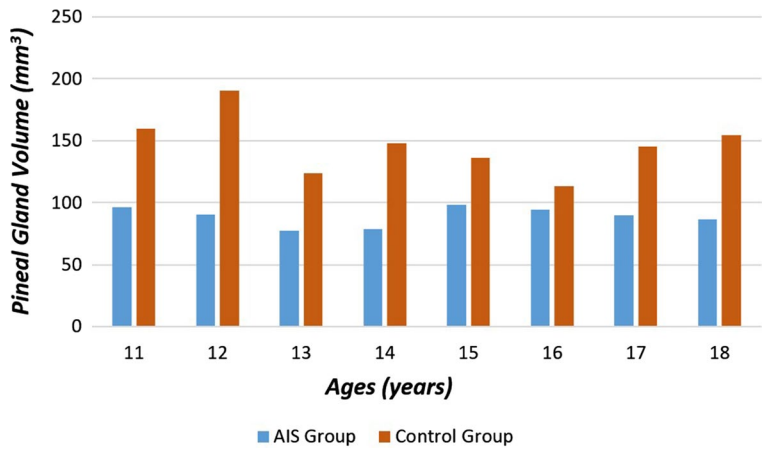


Fig. 5 The pineal gland volumes of the all cases in both groups according to the age

of scoliosis compared to melatonin [16]. However, Bagnall et al. reported that half of the chickens developed scoliosis after melatonin treatment and that melatonin treatment would not effectively reduce the incidence of scoliosis [17].

Although chickens are bipedal just like humans, due to their histological and anatomical differences with the human spine, the opinion that they cannot reflect the pathophysiology of scoliosis predominates [18]. The chicken spine has a thoracolumbar apex and an oblique rise from the pelvis in conjunction with ilium hypoplasia. Also, while the thoracic and lumbar vertebrae fuse in most chickens, human vertebrae do not spontaneously fuse. In chickens, the thoracic spine is lordotic, while in humans it is kyphotic. While chicken scoliosis has no relation with gender or side, it is known that it is more common

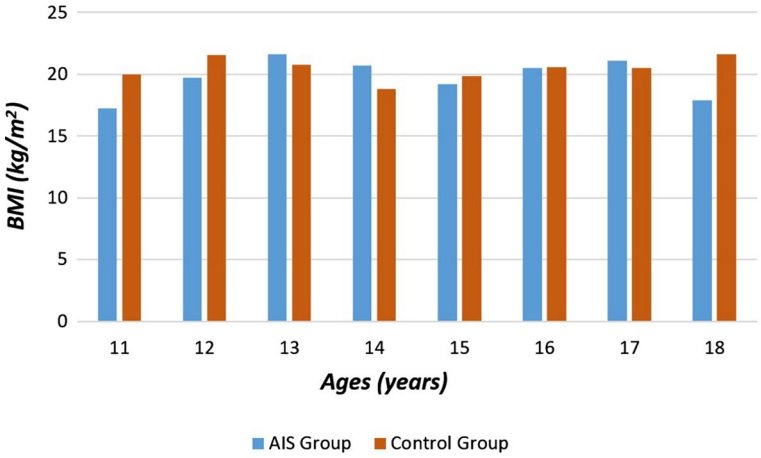


Fig. 6 Body mass index values of the all cases in both groups according to the age

in humans, in the female gender, and on the right side. [19] These features do not reflect the features of AIS [18, 19].

Therefore, bipedal rat models have been developed based on the theory that rodent subjects must also be exposed to the same postural and dynamic mechanical forces required for the development of scoliosis in accordance with human evolution [20]. Machida et al. reported that pinealectomized bipedal rats developed scoliosis after 3 months and almost all of them could be prevented from developing scoliosis with melatonin treatment [20].

Machida et al. reported that used surgically induced bipedal C57BL/6J mice to evaluate the rate of scoliosis development and the effect of daily injections of melatonin (8 mg/kg) in reversing scoliosis development. The development of scoliosis could be prevented with exogenous melatonin treatment [7].

