Melatonin and adolescent idiopathic scoliosis: The present evidence

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ABSTRACT

Introduction: Adolescent idiopathic scoliosis (AIS) is a multifactorial condition with genetic predisposing factors, and several causes have been put forward for its aetiopathogenesis, including possible hormonal dysfunction. Melatonin seems to play significant role in AIS.
Methods: A systematic search in different database, to July 2021, was performed to define the role of melatonin in the pathophysiology of adolescent idiopathic scoliosis. Eight suitable studies were identified.
Results: The concentration and rhythm of melatonin secretion can play an important role by influencing the pathogenesis of adolescent idiopathic scoliosis.
Conclusions: Although there are many alterations of melatonin in subjects with adolescent idiopathic scoliosis, the many variables present do not allow to establish a direct cause–effect relationship.
Level of evidence: Level IV.

Introduction

Scoliosis is a three dimensional deformity of the spine: patients present a lateral curvature of the spine greater than 10° in the coronal plane, with rotation of the vertebral bodies.[1–3] Classically, scoliosis is classified into three types, namely syndromic, congenital, and idiopathic. In the congenital form, the spinal deformity is caused by vertebrae which have developed abnormally.[4] Skeletal, neuromuscular, or connective tissue disorders, neurofibromatosis, or other conditions are classically associated with syndromic scoliosis. In idiopathic scoliosis, on the other hand, there is no identified cause.[5] Idiopathic scoliosis is classified according to the age of onset: infantile idiopathic scoliosis, in patients between 0 and 3 years; juvenile idiopathic scoliosis, in patients between 4 and 10 years; and adolescent idiopathic scoliosis (AIS) in patients older than 10 years.[6] AIS is the most prevalent spinal deformity, commonly seen by a variety of health workers, school nurses, general practitioners, paediatricians, and spinal surgeons.[6] The diagnosis of AIS is formulated when other vertebral syndromes, malformations, and neuromuscular disorders have been excluded. In population studies, 1–3% of children between 10 and 16 present some spinal curvature, but the vast majority of subjects with a spinal curve will never require surgery.[7,8] The aetiopathogenesis of AIS continues to puzzle basic scientists and clinicians, and mechanical, hormonal, metabolic, disordered

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growth, neuromuscular, and genetic abnormalities have been studied, though none has ever been proven to directly cause AIS. AIS is therefore considered a multifactorial condition, in which genetic predisposing factors may play a role.[9] Some studies have addressed the possible relationship between hormones and idiopathic scoliosis, analyzing sex hormones, leptin, growth hormone (GH), and melatonin. Melatonin is considered by some researchers to play a role in AIS.[10] The primary producers of melatonin, chemically N-acetyl-5-methoxytryptamine, are pinealocytes in the pineal gland, located in the diencephalon.[11] Melatonin is then secreted into the cerebrospinal fluid of the third ventricle, and from there in enters blood circulation. Smaller quantities of melatonin are also produced peripherally by the retina and the gastro-intestinal system.[12,13] The suprachiasmatic nuclei of the hypothalamus, the activity of which is mediated by the photoperiod, closely control the production of melatonin from the pineal gland.[14] In mice and humans, the peripheral production of melatonin from bone marrow cells[15] and lymphocytes[16] does not impact its photoperiod-mediated production.[17] Melatonin has been detected in many animals and plants,[18] and is involved in a variety of regulatory functions, including embryonic development,[19] circadian rhythm,[20] seasonal reproductive changes,[21] tumour growth, and skeletal growth.[22] Moreover, the free-radical scavenging and antioxidant properties confer melatonin an antiaging potential,[23] and allow it to protect nuclear and mitochondrial DNA[24] (Fig. 1).

