Melatonin Levels in Women with Fibromyalgia and Chronic Fatigue Syndrome

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ABSTRACT. ***Objective.*** Fibromyalgia (FM) and chronic fatigue syndrome (CFS) are stress associated disorders mainly affecting women. FM is characterized primarily by widespread musculoskeletal pain, and CFS by profound debilitating fatigue, but there is considerable overlap of clinical symptoms between these 2 syndromes. Neuroendocrine abnormalities have been noted in both FM and CFS and desynchronization of circadian systems has been postulated in their etiology. The pineal hormone melatonin is involved in synchronizing circadian systems and the use of exogenous melatonin has become widespread in patients with FM and CFS.

Methods. We examined the characteristics and relationship of melatonin and cortisol levels in premenopausal women with FM (n = 9) or CFS (n = 8), compared to age and menstrual cycle phase matched controls. Blood was collected from an indwelling intravenous catheter every 10 min over 24 h, and plasma melatonin and cortisol were determined by radioimmunoassay at 60 and 10 min intervals, respectively.

Results. Night time (23:00–06:50) plasma melatonin levels were significantly higher in FM patients compared to controls ($p < 0.05$), but there was no significant difference in melatonin levels between CFS patients and controls. No differences in the timing of cortisol and melatonin secretory patterns and no internal desynchronization of the 2 rhythms were found in either patient group, compared to controls.

Conclusion. Raised plasma melatonin concentrations have been documented in several other conditions that are associated with dysregulation of neuroendocrine axes. Increased melatonin levels may represent a marker of increased susceptibility to stress induced hypothalamic disruptions. These data indicate that there is no rationale for melatonin replacement therapy in patients with FM and CFS. (J Rheumatol 1999;26:2675–80)

Key Indexing Terms:
MELATONIN FIBROMYALGIA CHRONIC FATIGUE SYNDROME WOMEN

Fibromyalgia (FM) and chronic fatigue syndrome (CFS) are 2 common clinically related syndromes that primarily affect women[1,2]. FM is characterized by widespread chronic pain affecting the musculoskeletal system, with well defined tender points on examination and associated symptoms of sleep disturbance and fatigue[3]. The high frequency of fatigue in patients with FM suggests overlap with CFS, for which operational criteria for diagnosis have been developed by the Centers for Disease Control and Prevention[4,5]. This requires debilitating fatigue of more than 6 months' duration, in the absence of an identifiable medical or psychiatric etiology. In addition, patients with CFS often complain of musculoskeletal discomfort that is accompanied by tender points.

FM and CFS are widely regarded as stress related syndromes because of the increase in symptoms associated with physical or emotional stress. Significant progress has been made in recent years in defining the neuroendocrine disturbances of FM and CFS. Abnormalities in serotonin metabolism, adrenergic sympathetic nervous system activity, and hypothalamic-pituitary-adrenal (HPA) axis function have been reported in these conditions[6]. All these neuroendocrine systems are closely related to the synthesis and function of the pineal hormone, melatonin.

Melatonin is involved in synchronization of circadian, or near 24 hour, rhythms by acting as an interface between the brain and the environmental light–dark cycle. Photic information from the retina is transmitted to the pineal gland through the primary pacemaker, the suprachiasmatic nucleus in the hypothalamus, which sends circadian signals over a multisynaptic sympathetic neural pathway driving rhythmic melatonin production. The synthesis and release of melatonin are

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stimulated by darkness and inhibited by light. In humans, melatonin secretion increases soon after the onset of darkness, peaks in the middle of the night (02:00–04:00) and gradually falls during the second half of the night[7]. The timing of the melatonin secretory rhythm is a reliable marker for circadian phase position[8]. There have been several studies describing interaction between the pineal gland and the HPA axis, the principal stress–response system, suggesting a coupling between the rhythms of cortisol and melatonin[9–12]. The HPA axis exhibits a circadian rhythm in antiphase to the melatonin rhythm, with peak plasma cortisol concentrations occurring before awakening around the onset of daylight and then falling progressively to a nadir around the early to midpoint of sleep.

