
The involvement of melatonin in the clinical status of patients with fibromyalgia syndrome

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ABSTRACT

Objective. *The aim of this study was to evaluate the levels of 6-sulphatoxymelatonin (6-SMT) in the urine of patients with fibromyalgia (FM) and correlate them with the score obtained by these patients in four clinical assessment instruments.*

Methods. *Fifty-eight women with primary FM and 39 healthy women matched for age and body mass index were included in the study sample. The levels of 6-SMT were evaluated in urine collected from 8 pm until 8 am the next day by the immunosorbent assay. For the clinical evaluation we used the Fibromyalgia Impact Questionnaire (FIQ); Pittsburg Sleep Quality Index (PSQI); Medical Outcomes Study 36-item Short-Form Health Survey (SF-36) and Satisfaction with Life Scale (SWLS). Data normality was assessed using the Kolmogorov-Smirnov test, the differences between groups by means of the Mann-Whitney test and correlation analysis by Spearman's correlation test.*

Results. *The levels of 6-SMT in the urine of patients with FM were significantly lower than those found in the urine of healthy controls. The score obtained by patients with FM was significantly different from the score achieved by the healthy controls in the four assessment tools. However, no significant correlation between urinary levels of 6-SMT and scores on assessment instruments was observed.*

Conclusion. *The results of this study do not discard the involvement of melatonin in the pathophysiology of FM, but may suggest that changes in melatonin levels when associated with other neuroimmunoendocrine changes may impact directly and negatively on the manifestation of symptoms that make up the clinical picture of FM.*

Introduction

Fibromyalgia (FM) is a complex clinical condition characterised by chronic

and widespread pain, besides pain on palpation of at least 11 of 18 tender points. It is often associated with other symptoms such as anxiety, chronic fatigue, morning stiffness, sleep disturbance and depression (1-3). FM mainly affects women in a proportion of up to nine women for every man affected (4). To date, the pathophysiology of FM is not completely understood, and several hypotheses have been tested in order to elucidate this issue, among them: central or peripheral sensitisation, oxidative stress, genetic, mood disorders, induction of pain by stress, immunological and inflammatory changes (2, 3, 5). Moreover, in most patients, it is possible to observe an association between these etiological factors, which makes FM become even more difficult to be treated and understood (5-7). Several studies have investigated the involvement of neuroendocrine mechanisms in the genesis and or evolution of FM (8-11), including those looking for changes in levels of melatonin produced by FM patients (12-18). However, these studies are contradictory, sometimes showing similar levels of this biomarker between controls and FM patients (13, 15) and sometimes demonstrating that patients have altered levels of melatonin and or its precursors (16, 17).

Melatonin (N-acetyl-5-methoxytryptamine) is a neurohormone produced mainly by the pineal gland. Its production is regulated by light and its release is the main event indicator of the evening to the body (19). Melatonin is synthesised from tryptophan and serotonin and, when released, part of the melatonin crosses the blood-brain barrier and diffuses in the cerebrospinal fluid, while another part is released into the bloodstream (20). Metabolisation of this hormone occurs in the liver in two steps: (i) hydroxylation transforms the hormone into 6-hydroxymelatonin, (ii) the association with sulfuric or glu-

curonic acid results in the major melatonin metabolite, 6-sulphatoxymelatonin (6-SMT) which is excreted in the urine (14, 21, 22).

Recent studies have shown that melatonin has sleeping promoter properties (23), as well anti-inflammatory (24), anxiolytic (25), anti-depressant (14), and anti-oxidants properties (26), but especially analgesic properties (27). The analgesic properties of melatonin have been demonstrated in several studies with animals models and humans (28), including those patients with FM (29). The mechanism of antinociceptive actions of melatonin has not been fully elucidated, but it appears to involve signalling through opioid, benzodiazepine, $\alpha 1$ - and $\alpha 2$ -adrenergic, serotonergic and cholinergic receptors and Gi-coupled melatonin receptors, to Gi-coupled opioid l-receptors or GABA-B receptors with unknown downstream changes resulting in a reduction in anxiety and pain (29, 30). Thus, the hypothesis of a reduced release of melatonin by FM patients could explain, at least in part, the emergence or worsening of some of the main symptoms of this condition.