Material and methods

The review follows the Preferred Reporting guidelines for systematic reviews and meta-analyses (PRISMA)[25] (Fig. 2). All published investigations reporting the possible role played by hormones in the aetiopathogenesis of juvenile idiopathic scoliosis were evaluated according to *a priori* established inclusion criteria. Studies in languages other than English were excluded from the present investigation. Narrative and systematic reviews, meta-analyses, technical notes and case reports were excluded. Two investigators independently conducted the systematic search, through July 2021, from the full-text archives of Embase, Google Scholar, Scopus and PubMed. The keywords adolescent idiopathic scoliosis, spine deformity, hormonal imbalance, melatonin, melatonin receptors were employed in single and combined searches. Two investigators independently examined the titles and abstracts to remove duplicates, and evaluated the eligible studies according to the pre-established inclusion criteria. If titles and abstracts did not allow to decide on inclusion or exclusion, the relevant full text was examined. The bibliographies of the articles included were reviewed by hand to identify further

Fig. 1 – Melatonin effects.

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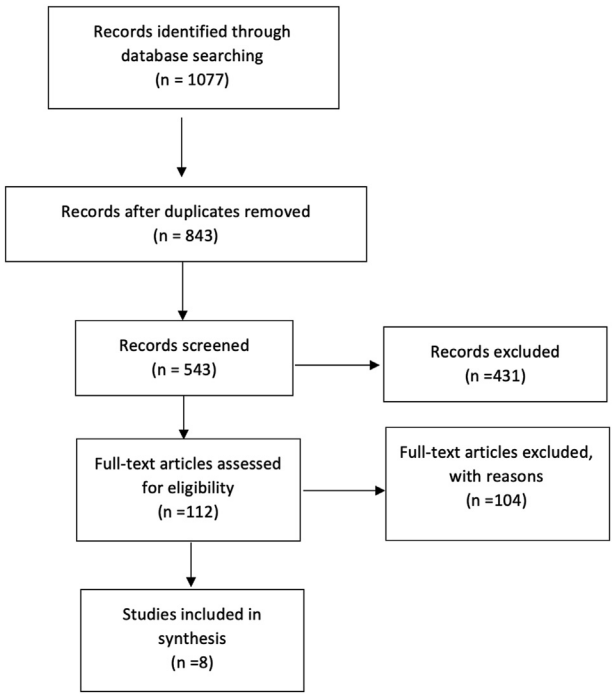

Fig. 2 – Flow chart of the literature search.

related articles. If discrepancies persisted, discussion with the senior investigator allowed to resolve them. Seven studies satisfied the inclusion criteria, and were thus included in the analysis. The details of the search are detailed in the flowchart in Fig. 2.

The detailed information of qualified studies was extracted: i) study characteristics including author, year of publication, ii) Hormone or receptor and Patients included; iii) method of assessment. Data from the selected studies were extracted and eligible studies were assessed by means of the revised Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) criteria[26] The methodological quality of the included studies was valuated throught four key domains (patient selection, index test, reference standard and flow and timing). Signalling questions were applied to evaluate the risk of bias and clinical applicability. These questions were responded as "yes" for low risk of bias/concerns, "no" for high risk of bias/concerns or "unclear".

Results

A total of 1077 articles were identified by the search engines used, and the duplicates were subsequently removed, obtaining 843 articles. At this point, 431 articles were excluded following reading the titles and abstracts. Narrative and systematic reviews, meta-analyses, technical notes and case reports were excluded. There were 112 articles left, and 104 articles were excluded as they were not appropriate for the topics covered or for the incomplete amount of information possessed.