Abnormal phase positions of circadian systems relative to one another or to the day–night cycle, as seen in conditions such as jet lag and shift work, may result in symptoms of sleep disruption, daytime fatigue, cognitive dysfunction, and depression[13]. Melatonin and bright light have been used successfully to treat these conditions[8]. Similar symptoms are characteristic of both CFS and FM and may be associated with secretory abnormalities and/or desynchronization of circadian rhythms. A recent study of patients with CFS reported a dissociation of the circadian rhythms of body temperature and melatonin secretion[14].

Exogenous melatonin has direct effects on physiological rhythms including sleep and, at appropriate doses, increases sleep propensity and duration[15]. It has become widely available, and its use by patients with FM and CFS is widespread, largely based on scientifically unsupported reports in the media and on the Internet that these conditions result from melatonin deficiency.

Our aim was to examine the circadian pattern of melatonin secretion in women with FM and/or CFS compared to matched controls. We also tested the hypothesis that there is desynchronization between melatonin and cortisol secretory rhythms in FM and CFS. Our results explore the rationale underlying the therapeutic use of melatonin in this patient population.

MATERIALS AND METHODS

Subjects. Subjects with FM and/or CFS were recruited from among consecutive patients presenting to 2 University of Michigan outpatient clinics, the rheumatology subspecialty clinic and the chronic fatigue clinic (Division of Infectious Diseases). They comprised 17 premenopausal women who had been diagnosed with FM (with or without comorbid CFS) (n = 9), or with CFS only (n = 8) (Table 1).

The diagnosis of FM was based on the 1990 criteria of the American College of Rheumatology[3] and tender point examination was carried out within one month of study; CFS was diagnosed according to the US Centers for Disease Control case definition[4]. Seventeen sedentary control subjects were individually age matched (± 2 yrs). Controls were not matched for race. All subjects were screened to exclude any recent chronobiological disruptions such as shift work or travel across time zones. All patients and controls were evaluated by structured psychiatric interview (SCID-IIIR or IV) to exclude any major Axis I disorders prior to inclusion in the study. All subjects had a body mass index < 30 and were free of all medications except thyroid hormone replacement in stable individuals with treated hypothyroidism. All psychoactive medications were discontinued for at least 2 weeks prior to study. Subjects and controls were all studied during the follicular phase of the menstrual cycle, that is, within 10 days after the onset of menstruation.

Procedures. Subjects were admitted to the General Clinical Research Center on the evening prior to 24 h sampling to equilibrate to the unit. Meals were served at regular times (07:30, 12:00, 17:30, respectively) and a log was kept to record activities during the study period. At 07:00 the following morning, a large bore intravenous catheter was placed in an antecubital or other large arm vein and attached by a connection to a double stopcock assembly attached to an intravenous (iv) line for withdrawal of samples. Intravenous fluids (0.45 saline) were infused to keep the catheter open between sample withdrawal, and heparin (1000 u/l) was added to iv fluids if blood flow during sample withdrawal diminished. Samples of 2.8 ml of venous blood were collected every 10 min over 24 h to give a total of 406 ml. Blood was collected in chilled, sequentially labeled glass tubes containing EDTA to prevent clotting and inhibit proteolytic activity. Plasma was separated by centrifugation within 2 h of collection, then frozen and stored at –70°C until assayed.

Hormone assays. Plasma cortisol was determined by direct radioimmunoassay (RIA) in samples obtained at 10 min intervals (144 samples/subject) (Coat-a-Count™ Diagnostic Products Inc., Los Angeles, CA, USA). The intraassay coefficient of variation for the cortisol assay was 4.8% at a mean of 3.1 μg/dl and 4.4% at a mean of 34 μg/dl; the interassay coefficient of variation was 5.2% at a mean of 3.3 μg/dl and 6.4% at a mean of 36 μg/dl.

Because melatonin levels remain low during the day and increase nocturnally, we used more frequent sampling at night. Therefore, aliquots of 30 μl were taken from 6 consecutive samples and pooled over each hour during night time hours (17:00–08.50) from 12 consecutive samples for 2-hourly assays over daytime hours (09:00–16.50). Plasma melatonin was determined in these samples (total 20 samples/subject) by direct RIA (Elias USA, Inc., Osceola, WI, USA). The coefficient of variation for melatonin assays was 17.9% at a mean of 7.6 pg/ml, and 16.7% at a mean of 73.5 pg/ml.