Despite many studies, since the human-like model could not be used in the development of scoliosis, there were problems in reaching the target result. To overcome this problem, in 2005, Cheung et al., in their study using 18 rhesus primates as non-human subjects, reported that there was a significant loss in melatonin secretion, but they could not develop the expected scoliosis in their follow-up of more than two years [19]. They attributed this situation to the fact that the subjects could not adequately maintain their upright posture in the cage environment, whereas Fjelldal et al. used Atlantic salmon (*Salmo salar*) without the effect of bipedal posture and load bearing to investigate the effect of melatonin deficiency alone on the development of scoliosis. They reported that abnormal spinal curvature developed in 82% of pinealectomized salmon and that minerals such as calcium and phosphorus were significantly low in the vertebral corpuscles [21]. Kouwenhoven et al. mentioned in their comprehensive review as a keynote that the fully erect posture, which is unique to humans, seems to be a prerequisite for the development of idiopathic scoliosis [22]. These results prove that melatonin is an important marker in vertebral growth and bone mineralization. It also shows that posture and gravity may not be as important as thought in the development of scoliosis.

Melatonin is an endogenous neurohormone produced by the pineal gland, usually in the dark, and is claimed to be directly proportional to pineal volume [23, 24]. In a study by Machida et al., in which they compared five patients with AIS with the control group, serum melatonin levels were found to be significantly lower [8]. However, Bagnall et al. reported that there was no significant difference between day and night measurements in serum melatonin levels in seven cases [17].

Approximately 70% of melatonin in the blood is metabolized by the liver to 6-sulphatoxyl-melatonin and excreted in the urine. Suh et al. examined the urinary excretion of 6-sulphatoxyl-melatonin and glucose metabolism of the pineal gland in patients with AIS using brain positron emission tomography (PET). The most striking aspect of this study was that although melatonin deficiency could not be completely excluded, they reported that the concepts of melatonin deficiency due to AIS and pineal gland metabolism did not support each other [1].

Murata et al. reported that there was no increase in the incidence of scoliosis in children with pineal gland neoplasia despite melatonin deficiency developing after pinealectomy or irradiation [25]. However, in healthy subjects, serum melatonin levels vary with factors such as age, gender, sleep status, and stress. Therefore, melatonin should not be considered as a single factor in the development of AIS. In our current study, only female subjects were selected in order to be least affected by hormonal factors in the comparison between groups. Thus, we believe that we can base this study on the relationship between AIS etiopathogenesis and pineal gland volume on more specific grounds.

Gheban et al. measured the mean pineal gland volume as 112 mm^3 in cases aged 0–25 years and reported that it increased five times on average in the age range of

45–65 years [26]. And also, Golan et al., investigations of pineal gland volume in patients with age, height and weight, measured the pineal gland volume as 131 mm^3 under 30 years of age [27]. Moreover, they measured the pineal gland volume at the lowest level at 100 mm^3 in cases whose height was between 171 and 175 cm [27]. In this study, pineal gland volume was measured in accordance with the literature.

There were some limitations of the current study. First, the level of melatonin hormone in the blood, its functionality, receptor level, and hormone-receptor relationship could not be evaluated biochemically. Second, creating a sample in a single center and from a specific region addressed by that center is not a multi-centric study. Third, the study population was relatively small because we could not include patients with pineal calcification, although the sample size is sufficient according to power analysis. And finally, the current study was conducted on patients with a diagnosis of AIS and an indication for reconstructive surgery. Further studies are needed, including minor curves indicated for conservative treatment.

Although it is not a limitation, the authors discussed the possibility of the opposite of the current study hypothesis while designing this study. Thus, there should be a chance to predict AIS based on pineal volume, but this should be with a more detailed prospective, widest sample, longer follow-up period of at least ten years period, multi-centric, and multi-regional scoliosis screening program conducted by public health professionals. It has been assumed that it can only be done with a study described previously.

The etiology and pathogenesis of AIS remain unclear despite significant studies over the years. Although it mainly focuses on certain issues, it is obvious that it is a multi-factor event. We believe that further clarification and investigation of the etiopathogenesis of the AIS is warranted; in the future, more comprehensive and detailed molecular researches will provide beneficial results to uncover the AIS pathogenesis.

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Declarations

Conflict of interest The authors have no conflict of interest to declare.

Ethical approval The study protocol was approved by the local Clinical Research Ethics Committee numbered 2021/538. All procedures were performed in the Kayseri City Education and Research Hospital, Kayseri, Turkey.

Informed consent Written informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki.

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