8 studies met the inclusion criteria, and data were extracted and collected (Table 1). Of these studies, three analysed the melatonin[27–29] values only, two additionally also analysed the MT2 receptor values[31,31] and three studies analysed melatonin MT1 receptor and MT2 receptor. [32–34]Three studies have been published in the last five years,[29,31,34] four studies have been published in the last ten years[27,30,32,33] and one study, the first investigation on the topic, was published 24 years ago.[28] QUADAS-2 quality assessment for the included studies is shown in Table 2 and Fig. 3. This systematic review involves 176 patients with scoliosis and 108 subjects without scoliosis. In all the clinical studies where a control group was used, this was always composed of healthy individuals. Indeed, subjects with other forms of spinal deformity, abnormal or melatonin-related metabolic diseases and endocrine disorders were excluded from clinical studies. The study of melatonin and its receptors was performed in a non-uniform fashion by the various authors. Measurements were made on urine or serum,[27,28] on cell samples and cultures on chondrocytes, bone and muscle tissue.[29,34] Hilibrand et al.[28] showed that nocturnal melatonin levels were high in both healthy subjects and AIS patients. Diurnal hormone levels were lower but similar in the two groups. The data obtained were collected and evaluated also in relation to the normal rhythm of melatonin secretion in the human body and its relative presence in the urine.[28] Goultidis et al.[27] assessed the value of monitoring the serum levels of melatonin in AIS patients managed conservatively. In 42 patients with AIS aged less than 14 and 29, age-, weight-, and height-matched healthy controls blood samples were collected at baseline and after one year. The serum levels of melatonin were evaluated with the enzyme-linked immunosorbent assay (ELISA) method. The baseline mean serum melatonin value was 12.23 pg/mL for the control group and 19.32 pg/mL for the AIS group. After one year, the average serum melatonin levels had increased in both groups, 52.43 (N = 34 patients with AIS) and 68.44 pg/mL (N = 23 controls).[27] There were no statistically significant differences between the two groups. Comparing the serum melatonin levels of AIS patients who exhibited a progression of the scoliotic curve >5° with patients with stable AIS or the control group failed to show that the deficiency of melatonin was not associated with the progression of the condition.[27] A case–control study[31] of osteogenic and chondrogenic differentiation performed using human mesenchymal stem cells (hMSCs) showed that the expression of MT1 and MT2 receptors was irregular in the AIS group. In particular, the expression of the MT2 receptor was reduced in the AIS group. Furthermore, melatonin increased alkaline phosphatase activity and the synthesis of glycosaminoglycans, and upregulated the expression of genes involved in osteogenic and chondrogenic differentiation including, ALP, osteopontin, osteocalcin, runt-related transcription factor 2, collagen type II, collagen type X, aggrecan and sex-determining region Y-box 9 in the normal control hMSCs, but did not affect the AIS groups.[31] The hMSCs of AIS patients manifest abnormal responses to melatonin during chondrogenic and osteogenic differentiation.[29,31] Man et al.[33] performed a study on osteoblasts harvested from patients with AIS and non-AIS to evaluate their proliferation after melatonin stimulation. Melatonin stimulated osteoblast proliferation in control subjects, but the effect was reduced in patients with AIS, who exhibited lower MT2 expression.[33] Another study, conducted on paraspinal muscles biopsy, analysed the expression of

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Table 1 – Studies included.

Study	Hormone or receptor/Methods	Patients included
Goultidis et al.[27] (2014)	Melatonin/serum value of melatonin	42 AIS patients; 29 non-AIS patients
Hilibrand et al.[28] (1996)	Melatonin/urine value of melatonin	9 AIS patients; 18 non-AIS patients
Li et al.[29] (2019)	Melatonin/bone marrow-derived mesenchymal stem cells	23 AIS Patients; 12 non-AIS patients
Wang et al.[30] (2014)	Melatonin; Receptor MT2/chondrocyte culture	20 AIS patients; 10 non-AIS patients
Chen et al.[31] (2016)	Melatonin; Receptor MT2/bone marrow derived mesenchymal stem cells	12 AIS patients; 12 non-AIS patients
Yim at al.[32] (2013)	Melatonin; Receptor MT1, MT2/cultured osteoblasts	41 AIS patients; 9 non-AIS patients
Man et al.[33] (2011)	Melatonin; Receptor MT1, MT2/bone biopsies and receptor isolation	11 AIS patients; 8 non-AIS patients
Zamecnik et al.[34] (2016)	Melatonin; Receptor MT1, MT2/paraspinal muscles biopsy	18 AIS patients; 10 non-AIS patients

mRNA from melatonin 1A receptors (MTNR1A) and melatonin 1B receptors (MTNR1B) in patients with AIS and controls. The observed expression levels of mRNA for MTNR1A and MTNR1B were very low or absent in patients with AIS and controls.[34] The studies conducted on messenger ribo-nucleic acid (mRNA) of chondrocytes led to similar results.[30,32] Indeed, in 30 subjects (20 AIS and 10 non-AIS)[30] the expression of MT2 receptor mRNA in chondrocytes of the growth plate of patients with AIS, determined by quantitative real-time polymerase chain reaction (qRT-PCR), was significantly lower than

Table 2 – Quality assessment of included studies using QUADAS-2 tool criteria.

