0021-972X/01/$03.00/0
The Journal of Clinical Endocrinology & Metabolism

Vol. 86, No. 3
Printed in U.S.A.

Circadian Rhythms of Women with Fibromyalgia*

ELIZABETH B. KLERMAN, DON L. GOLDENBERG, EMERY N. BROWN, ANNE M. MALISZEWSKI, AND GAIL K. ADLER

Endocrine-Hypertension Division, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School (E.B.K., A.M.M., G.K.A.), Boston, Massachusetts 02115; Division of Rheumatology, Newton-Wellesley Hospital (D.L.G.), Newton Massachusetts 02462; Department of Medicine, Tufts University School of Medicine (D.L.G.), Boston, Massachusetts 02111; and Department of Anesthesiology and Critical Care, Harvard Medical School/Massachusetts Institute of Technology Division of Health Sciences and Technology (E.N.B.), Boston, Massachusetts 02114

ABSTRACT

Fibromyalgia syndrome is a chronic and debilitating disorder characterized by widespread nonarticular musculoskeletal pain whose etiology is unknown. Many of the symptoms of this syndrome, including difficulty sleeping, fatigue, malaise, myalgias, gastrointestinal complaints, and decreased cognitive function, are similar to those observed in individuals whose circadian pacemaker is abnormally aligned with their sleep-wake schedule or with local environmental time. Abnormalities in melatonin and cortisol, two hormones whose secretion is strongly influenced by the circadian pacemaker, have been reported in women with fibromyalgia. We studied the circadian rhythms of 10 women with fibromyalgia and 12 control healthy women. The protocol controlled factors known to affect markers of the circadian system, including light levels, posture, sleep-wake state, meals, and activity. The timing of the events in the protocol were calculated relative to the habitual sleep-wake schedule of each individual subject. Under these conditions, we found no significant difference between the women with fibromyalgia and control women in the circadian amplitude or phase of rhythms of melatonin, cortisol, and core body temperature. The average circadian phases expressed in hours posthabitual bedtime for women with and without fibromyalgia were 3:43 ± 0:19 and 3:46 ± 0:13, respectively, for melatonin; 10:13 ± 0:23 and 10:32 ± 0:20, respectively for cortisol; and 5:19 ± 0:19 and 4:57 ± 0:33, respectively, for core body temperature phases. Both groups of women had similar circadian rhythms in self-reported alertness. Although pain and stiffness were significantly increased in women with fibromyalgia compared with healthy women, there were no circadian rhythms in either parameter. We suggest that abnormalities in circadian rhythmicity are not a primary cause of fibromyalgia or its symptoms. (*J Clin Endocrinol Metab* **86:** 1034–1039, 2001)

FIBROMYALGIA SYNDROME is a chronic, poorly understood disorder characterized by widespread nonarticular, musculoskeletal pain (1). It affects 2% of the population, is 7 times more likely to occur in women than men (2), and is a significant source of suffering, with approximately one quarter of all patients receiving disability payments (3). During the past 10 yr, many lines of evidence have suggested that central nervous system dysfunction, rather than primary muscle pathology, may contribute to the pathophysiology of fibromyalgia (4).

Many of the symptoms associated with fibromyalgia (difficulty sleeping, fatigue, malaise, myalgias, gastrointestinal complaints, and decreased cognitive function) are similar to those observed in individuals whose circadian pacemaker is abnormally aligned with their sleep-wake schedule and/or with local environmental time. Misalignment of the phase of the circadian pacemaker occurs in individuals experiencing jet lag, in individuals working night or rotating shifts, and in blind persons (for a review, see Ref. 5). In the case of shiftworkers, when light therapy is used to realign the circadian phase with their sleep-wake cycle, these symptoms decrease or resolve (6).

The circadian pacemaker, located in the hypothalamus, influences melatonin secretion and activity of the hypothalamic-pituitary-adrenal (HPA) axis. Abnormalities in both of these systems have been described in individuals with fibromyalgia. Studies comparing melatonin levels in patients with fibromyalgia to healthy controls have shown normal (7), decreased (8), and increased (9) melatonin levels in the patients. It has been postulated that a change in melatonin secretion causes changes in sleep, pain, the somatotropic axis, and the HPA axis (10). One nonplacebo-controlled study showed a beneficial effect of melatonin supplementation on fibromyalgia symptoms (11).

