

# Melatonin and adolescent idiopathic scoliosis

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**Scoliosis seen in the chicken after pinealectomy resembles adolescent idiopathic scoliosis in man. It has been suggested that in both species, deficiency of the pineal hormone, melatonin, is responsible for this phenomenon.**

**In nine patients with adolescent idiopathic scoliosis and in ten age- and gender-matched controls, the circadian levels of serum melatonin and the excretion of urinary 6-hydroxy-melatonin-sulphate, the principal metabolite of melatonin, were determined. There were no statistically significant differences in the secretion of serum melatonin or the excretion of urinary 6-hydroxy-melatonin-sulphate between the patients and the control group. The hypothesis of melatonin deficiency as a causative factor in the aetiology of adolescent idiopathic scoliosis cannot be supported by our data.**

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A number of suggestions concerning the aetiology of adolescent idiopathic scoliosis (AIS) have been proposed including neuromuscular, genetic, mechanical, growth-related and developmental, but no single factor has been identified so far. In clinical trials, patients with scoliosis have been compared with normal control subjects. Equilibrium dysfunction<sup>1,2</sup> and impairment of proprioception<sup>3,4</sup> have been found, leading to the idea that a disturbance of

postural control may be the cause. Cortical rearrangement of the internal representation of the body with misperception of the posture of the spine and resulting deformity has also been postulated.<sup>5</sup> Asymmetry in the brainstem, detected by MRI, further supports this idea of a possible neuromuscular origin of idiopathic scoliosis.<sup>6</sup> An increased familial incidence of scoliosis,<sup>7,8</sup> especially among monozygotic twins,<sup>9,10</sup> points to a genetic factor in its aetiology. Abnormality of the disc,<sup>11</sup> asymmetrical rib growth<sup>12</sup> and reduction of thoracic kyphosis<sup>13</sup> have also been described as possible causes. Growth is closely related to the progression of the curve.<sup>14</sup> Greater release of growth hormone<sup>15,16</sup> has been detected in patients with scoliosis as well as an earlier onset of the menarche.<sup>17,18</sup> Finally, a developmental theory has been proposed assuming disturbed ontogenesis under physiological stress without a true disease process.<sup>19</sup>

The observation that experimental pinealectomy in newborn chickens leads to a spinal deformity similar to idiopathic scoliosis in man<sup>20,21</sup> initiated a new neuroendocrine hypothesis for the cause of idiopathic scoliosis. A deficiency of melatonin, the principal product of the pineal gland, was held to be responsible for this deformity, as both autografting of the pineal gland and substitution of melatonin prevented the development of scoliosis in the pinealectomised chicken.<sup>22</sup> Later, Machida et al<sup>23</sup> also reported significantly lower levels of serum melatonin in adolescents with progressive scoliosis compared with patients with stable scoliosis or healthy control subjects, but no alteration in serum or urinary melatonin in patients with AIS was found by others.<sup>24-26</sup> Thus, a decisive role for melatonin in the pathogenesis of human AIS required further investigation.

We examined the circadian pattern of secretion of melatonin and the urinary excretion of 6-hydroxy-melatonin-sulphate (6-OH-MLTs) in patients with AIS and in age- and gender-matched healthy control subjects.

## Patients and Methods

We studied nine adolescent patients who had been admitted to our department for the surgical correction of scoliosis. The Cobb angles of the curves were measured on plain radiographs, the Risser sign determined and the scoliosis

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**Table I.** Details of the patients with AIS and the control group

	Patients	Control group
Number	9	10
Gender		
Female	6	8
Male	3	2
Median age in years (lower to upper quartile)	14.7 (14.5 to 15)	14.7 (14.2 to 15.3)
Median height in cm (lower to upper quartile)	168 (163 to 171)	168.5 (163 to 172)
Median weight in kg (lower to upper quartile)	54 (46 to 67)	53 (49 to 55)