In this study we evaluated the concentrations of 6-SMT in the urine of healthy controls and FM patients in order to identify changes that might sustain the involvement of melatonin in the pathogenesis of FM. Furthermore, we correlated the levels of this biomarker with the score obtained by fibromyalgia patients in four validated questionnaires in Brazil that proposes to assess the general impact of fibromyalgia, quality of sleep, quality of life and satisfaction with life in fibromyalgia patients, in order to determine whether concentrations of 6-SMT may interfere with the clinical status of FM patients.

Materials and methods

Ethics statement

This study was approved by the Human Research Committee of Federal University of Minas Gerais (UFMG) protocol number 0224.0.203.000-10 and University Centre of Formiga – MG (UNIFOR-MG) protocol number 158/2010. All patients and control subjects gave written informed consent

before inclusion in this study. All the ethical concerns were based on the recommendations of the Declaration of Helsinki.

Patients and controls

Sixty-five women with primary FM were enrolled to participate in this study. They were diagnosed according to the American College of Rheumatology criteria by a specialised clinician (31). The new diagnostic criteria were not used because the patient recruitment phase occurred before the release of the new criteria (32). Seven patients were excluded because they met some of the exclusion criteria, which were: history or presence of chronic inflammatory conditions (*e.g.* spondyloarthritis and ankylosing spondylitis), autoimmune diseases (*e.g.* systemic lupus erythematosus and rheumatoid arthritis), psychiatric disorders (*e.g.* major depressive disorder, schizophrenic or paranoid disorder) and or presenting infectious, patients who had used anti-inflammatory drugs in the past six months, pregnant patients or women who were currently breastfeeding. The final sample was composed of 58 patients.

Thirty-nine healthy adults, who were matched for age, body mass index (BMI) and sex, were selected for the control group. They had no past or present of psychiatric and clinical disorders.

6-Sulphatoxymelatonin (6-SMT)

Patients and controls provided urine samples collected over 12 hours. For this purpose, they were instructed to store in an appropriate plastic container all their urine collected between 8 pm and 8 am of the next day. All patients were advised not to collect urine five days before or five days after menses. On the same day, the samples were collected by researchers, the total volume was recorded and five milliliters was subtracted from the total. This aliquot was frozen and stored in a freezer at -20°C until analysis. In the moment of analysis the samples were thawed and subsequently centrifuged, the supernatant was aspirated and discarded, the remaining material was used to determine levels of 6-SMT by Enzyme-Linked Immunosorbent Assay (ELISA)

according to the manufacturer's recommendations (Bühlmann Laboratories AG, Schönenbuch, Switzerland). The sensitivity of the assay was 0.14 ng/ml and the coefficient of variation intra-assay and inter-assay were 7.1% and 11.9%, respectively.

Assessment tools

The four assessment instruments listed below were completed by the FM patients. All of them have reliability and validity ensured in Brazil.

The Fibromyalgia Impact Questionnaire (FIQ) is a self-administered questionnaire that involves issues related to functional capacity, employment status, psychological distress and physical symptoms. Through this questionnaire is possible to identify the presence and intensity of the main symptoms of FM. This questionnaire consists of 19 questions organised into 10 items. The score on this questionnaire can range from zero to 100 points, higher scores reflect more severe impact of FM on quality of life of FM patients (33).

The Pittsburg Sleep Quality Index (PSQI) is a self-administered questionnaire, developed to measure the quality and patterns of sleep over the last month. It consists of seven components which, summed together, give a total score that range from 0 (no difficulties) to 21 (severe difficulties) (34).

The Medical Outcomes Study 36-item Short-Form Health Survey (SF-36) is a self-administered questionnaire, in which eight dimensions of health-related quality of life are assessed: physical functioning (PF), role-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role-emotional (RE) and mental health (MH). Each scale is scored using norm-based methods, with higher scores indicating better health. Scores are aggregated further to produce physical and mental component summary measures of health status. The domains scores are standardised and range from 0 to 100 with higher scores reflecting better health-related quality of life in the domain being measured (35).