Statistical analysis. Comparison of mean melatonin levels between patients with (a) FM and (b) CFS and their respective controls was made over the following three 8 h periods: 07:00–14:50, 15:00–22:50, 23:00–06:50. An unpaired Student's t test was used, as patients and controls were not individually matched for the time of year in which the study was carried out. However, data collection was performed in equal distribution between the 2 groups throughout the year.

Melatonin and cortisol data were subjected to cosinor analysis (i.e., fitting of a cosine curve using a least-squares regression analysis) to determine MESOR (rhythm adjusted mean value), amplitude (distance from MESOR to the peak or trough of the cosine curve), and acrophase (the timing of the peak of the cosine curve)[16]. Differences in cosinor variables of cortisol and melatonin secretion in patients versus controls were analyzed using the method of Bingham and colleagues[17]. Differences between groups were investigated by analysis of variance.

To determine whether there was any desynchronization of melatonin and cortisol rhythms, the differences in acrophase between melatonin and cortisol were found by the Bingham test[17].

RESULTS

Rise of melatonin secretion. FM patients showed an increased nocturnal rise of melatonin secretion compared to controls. The mean level of nocturnal melatonin (23:00–06:50) was significantly increased in patients with FM (75.20 ± 7.50 pg/ml) compared to controls (58.46 ± 4.79 pg/ml) ($p < 0.05$) (Figure 1). There was no significant difference in nocturnal melatonin in patients with CFS compared to controls. There was no relationship between patients' levels of pain, as represented by the number of tender points present on examination,

Table 1. Characteristics of patients and their matched controls.

Patient-Control Pair	Age		Patient Diagnosis	No. of Tender Points		Month of Study†	
	Patients	Controls		Patients	Controls	Patients	Controls
1	42	45	FM	17	2	3	1
2	44	44	FM	18	0	9	6
3	23	24	FM	12	4	2	1
4	36	37	FM	17	1	4	9
5	40	42	FM	17	0	6	12
6	37	34	FM	13	0	8	3
7	42	42	FM	18	0	8	1
8	35	37	FM	13	0	10	11
9	18	21	FM	11	2	12	4
Mean (± SEM)	34.44 (± 2.93)	36.22 (± 2.87)		15.11 (± 0.93)	1 (± 0.47)		
10	33	29	CFS	3	0	3	11
11	35	35	CFS	6	2	5	6
12	37	39	CFS	1	0	8	3
13	29	28	CFS	7	0	10	5
14	40	44	CFS	9	4	4	8
15	18	19	CFS	6	0	7	5
16	23	24	CFS	0	3	10	7
17	47	46	CFS	5	0	2	3
Mean (± SEM)	32.5 (± 3.29)	33 (± 3.40)		4.63 (± 1.08)	1.13 (± 0.58)		

and mean melatonin levels. Both patients and controls showed a similar decline in melatonin levels with age.

Timing of melatonin secretion. There were no differences in the timing of the offset, onset, or peak time of melatonin secretion between the 2 groups. Similarly, there was no significant difference between MESOR, amplitude or acrophase in cortisol secretion in patients compared to controls. There was no evidence of desynchronization between the rhythms of the 2 hormones in patients compared to controls (Figure 2). In patients with CFS the difference between the acrophase of melatonin and cortisol was 7 h 16 min compared to 6 h 44 min in controls. Patients with FM showed a difference of 7 h 4 min compared to 6 h 36 min in the control group.

DISCUSSION

Contrary to our expectations based on reports[14] that patients would show decreased melatonin levels and a possible phase shift of hormone rhythms, we found that premenopausal women with FM showed a significant increase in nocturnal melatonin levels compared to controls and patients with CFS showed no differences. We found no differences in the timing of melatonin and cortisol secretory rhythms.

While patients and controls were not individually matched for the time of the year in which the study was carried out, data collection was performed in equal distribution between the 2 groups throughout the year. This is notable, because in order for time of year to act as a confounder, it would have to be associated not only with melatonin levels, but also with disease status. Therefore, while the effect of time of year on melatonin levels is important to consider, it is highly unlikely that our results have suffered from temporal confounding.

As discussed below, the increased melatonin levels in FM cannot be attributed merely to disrupted sleep and social routines. However, the possibility remains that reduced elimination or altered distribution may explain the increased melatonin levels or tissue resistance to melatonin action that could result in increased production. Although the exact significance of this finding is unknown, it is intriguing that similar patterns of increased melatonin levels have been reported in other syndromes that affect women and are associated with neuroendocrine dysregulation, in particular of the reproductive hormonal axis, e.g., functional amenorrhea[18,19], exercise induced amenorrhea[20], and anorexia nervosa[21,22] (Table 2).