**Table II.** Clinical features and data on melatonin for the nine patients with AIS

Case	Age (yr)	Height (cm)	Weight (kg)	Progression	Risser sign	Curves* (Cobb angle/region)	MLT AUC (pg-hrs/ml)	6-OH-MLTs (µg/16hrs)
1	16.6	181	90	Yes	3	70/RT	684.1	–
2	14.7	169	67	Yes	4	48/59/RT/LL	1100.6	9.1
3	15.0	171	62	No previous data	2	55/41/RT/LTL	2339.6	24.2
4	14.5	163	46	No	4	25/40/LT/RL	1739.4	–
5	14.5	160	45	No	4	52/59/RT/LTL	1079.6	9.8
6	12.5	163	50	Yes	3	58/68/RT/LTL	1087.5	5.6
7	16.0	168	54	No previous data	5	35/61/RT/LTL	313.2	4.1
8	15.0	180	80	No previous data	2	59/48/RT/LTL	1108.3	16.4
9	14.2	155	41	No	3	48/LTL	793.2	9.1

\* RT, right thoracic; LT, left thoracic; RL, right lumbar; LL, left lumbar; LTL, left thoracolumbar

classified as 'progressive' if more than 10° of progression had occurred during the previous 12 months. Otherwise, it was classified as 'stable'. Except for their spinal deformity, the patients were healthy (Tables I and II).

Ten healthy age- and gender-matched adolescents, children of nurses and doctors from our department and their friends, served as a control group (Table I). All had a straight spine and a normal forward bending test on physical examination with no history of spinal disease.

All voluntarily agreed to participate and written consent was obtained from the participants and their parents. Monetary compensation was given to the control group.

All the patients and the control group were admitted to our department to obtain a circadian profile of serum melatonin. From each individual, serum samples (5 ml) were collected through an antecubital indwelling venous cannula at 6 pm, 8 pm, 11 pm, 2 am, 6 am, 8 am and 10 am. The samples were stored at -20°C until the melatonin was measured. Urine was collected from 6 pm to 10 am, the volume recorded and a 10 ml aliquot stored at -20°C until measurement was made of 6-OH-MLTs. To avoid nocturnal suppression of melatonin, light was restricted to less than 200 lux from 9 pm to 7 am. Throughout this period a dim flashlight was used for the collection of blood. To avoid a possible influence of stress on the secretion of melatonin in the patients, serum and urine were collected at least one day before surgery.

Serum concentrations of melatonin were measured by a radioimmunoassay (RIA).<sup>27,28</sup> The concentration of 6-OH-MLTs in urine was estimated by means of a commercially available RIA (Stockgrand, Guildford, UK). The characteristics and performance data of this assay have already been described.<sup>29,30</sup> In two patients and in one control subject no measurement of 6-OH-MLTs was carried out because of problems with collection of urine.

From the seven serum melatonin measurements taken in each subject, a circadian melatonin profile was determined for each individual and the area under the concentration time curve (AUC) calculated according to the 'trapezoid method'.<sup>31</sup> The concentration of 6-OH-MLTs was measured in the urine collected over a 16-hour period from each subject and the total amount of 6-OH-MLTs excreted computed. All data were described by their medians and quartiles. The Wilcoxon rank-sum test was used to describe differences in the melatonin secretion (AUC), excretion of 6-OH-MLTs and the age, height and weight between patients and the control group. The relationship between the serum melatonin profile (AUC) and excretion of 6-OH-MLTs over a 16-hour period was determined using the Spearman correlation coefficient.  $P < 0.05$  was regarded as being statistically significant.