With respect to the HPA axis, alterations in its response to administered secretagogues (12, 13) have been reported in this disorder. We found a blunted rise in ACTH in women with fibromyalgia during a hypoglycemic-hyperinsulinemic clamp performed in the morning (14). Similarly, women with fibromyalgia showed a delayed rise in ACTH in response to infused interleukin-6 (15). Some, but not all, studies have shown blunting of the normal diurnal cortisol rhythm, with elevated evening serum cortisol levels in fibromyalgia (12, 14, 16).

The similarity in symptoms between patients with fibro-

Received June 12, 2000. Revision received September 22, 2000. Rerevision received November 15, 2000. Accepted November 16, 2000.

Address all correspondence and requests for reprints to: Elizabeth B. Klerman, M.D., Ph.D., Circadian, Neuroendocrine, and Sleep Disorders Section, Endocrine-Hypertension Division, Brigham and Women's Hospital, 221 Longwood Avenue, Boston, Massachusetts 02115. E-mail: ebklerman@hms.harvard.edu.

* This work was supported in part by NIH Grants RO1-AR-43130 (to G.K.A.), M01-RR-20635 (to Brigham and Women's Hospital General Clinical Research Center), K01-AG-00661 (to E.B.K.), and R01-GM-53559 and K02-MH-61637 (to E.N.B.) and NASA Cooperative Agreement NCC9-58 with the National Space and Biomedical Research Institute.

myalgia and individuals with misaligned circadian phase as well as the observations of abnormalities in two hormone systems tightly regulated by the circadian pacemaker raise the possibility that there is an abnormality in circadian phase in patients with fibromyalgia. Controlled studies of circadian rhythms have not been performed in individuals with fibromyalgia.

In this study we assessed circadian phase and amplitude in women with fibromyalgia and healthy women using a 40-h constant routine protocol scheduled relative to each subject's habitual sleep-wake cycle. Under the constant routine conditions, factors known to affect markers of circadian phase, including sleep-wake state, changes in posture, changes in diet, and changes in light levels, are minimized or are evenly distributed across the constant routine protocol. The amplitude and phase of three acknowledged markers of circadian rhythms (cortisol, melatonin, and core body temperature) were determined (17). The use of three circadian markers decreases the possibility that our assessment of circadian phase will be confounded by an underlying dysfunction in one system. Diurnal rhythms in pain and fatigue symptoms have also been reported in patients with fibromyalgia (18). For this reason, we assessed whether patients with fibromyalgia have a normal circadian variation of alertness and examined subjective measurements of pain and stiffness for circadian rhythmicity.

Subjects and Methods

Subjects

Ten premenopausal women with fibromyalgia as defined by American College of Rheumatology criteria (1) and 12 healthy premenopausal women were studied. Fibromyalgia subjects were recruited from the clinical practice of one author (D.L.G.), and control subjects were recruited using advertisements in local newspapers. All subjects underwent a Structured Clinical Interview from Diagnostic and Statistical Manual of Mental Disorders, fourth edition, to identify past and present psychiatric diagnoses. Control subjects with a current or past psychiatric diagnosis were excluded, except for one subject with a past acute stress disorder secondary to date rape. All subjects underwent a detailed history, physical exam, and measurement of blood and urine chemistries, including thyroid function studies. Potential subjects with abnormal laboratory studies, body mass index above 29.9 kg/m^2, or current medical problems other than fibromyalgia were excluded. Diagnosis of active fibromyalgia was confirmed and documented before initiation of study procedures by one author (D.L.G.) using published classification criteria (1). Subjects completed a Fibromyalgia Impact Questionnaire (19) that assesses pain, sleep disturbances, as well as other symptoms.

Prescription and nonprescription medications (except for thyroid hormone and acetaminophen) were discontinued for 2 weeks before the in-patient portion of the protocol in all participants. The one patient with fibromyalgia who was receiving thyroid replacement medication had a normal TSH level and continued to receive T_4 during the study. Acetaminophen was allowed up to 48 h before hospitalization. No women had received any form of glucocorticoids within the year before study or estrogen/progesterone within the previous 4 months.

All study procedures were reviewed and approved by the Human Research Committee of the Partners HealthCare System. Before enrolling in the study, informed written consent was obtained by each participant. All studies took place at the General Clinical Research Center of Brigham and Women's Hospital.