Insomnia is a prominent feature of FM and CFS and many patients complain of disturbed or nonrefreshing sleep[23]. It has been suggested, in CFS in particular, that neuroendocrine abnormalities occur as a consequence of disrupted sleep–wake cycles[24]. However, studies correlating sleep with neuroendocrine rhythms show a reduction in melatonin levels associated with fragmented sleep and insomnia in both elderly individuals[24–26] and younger patients[25]. Interestingly, the most severely reduced nocturnal levels were found in those patients with a longer history (> 5 years) of sleep disturbance. It is thus unlikely that the present finding of increased nocturnal melatonin levels in FM patients can be attributed to disturbed sleep patterns. Furthermore, melatonin is an excellent marker of phase position[8], therefore if symptoms were due to disrupted sleep–wake cycles, one would expect some phase abnormalities in melatonin secretory rhythms.

Williams and colleagues[14] have reported dissociated temperature and cortisol rhythms in patients with CFS, suggesting that desynchronization of circadian rhythms may play a sig-

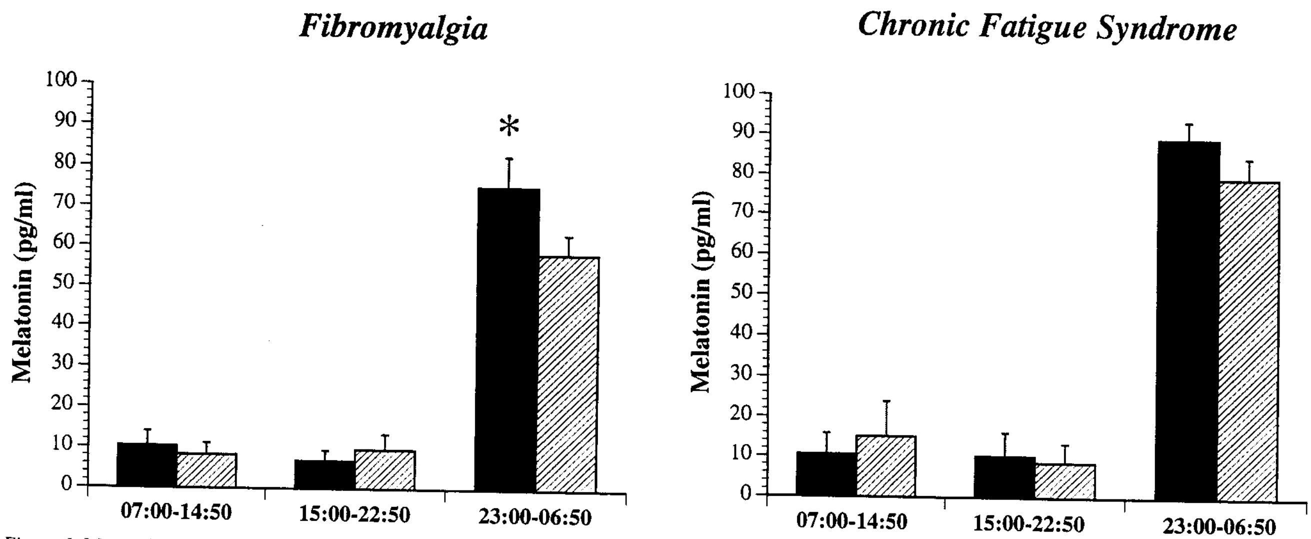

Figure 1. Mean plasma melatonin levels (± SEM) in 9 women with FM and 8 women with CFS and their matched controls over three 8 h periods.