## Results

The serum melatonin profiles of the patients and the control group are shown in Figure 1. The AUC of the patients showed a median of 1088 pg-hrs/ml (quartiles, 793 to 1108), whereas in the control group the median was 1249 pg-hrs/ml (657 to 1321). The Wilcoxon rank-sum test showed no statistically significant differences between the patients and the control group ( $p = 0.90$ ). The patients excreted a median of 9.1 µg (5.6 to 16.4) of 6-OH-MLTs during the 16-hour period of collection compared with 11.0 µg (9.7 to 12) in the control group (Fig. 2). No statistically significant difference was found ( $p = 0.39$ ). For the patients, individual values of serum melatonin (AUC) and 6-OH-MLTs excretion are given in Table II. There was a statistically significant correlation ( $r = 0.62$ ;  $p = 0.01$ ) between the serum melatonin profiles (AUC) and excretion of 6-OH-MLTs over the 16-hour period. This is in agree-

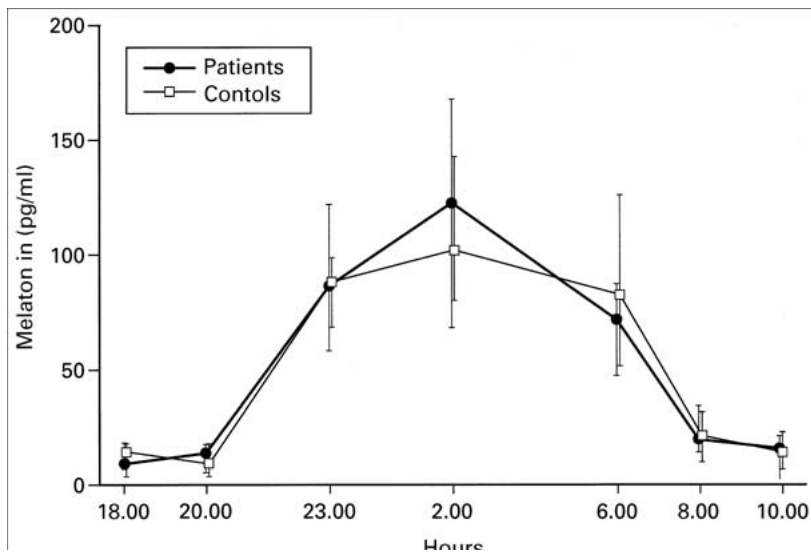


Fig. 1

Circadian profile of serum melatonin (median and quartiles) for patients with AIS and for the gender- and age-matched control group. The AUC showed no statistically significant differences between the groups.

ment with previous observations<sup>29</sup> and indicates that both the melatonin profile and 6-OH-MLTs excretion are good indicators of the endocrine activity of the pineal gland.

## Discussion

In all species studied, the pineal hormone, melatonin, displays a circadian pattern of secretion with low levels during the day and high concentrations at night. Nocturnal melatonin, however, can be suppressed within minutes by ambient light of sufficient strength. Man is sensitive to light above approximately 150 to 200 lux.<sup>32</sup> The amplitude of the circadian secretion of melatonin undergoes remarkable alteration during a human life-time. In the first three months of infancy nocturnal levels of melatonin are low with almost no circadian variation. They then increase steadily until the highest concentrations are reached by the age of two years. From then they decrease constantly by some 80% until late adolescence.<sup>28</sup> Approximately 70% of blood melatonin is metabolised to 6-OH-MLTs by the liver and excreted in the urine. The physiological significance of melatonin and the age-dependent alteration of its circadian secretion is at present unknown.<sup>33,34</sup>

The findings in pinealectomised chickens introduced the 'melatonin-deficiency hypothesis' as a possible cause of human AIS.<sup>20</sup> Our study does not support the concept of permanent melatonin deficiency in AIS, since we were unable to detect any differences in the circadian serum melatonin profiles or in urinary excretion of 6-OH-MLTs between patients with AIS and the control group. These results are consistent with previous reports by others,<sup>23-26</sup> despite wide differences in the designs of study, output measures and features of the patients investigated. Some of these reports, however, are based either on only a few single serum measurements, on urinary concentrations instead of total excretion or do not mention important factors such as ambient illumination at night (Table III).