The Satisfaction with Life Scale (SWLS) is a self-administered questionnaire, developed to evaluate the

cognitive component of subjective well-being, *i.e.* how satisfied people are with their lives. This scale consists of five items, ranging from 1 (strongly disagree) to 7 (strongly agree). Responses to each item are then inverted using the formula 8-1, resulting in five values that are summed to form the final score. This can range from 5 to 35, *i.e.* extremely dissatisfied to highly satisfied (36).

Statistics analysis

Ordinal data were analysed by Kolmogorov Smirnov, followed by a Mann-Whitney test for non-parametric data. The analyses of correlations between variables were performed using the Spearman's Correlation Test. All data were analysed using GraphPad Prism 5.0 software (San Diego, CA, USA). Data were expressed as minimum, maximum, mean and ± standard deviation. Significance was defined as $p \leq 0.05$ ($\alpha = 0.05$).

Results

Clinical features

This study was conducted on 58 FM patients and 39 health controls. There were no statistically significant differences in age and the body mass index (BMI) between the FM patients and health controls (Table I).

Levels of 6-SMT

Levels of 6-SMT found in urine collected from 8 pm to 8 am of the next day, were significantly lower in FM patients than in healthy controls ($p = 0.017$) (Fig. 1). In the healthy control group the values of 6-SMT in urine ranged from 0.51 ng/ml to 39.82 ng/ml with a mean of 13.32 ng/ml, whereas in the FM group these metabolite levels ranged from 0.32 ng/ml to 24.44 ng/ml, with a mean of 8.52 ng/ml. The mean of 6-SMT was around 36% less in the FM group than the control group. Moreover, the urinary levels of 6-SMT in FM patients are below the median values (12.18 ng/ml) found in the healthy control group in 67.27% of cases (Fig. 1).

Assessment tools

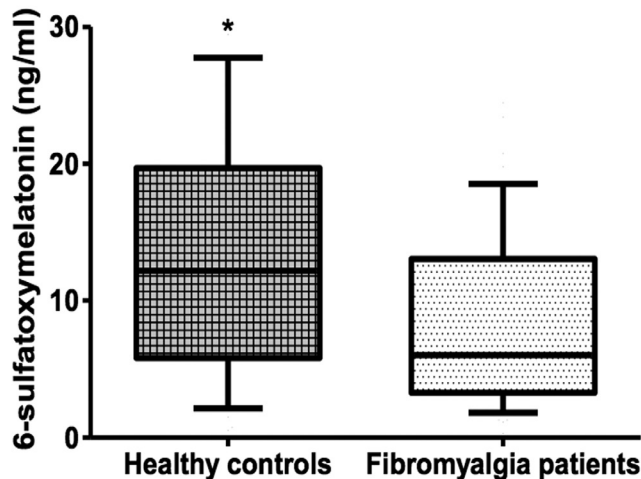
FM patients had a mean of 77.02 points in the FIQ on a scale that goes up to 100 points, indicating that FM is interfering badly on the quality of life of

Table I. Clinical features of health controls and FM patients.

	Controls (Mean ± SD)	FM patients (Mean ± SD)	p-value
Age (years)	50.3 ± 7.7	49.7 ± 10.7	>0.05
BMI (kg/cm ²)	26.7 ± 2.4	26.3 ± 4.5	>0.05
Disease duration (years)	-	5.7 ± 5.6	-
Number of tender points	-	16.4 ± 1.9	-

The clinical features of patients were expressed as mean ± standard deviation. Differences were considered significant when $p \leq 0.05$.

Fig. 1. Box plots (10th, 25th, 50th, 75th and 90th percentiles) showing urinary 6-SMT levels in healthy controls (grey box) and FM patients (white box). The asterisk represents significant difference ($p \leq 0.05$) between the two groups.



these patients (Table II). The controls did not meet the FIQ because this is a specific questionnaire for use in patients with FM.

Regarding the PSQI the average achieved by FM patients was 11.69 points, which means that these patients have moderate deficits regarding quality and sleep patterns (Table II). The mean achieved by the controls in PSQI was 7.64 points, which resulted in a significant difference between groups ($p < 0.0001$).

According to the SF 36 questionnaire, FM patients had significant low scores in all eight domains of the questionnaire, when compared to the controls. The difference between the averages for FM and controls was highly significant, with $p < 0.0001$ in seven out of eight domains (PF, RP, BP, GH, VT, RE, MH) and $p = 0.0009$ in SF domain. On the SWLS, FM patients had an average score of 19.60 points, which means they are slightly dissatisfied with their lives. The healthy controls had a score average of 23.5 points, which means they are slightly satisfied with life.