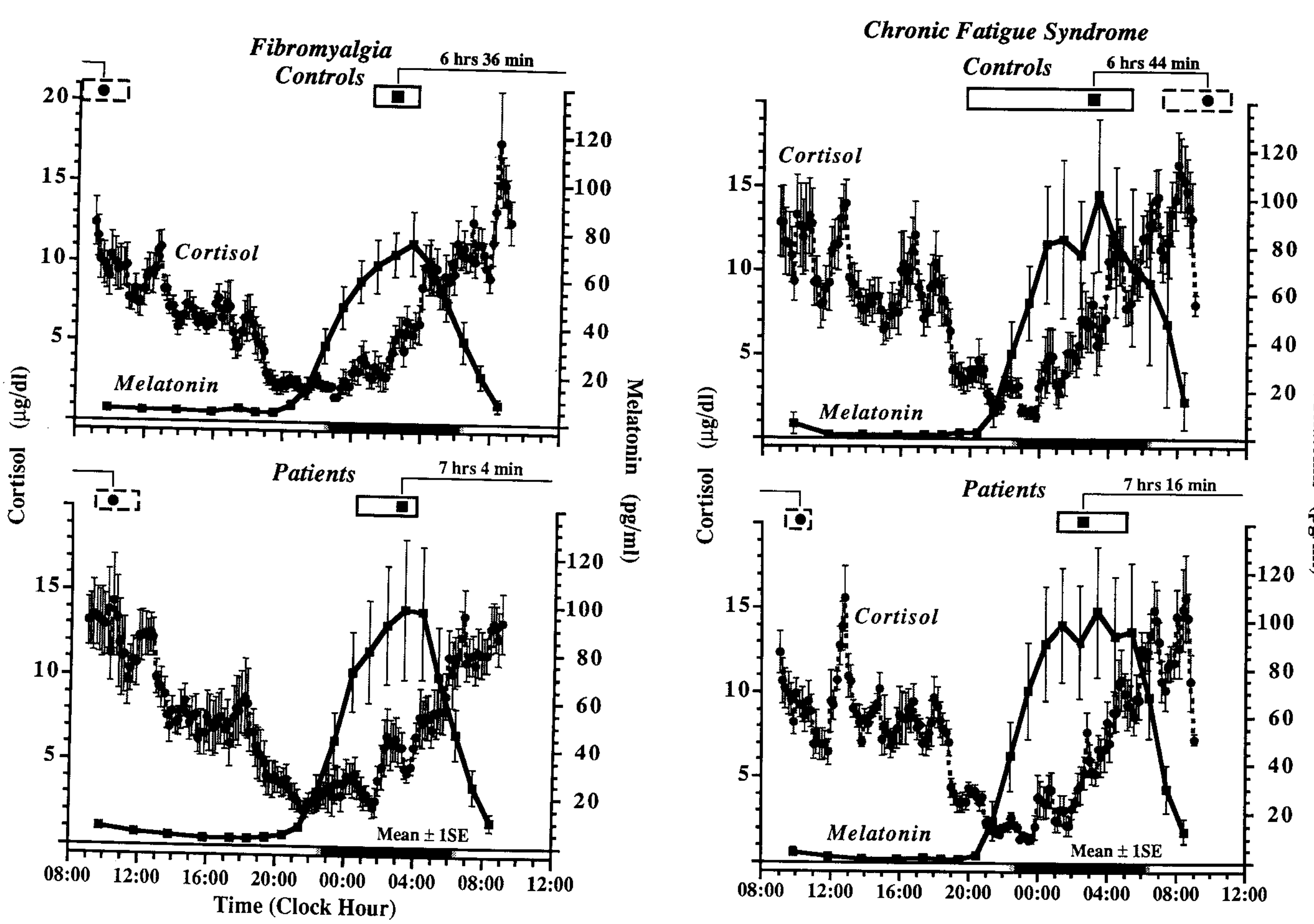

Figure 2. Plasma cortisol and melatonin secretion over 24 h in patients and controls with (a) fibromyalgia and (b) chronic fatigue syndrome. The acrophase of melatonin is represented by a solid square and that of cortisol by a circle. The boxes around the acrophase times indicate 95% confidence intervals. There is no significant difference in the timing of either rhythm in patients versus controls and no desynchronization between the rhythms of cortisol and melatonin. The period of "lights off" is marked by a solid bar overlying the corresponding clock hours.

Table 2. Summary of altered melatonin amplitude reported in other stress associated conditions.