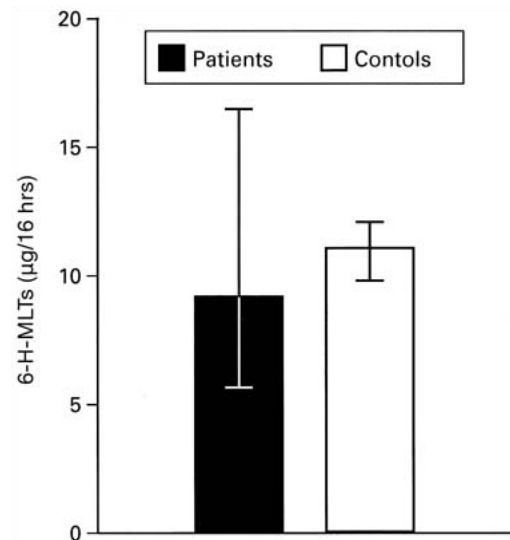


Fig. 2

Urinary excretion (median and quartiles) of 6-OH-MLTs in patients with AIS and in the gender- and age-matched control group. There is no statistically significant difference between the groups.

Nevertheless, a transient melatonin deficiency before the onset and/or during progression of AIS has not been completely excluded. Findings relating to this were published by Machida et al,<sup>23</sup> who reported significantly lower serum melatonin profiles in five patients with progressive AIS compared with a control group. No difference was found by Bagnall et al<sup>24</sup> in single day- and night-time measurements of serum melatonin in a control group and seven patients with progressive AIS. Unfortunately, the patients were studied 1.3 years after surgical intervention, and therefore no conclusions could be made about the activity of the scoliotic process at the time of examination. Our study included three subjects with progressive scoliosis. Because

**Table III.** Survey of MLT and 6-OH-MLTs studies in patients with AIS

Authors	Patients			Control group		Nocturnal light regimen	Output measures	Assay	p value
	Scoliosis characteristics	Number	Age (yr)	Number	Age (yr)				
Machida et al <sup>23</sup>	Stable	5	15.0	15	15.0	Lights off	Serum melatonin profile	RIA	NS
	Progressive	5							<0.05
Bagnall et al <sup>24</sup>	Severe, progressive*	6	14.7	7	14.7	Ordinary room light at blood collection	1 day- and 1 night-time serum melatonin sample	RIA	NS
	Moderately severe	1							
Hilibrand et al <sup>25</sup>	Unknown	9	13.5	18	13.1	Unknown	Melatonin/creatinine ratio in 1 morning and 1 night-time urine	HPLC†	NS
Fagan et al <sup>26</sup>	Stable	19	14.9	23	14.5	Unknown	24-hour 6-OH-MLTs excretion	RIA	NS
This series	Stable	3							
	Progressive	3	14.7	10	14.7	Lights off	Serum melatonin profile, 16 hour 6-OH-MLTs	RIA	NS
	Unknown	3					excretion	RIA	

\* studied 1.3 years after surgery

† high-performance liquid chromatography

of the small number of subjects no statistical examination was warranted, but no trends were visible in the individual data for melatonin (Table II). Since large differences in the secretion of melatonin between individuals are well documented in healthy subjects,<sup>35</sup> the question of a transient melatonin deficiency in AIS remains open until a sufficient number of subjects has been studied at the onset of, or during the progression of AIS.

An increased incidence of scoliosis has not been observed in children after pinealectomy or pineal irradiation because of pineal neoplasias, although they have a lack of serum melatonin.<sup>36-39</sup> Hilibrand et al<sup>25</sup> examined patients with scoliosis who were considerably younger than those in all relevant studies,<sup>23,24,26</sup> including ours, and made similar observations. Their patients were not melatonin-deficient, had only mild or moderate curves and were not scheduled for surgical treatment. They were suffering either from an early stage or a mild course of the disease. Assuming it was an earlier stage of the disease, the development of the curve seems to have occurred even if no deficiency of melatonin was detectable.

Although the morphology of scoliosis in melatonin-deficient chickens closely resembles human scoliosis and despite the constant reproducibility of this effect in newborn chickens, the effect of melatonin on human AIS remains uncertain. No permanent deficiency of secretion of melatonin occurs in patients with AIS. Evidence for a transient deficiency before and/or during development of scoliosis is scant and requires confirmation in a large number of subjects.

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