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of partecipants and personnnel (performance bias)	Blinding of outcome assessement (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Goultidis et al. [27] (2014)	+		-		+	+	+
Hilibrand et al. [28] (1996)	+	+		+	+	+	+
Li et al. [29] (2019)	+	+	-	+	+	+	+
Wang et al. [30] (2014)	+	+	+	+		+	
Chen et al. [31] (2016)		+			+	+	+
Yim at al. [32] (2013)	+	+		+	+		+
Man et al. [33] (2011)	+	+	+		+	+	
Zamecnik et al. [34] (2016)	+	+	-		+	+	+

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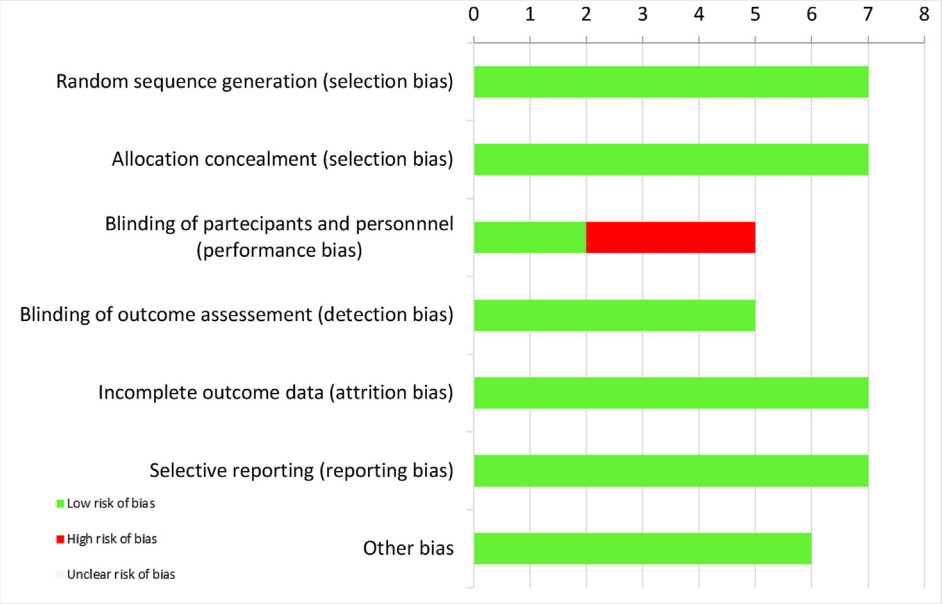

Fig. 3 – Quality assessment of included studies using QUADAS-2 tool criteria.

in the control chondrocytes.[30] Yim et al.,[32] studying osteoblast cultures from AIS girls and control girls, showed instead that M2 mRNA expression was reduced in AIS patients but M1 mRNA expression had similar values in 50 female patients (41 AIS and 9 non-AIS).[32]