Disorder	Melatonin	Study
Hypothalamic amenorrhea	Increased	Berga, *et al*, 1995[18]
		Brzezinski, *et al,* 1988[19]
Exercise induced amenorrhea	Increased	Laughlin, *et al,* 1991[20]
Anorexia nervosa	Increased	Brambilla, *et al,* 1988[21]
		Tortosa, *et al,* 1989[22]
Depression	Increased	Rubin, *et al*, 1992[26]

nificant role in the pathogenesis of CFS. However, their results are difficult to interpret as most of the patients were not medication-free or had comorbid depressive disorders. Our data, although based on small samples, were stringently controlled for these and other variables, and did not show significant dissociation between cortisol and melatonin secretion in patients with CFS or FM. In both FM and CFS, the acrophase of cortisol was delayed relative to melatonin. It is possible that significance could be detected with larger patient groups.

It is of great interest that similar changes in the pattern of melatonin concentrations have been reported in other stress associated syndromes affecting women (Table 2). For instance, both elevated amplitude and extended duration (delay in offset time) of nocturnal melatonin have been reported in women with functional hypothalamic amenorrhea[18,19]. In this condition amenorrhea is thought to occur as a result of stress mediated dysregulation of the HPA axis, which in turn causes decreased hypothalamic gonadotropin releasing hormone (GnRH) input to the pituitary–ovarian axis[18].

Rubin and colleagues[26], in a study of melatonin secretion in depressed patients, found that premenopausal and postmenopausal women showed significantly elevated average nocturnal melatonin concentrations compared to men. There was a 48% increase in average nocturnal melatonin concentrations in the female patients compared to their matched controls, but no difference between male patients and their controls. Furthermore premenopausal patients (but not controls) had a trend toward higher nocturnal melatonin levels than the postmenopausal women. Prior studies had reported reduced melatonin levels in depressed patients, but these were methodologically flawed mainly because subjects were taking psychotropic drugs, which are known to influence melatonin secretion[27,28]. Again, depression is a stress associated disorder affecting women twice as commonly as men and characterized by neuroendocrine disruptions involving the hypothalamus.

Considering all these data together, it is possible that there is a group of women who are more susceptible to hypothalamic disruptions secondary to stress, resulting in neuroendocrine abnormalities including raised nocturnal melatonin levels. These women would be at higher risk of developing stress associated syndromes such as FM, and increased nocturnal levels of melatonin are associated with hypothalamic disruption of both stress and gonadal hormonal axes.

The popular press has touted melatonin as a hormone that has therapeutic effects in many diverse conditions[29], and the use of exogenous melatonin as a sleeping aid is widespread among patients with FM and CFS to improve the quality of their sleep. However, a blinded randomized clinical trial of the effects of melatonin supplementation on these groups of patients has not been carried out. Furthermore, the present data suggest that there is no physiological rationale for melatonin replacement therapy in patients with FM or CFS, as their nocturnal levels are either normal or increased.

REFERENCES

1. Wolfe F, Ross K, Anderson J, Russell IJ, Hebert L. The prevalence and characteristics of fibromyalgia in the general population. Arthritis Rheum 1995;38:19–28.
2. Gunn WJ, Connell DB, Randall B. Epidemiology of chronic fatigue syndrome: the Centers for Disease Control study. In: Bock GR, Whelan J, editors. Chronic fatigue syndrome. Chichester, England: John Wiley & Sons; 1993:83–101.
3. Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia: report of the multicenter criteria committee. Arthritis Rheum 1990;33:160–72.
4. Holmes GP, Kaplan JE, Gantz NM, et al. Chronic fatigue syndrome: a working case definition. Ann Intern Med 1988;108:387–9.
5. Fukuda K, Straus S, Hickie I, et al. The chronic fatigue syndrome: a comprehensive approach to its definition and study. Ann Intern Med 1994;121:953–9.
6. Crofford LJ, Engleberg NC, Demitrack MA. Neurohormonal perturbations in fibromyalgia. Bailliere's Clin Rheumatol 1996;10:1–14.
7. Brzezinski A. Melatonin in humans. N Engl J Med 1997;16:336:186–95.
8. Lewy AJ, Sack RL, Blod ML, et al. Melatonin marks circadian phase position and resets the endogenous circadian pacemaker in humans. In: Chadwick DJ, Ackrill K, editors. Circadian clocks and their adjustment. New York: John Wiley & Sons; 1995:303–21.
9. Brismar K, Werner S, Thoren M, Wetterberg L. Metyrapone: an agent for melatonin as well as ACTH and cortisol secretion. J Endocrinol Invest 1985;8:91–5.
10. Beck-Friis J, Hanssen T, Kjellman BF, Ljundgren JG, Unden F, Wetterberg L. Serum melatonin and cortisol in human subjects after the administration of dexamethasone and propranolol. Psychopharm Bull 1983;19:646–8.
11. Catapano F, Monteleone P, Fuschino A, Maj M, Kemali D. Melatonin and cortisol secretion in patients with primary obsessive-compulsive disorder. Psychiatry Res 1992;44:217–25.
12. Soszynski P, Stowinska-Srzednicka J, Kasperlik-Zatuska A, Zgliczynski S. Decreased melatonin concentration in Cushing's syndrome. Horm Metab Res 1989;21:673–4.