Again, significant difference was observed between patients and healthy controls with $p = 0.004$.

Correlations

The levels of 6-sulphatoxymelatonin and scores on assessment tools obtained by FM patients were tested using the Spearman's correlation test. Table III corresponds to the matrix of correlation between the variables; where it can be seen that none of the correlations analysed was statistically significant.

Discussion

Our results demonstrate that the excretion of 6-SMT in the darkness hours was 36% lower in FM patients than in healthy subjects matched for sex, age and BMI. Our findings corroborate with the data of Wikner *et al.*, (1998) that demonstrated 31% reduction in serum melatonin secretion during the night (6 pm to 8 am) and 36% reduction in peak release of this marker in FM patients (17). One possible explanation for the low levels of melatonin and 6-SMT in FM patients may be re-

Table II. Score obtained by FM patients in assessment tools.

Assessment tools	Healthy Controls (Mean \pm SD)	Fibromyalgia patients (Mean \pm SD)	<i>p</i> -value
FIQ	–	77.02 \pm 16.19	–
PSQI	7.64 \pm 4.73	11.69 \pm 3.94	<0.0001
SF-36	Physical Functioning (PF)	76.67 \pm 13.15	<0.0001
	Role Physical (RP)	74.36 \pm 19.44	<0.0001
	Bodily Pain (BP)	79.05 \pm 9.63	<0.0001
	General Health (GH)	75.92 \pm 11.61	<0.0001
	Vitality (VT)	70.13 \pm 10.29	<0.0001
	Social Functioning (SF)	60.21 \pm 12.49	0.0009
	Role Emotional (RE)	77.87 \pm 23.38	<0.0001
	Mental Health (MH)	77.49 \pm 9.93	<0.0001
SWLS	23.05 \pm 3.90	19.60 \pm 7.72	0.004

Score achieved by healthy controls and patients with FM in Fibromyalgia Impact Questionnaire (FIQ), Pittsburgh Sleep Quality Index (PSQI), Satisfaction with life scale (SWLS) and in domains of Medical Outcomes Study 36-item Short-Form Health Survey (SF-36). The data were expressed as mean \pm standard deviation.

Table III. Correlation between urinary levels of 6-SMT and score obtained in assessment tools by FM patients.

Assessment tools	6 - SMT		
	Spearman's rho	<i>p</i> -value	
Fibromyalgia Impact Questionnaire (FIQ)	0.79	0.58	
Pittsburgh Sleep Quality Index (PSQI)	-0.19	0.32	
SF-36	Physical Functioning (PF)	0.05	0.80
	Role Physical (RP)	-0.06	0.75
	Bodily Pain (BP)	0.09	0.63
	General Health (GH)	0.05	0.78
	Vitality (VT)	-0.16	0.39
	Social Functioning (SF)	-0.20	0.29
	Role Emotional (RE)	-0.10	0.58
	Mental Health (MH)	-0.14	0.44
The Satisfaction with Life Scale (SWLS)	0.15	0.40	

Matrix of correlation between urinary levels of 6-SMT and score obtained by FM patients in Fibromyalgia Impact Questionnaire (FIQ), Pittsburgh Sleep Quality Index (PSQI), Satisfaction with life scale (SWLS) and domains of Medical Outcomes Study 36-item Short-Form Health Survey (SF-36). The correlations were considered significant when $p \leq 0.05$.

lated to changes in the concentrations of its precursors such as tryptophan and serotonin. These situations have been described in FM and other conditions characterised by chronic pain (14, 18, 37-40). However, this is just an attempt to speculate on the factors that led to reduced levels of 6-SMT in the urine of the participants in our study, since we did not analyse the concentrations and behaviours of any of the precursors of melatonin in the present study. Nevertheless, our results are contradictory to the results of Korszun *et al.* (1999) with showed significant elevated levels of melatonin in the plasma of FM patients compared to healthy controls (16). Besides, many other studies