Discussion

The causes of AIS remain elusive, and melatonin secretion, its expression and regulation have been hypothesised to play a role. Indeed, the blood serum levels of melatonin were significantly higher in AIS patients when compared to weight-, age-, and height-matched controls, with no evidence that the deficiency in melatonin was associated with the progression of the scoliosis.[27] On the other hand, higher serum melatonin levels in patients with less severe AIS may point towards either a milder clinical form of AIS or an early stage of the condition. It may be possible that, at the beginning of AIS and while the deformity is still not pronounced, the levels of melatonin rise, possibly in response to the signalling dysfunction on the cell membrane.[27] Further along, when the severity of AIS increases, the biological potential for increased production of melatonin has been exhausted, and therefore this dysfunction can no longer be counterbalanced.[27] A study on human mesenchymal stem cells (hMSCs) of AIS patients and controls analysed osteogenic and chondrogenic differentiation after stimulation with melatonin.[31] Melatonin may exert a modulating role, via its MT2 receptor, on osteogenic and chondrogenic differentiation in patients with AIS.[31] Specifically, alterations of the melatonin signalling pathway could be the cause of the failure of hMSC to respond to stimulation with melatonin and the lack of differentiation towards the osteogenic and chondrogenic line.[31] Moreover, MT2 mRNA is expressed asymmetrically in the paravertebral muscles, with higher levels of expression on the concavity than the convexity of the curve in patients with AIS.[31] Also, the expression of MT1 seems to play an important role: indeed, it was lower in 4 AIS patients, and the expression of MT2 was lower in 6 AIS patients, being extremely low in 2 patients.[31] Two patient with Cobb angles of 51° and 55° (not the most severe in the population studied) exhibited low expression of MT1 and extremely low expression of MT2, but these factors did not show evidence of a statistically significant association with the severity of AIS.[31] Furthermore, AIS patients whose osteoblasts showed low level of expression of MT2 receptor had a longer arm span than AIS patients in whom the levels of expression level of the MT2 receptor were normal.[31] Yim et al., recruiting 50 patients, and Man et al.,[33] recruiting 19 patients, showed abnormalities in the expression of MT1 and MT2 receptors of melatonin, possibly accounting for the dysfunction of melatonin signalling in osteoblasts.[32] Yim et al. evidenced a lower rather than the absence of expression of MT2, as suggested by Man et al.[33] However, these two research groups used different experimental procedures: the antibodies chosen, the method and timing for absorption and the timing of development and analysis of protein expression are some of the disparities between the investigations.[32] The expression level of mRNA for MT2 in AIS patients was significantly lower than the controls, but the expression level of mRNA for MT1 was similar between the two groups.[32] After excluding the factors that could influence mRNA expression, such as defects in translation processes, it was hypothesized that the cause could concern gene expression.[32] Instead, Man et al.,[33] using Western

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blotting, demonstrated the total absence of MT2 receptors in AIS patients. The mRNA levels for these AIS girls were lower than non-AIS patients. The MT1 receptor is expressed in the osteoblasts of both healthy subjects and patients with AIS. Evaluating osteoblasts, however, the MT2 receptor was detected in all healthy subjects but only in 7 of the 11 patients with AIS.[33] Melatonin administration resulted in different effects on osteoblasts in control patients and AIS patients.

The osteoblasts of the control subjects proliferated in a manner dependent on the concentration of melatonin. The osteoblasts of AIS patients did not show this proliferative thrust after melatonin administration.[33] Significant differences were detected regardless of the concentrations of melatonin in the proliferation of osteoblasts from controls and that of AIS osteoblasts which did not express the MT2 receptor. This was also the case between the osteoblasts from controls and the osteoblasts from AIS patients with MT2 receptor expression at the highest concentration of melatonin. Therefore, there could be a heterogeneous aetiology among the AIS population.[33] AIS osteoblasts with and without MT2 receptor expression showed slight variations in response to melatonin,[33] but the clinical implications of this finding are unclear.

This study presents several limitations. The limited number of included articles represents the most important limitation. The outcome measures were clearly defined by most studies, as was the timing of outcome assessment, with the relevant criteria expressly stated, which would increase reliability Although the risk of bias in the random sequence generation and allocation concealment were both low and the eligibility criteria were often clearly reported and unbiased, some between-studies variation were detected. Patient blinding was seldom performed and the timing of outcome assessment was biased by some studies, representing other limitations. Furthermore, the overall lack of quantitative data did not allow to perform further analyses. Future investigations are required to overcome these limitations and validate these findings in a clinical setting.

Conclusion

The present systematic review summarises the present published evidence on the possible association between melatonin and AIS. Animal studies have ascertained that melatonin does affect the cells of the musculoskeletal system. Some investigations studied the concentration of melatonin and its receptors in subjects with AIS and in healthy subjects. Other works have studied the response to stimuli produced by melatonin on specific cells, such as osteoclasts, chondrocytes, stem cells and muscles. To date, however, it is not possible to determine whether there is a cause–effect relationship between melatonin and the onset of AIS. Although there are alterations of melatonin in subjects with AIS, the studies have not enough statistical power to be able to define such relationship.

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