13. Arendt J. Melatonin and the mammalian pineal gland. London: Chapman & Hall; 1995.
14. Williams G, Pirmohamed J, Minors D, et al. Dissociation of body-temperature and melatonin secretion circadian rhythms in patients with chronic fatigue syndrome. Clin Physiol 1996;16:327–37.
15. Dollins AB, Zhdanova IV, Wurtman RJ, Lynch HJ, Deng MH. Effect of inducing nocturnal serum melatonin concentrations in daytime on sleep, mood, body temperature, and performance. Proc Natl Acad Sci USA 1994;91:1824–8.
16. Nelson W, Tong YL, Lee J-K, Halberg F. Methods for cosinor rhythmometry. Chronobiologia 1979;6:305–23.
17. Bingham C, Arbogast B, Guilaume GC, Lee J-K, Halberg F. Inferential statistical methods for estimating and comparing cosinor parameters. Chronobiologia 1982;9:397–439.
18. Berga SL. Stress and amenorrhea. The Endocrinologist 1995;5:416–21.
19. Brzezinski A, Lynch HJ, Seibel MM, Deng MH, Nader TM, Wurtman RJ. The circadian rhythm of plasma melatonin during the normal menstrual cycle and in amenorrheic women. J Clin Endocrinol Metab 1988;66:891–5.
20. Laughlin GA, Loucks AB, Yen SS. Marked augmentation of nocturnal melatonin secretion in amenorrheic athletes, but not in cycling athletes: unaltered by opioidergic or dopaminergic blockade. J Clin Endocrinol Metab 1991;73:1321–6.
21. Brambilla F, Fraschini F, Esposti G, Bossolo PA, Marelli G, Ferrari E. Melatonin circadian rhythm in anorexia nervosa and obesity. Psychiatry Res 1988;23:267–76.
22. Tortosa F, Puig-Domingo M, Peinado M-A, Oriola J, Webb SM, de Leiva A. Enhanced circadian rhythm of melatonin in anorexia nervosa. Acta Endocrinologica (Copenh) 1989;120:574–8.
23. Moldofsky H. Sleep, neuroimmune and neuroendocrine functions in fibromyalgia and chronic fatigue syndrome. Adv Neuroimmunology 1995;5:39–56.
24. Leese G, Chattington P, Fraser W, Vora J, Edwards R, Williams G. Night-shift working mimics the pituitary-adrenocortical dysfunction in chronic fagitue syndrome. J Clin Endocrinol Metab 1996;81:1867–70.
25. Rodenbeck A, Hajak G, Huether G. Melatonin in insomniac patients and effects of sleep medication. In: Filippini GA, editor. Recent advances in tryptophan research. New York: Plenum Press; 1996:113–7.
26. Rubin RT, Heist EK, McGeoy SS, Hanada K, Lesser IM. Neuroendocrine aspects of primary endogenous depression XI. Serum melatonin measures in patients and matched control subjects. Arch Gen Psychiatry 1992;49:558–67.
27. Wetterberg L, Beck-Friis J, Kjellman BF, Ljunggren JG. Circadian rhythms in melatonin and cortisol secretion in depression. In: Usdin E, Asberg M, Bertilsson L, Sjoquist F, editors. Frontiers in biochemical and pharmacological research in depression. New York: Raven; 1984.
28. Beck-Friis J, Kjellman BF, Aperia B, et al. Serum melatonin in relation to clinical variables in patients with major depressive disorder and a hypothesis of a low melatonin syndrome. Acta Psychiatr Scand 1985;71:319–30.
29. Reppert SM, Weaver DR. Melantonin madness. Cell 1995;83:1059–62.