evaluated the levels of 6-SMT in urine or melatonin levels in serum, but all of them failed to demonstrate any significant differences between FM patients and healthy controls (13-15, 18, 41). Part of those studies showed a trend towards a reduction of these biomarkers in FM patients (13, 14, 41), while others pointed to an increased secretion of melatonin in FM patients (15, 18), however, none of them reached statistical significance, which can be explained at least in part by the small number of patients who participated in the earlier studies. We still believe that such discrepancies in the earlier studies are related to clinical heterogeneity present in FM (42), as well as the methodological

variability (14, 15). Moreover, another factor that certainly contributed to this contradiction is related to the levels of light and the time of exposure to light that both the controls and the FM patients were exposed to on the day of sampling, since melatonin production is highly sensitive to light (43-45).

The lowest levels of 6-SMT identified in patients with FM in the present study may be related to the expression of several key symptoms of FM such as pain, sleep disturbances, fatigue, anxiety and depression. Since the literature is replete with work on the properties of melatonin, ranging from anxiolytic (25, 46), sleep promoter (23, 47, 48), antidepressant (14) antioxidant (27, 49), analgesic (27, 50, 51), and anti-inflammatory properties (24, 26). Due to the range of properties attributed to melatonin and its possible correlation with the symptoms of FM, recently drugs synthesised from melatonin have been tested for the treatment of FM and the results are promising (29, 41, 52, 53). In the pioneering study, four weeks of treatment with 3 mg melatonin resulted in a reduction in the number of tender points, severity of pain and improvement of sleep quality and patient global assessment (41). In another study, a dose of 6 mg was responsible for the significant improvement observed in the sleep/wake cycle of patients. The participants of the cited study also reported a reduction in fatigue, pain and behavioural improvements (53). Nevertheless, the two studies mentioned above, have been criticised because of the low number of the participants, 21 in the first and only 4 in the second (52). However, in 2010 a controlled, double-blind clinical trial provided new evidence supporting the use of melatonin in FM patients. This study included 101 patients divided into four groups (A - 20 mg of fluoxetine, B - 5 mg of melatonin, C - 20 mg of fluoxetine and 3 mg of melatonin, and D - 20 mg of fluoxetine and 5 mg of melatonin). It was demonstrated that the use of 3 mg or 5 mg melatonin with or without 20 mg of fluoxetine is capable of improving the FIQ total score and or their individual components, resulting in improvement in the quality of life of FM patients

(29). Studies on the therapeutic application of melatonin are justified, especially by its broad therapeutic potential, low cost and high level of safety, and the relative ineffectiveness of the treatments currently used in FM (52).

As well as demonstrating that patients with FM have lower levels of urinary 6-SMT, this study also demonstrated that these patients achieved worse scores in the four assessment tools when compared to healthy controls. Our findings corroborate with other studies that have already shown that patients with FM have lower levels of melatonin (17) and worse scores on assessment instruments than healthy individuals (54, 55). These findings led us to believe that melatonin could be interfering directly in the clinical presentation of these patients. To test this hypothesis we evaluated, for the first time, the likely correlation between the urinary concentrations of 6-SMT and the score obtained by patients in four assessment tools: FIQ, PSQI, SF-36 and SWLS. After analysis we found no significant correlation between urinary levels of 6-SMT and scores on self-assessment instruments, indicating that patients with FM in spite of presenting significant changes in sleep quality, quality of life, satisfaction with their lives, and have been strongly impacted by FM in various domains such as physical, psychological and functional, this situation does not occur exclusively due to low levels of 6-SMT found in their urine. Is worth noting that these results do not exclude the involvement of melatonin and its metabolites in the pathophysiology of FM, but rather confirm the multifactorial character already described in this syndrome (10, 11, 56). We believe it is likely that alteration on other neuroimmunoendocrine products such as cytokines and cortisol may be associated to a melatonin change, and that these modifications together could be directly responsible for the manifestation of symptoms that make up the clinical picture of FM.

The discussion on the involvement of melatonin in the pathogenesis of FM is still far from being complete. The clinical heterogeneity of these patients, associated with controversial results

of the studies hinders understanding of this situation. However, we cannot deny that drugs derived from melatonin are emerging as a potential treatment for this condition. More controlled studies should be performed in order to evaluate the real role of melatonin in both the pathophysiology and the treatment of this syndrome.

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