Protocol

For 3 weeks before the start of a 5-day in-patient protocol, subjects wore an actigraph on their wrist and were instructed to adhere to a sleep-wake schedule of 8 h in bed, based on their usual schedule. Habitual sleep-wake times were calculated for each subject, and subjects were admitted to the General Clinical Research Center. For 3 consecutive nights, subjects were scheduled to sleep for 8 h in the dark at their habitual sleep-wake times. Electrocardiograms and polysomnographic recordings of sleep were obtained.

Starting with night 2 and continuing through the end of the study, subjects remained in an environment free of time cues (no clock, watch, radio, or TV) and in dim light (<15 lux). Beginning 7 h before the night 3 sleep episode and continuing through the end of the protocol, subjects remained in bed, either supine with a 30° head-up tilt during scheduled wake episodes or flat during the scheduled night 3 sleep episode. During scheduled wake times, subjects assessed alertness, stiffness, and pain every 20–60 min using computerized, linear, nonnumeric visual analog scales (20). Core body temperature (CBT) was measured continuously using a rectal temperature sensor (YSI, Inc., Yellow Springs OH). Blood was sampled every 10–20 min for cortisol and every 60 min for melatonin through an iv catheter inserted 2 h before the initiation of blood sampling. Our intent in this study was to describe the circadian rhythms in these hormones and not to determine secretory pulse patterns.

Upon awakening on day 4, all subjects began a 40-h constant routine protocol. Subjects maintained continuous wakefulness with semirecumbent posture and consumed hourly, constant, small meals. A technician was in the room with the subjects to aid the subject in remaining awake, and electroencephalogram recordings were obtained to confirm wakefulness. At the end of the constant routine, subjects were allowed 1 night of recovery sleep before discharge.

Subjects consumed a controlled nutrient, isocaloric diet consisting of 125 mEq sodium, 100 mEq potassium, 1000 mg calcium, and 2500 cc fluid beginning 2 days before admission and continuing throughout the protocol. On in-patient days 1, 2, and 3, all subjects were given three meals and two snacks. During the constant routine on days 4 and 5, food was evenly distributed throughout the 40-h episode.

Melatonin was assayed in singlet by RIA methodology (DiagnosTech International, Osceola WI). The intra- and interassay coefficients of variation (CVs) are 9–10% at 710 pmol/L and 12–13% at 73 pmol/L. Cortisol was assayed in duplicate by chemiluminescence (Beckman Coulter, Inc., Chaska, MN), with an intraassay CV between 2.6–6.5% and an interassay CV between 6–10%.

Data analysis

Circadian markers of phase and amplitude were 1) for CBT, the fit minimum of a two-harmonic regression model with first order autoregressive noise and the amplitude of the fundamental of this model (21); 2) for melatonin, the midpoint of the crossings of the mean value for h 5–29 of the constant routine data, the average value for h 5–29 of the constant routine (22), and the width of the melatonin curve (time between up and down crossings); and 3) for cortisol, fit maximum and amplitude of a single harmonic curve. For CBT and cortisol data, only data collected starting at h 5 of the constant routine through the end of the constant routine were used to calculate the phase and amplitude of the rhythms because of the changes in posture and sleep-wake state at the beginning of the constant routine.

Average waveforms were created for each dataset (cortisol, melatonin, CBT, alertness, stiffness, and pain) by first referencing the time of each data point relative to the time of habitual bedtime or the time of the CBT phase. Then the average for each 1-h bin for each subject was created. Finally, the average for each 1-h bin across all subjects was calculated.

Statistical analyses were performed using SAS for Windows version 6.12. Results are reported as the mean ± SEM. Unpaired *t* tests were used to compare 1) the phase and amplitude of circadian rhythms in melatonin, cortisol, and CBT; and 2) the clinical characteristics between women with and without fibromyalgia. A two-factor (time, fibromyalgia *vs.* control) repeated measures General Linear Models was used for visual analog scale measures.

Sample sizes were chosen to have an 80% power at $\alpha = 0.05$ (23). This study had 80% power at $\alpha = 0.05$ to detect an average phase difference between the groups of 2.4 h for melatonin, 2.7 h for cortisol, and 2.3 h in CBT. We chose 2 h for our power and sample size calculations because the 95% confidence intervals for constant routine circadian phase determinations are approximately 1.5 h (21). With this sample size, the study also had 80% power at $\alpha = 0.05$ to detect an average difference

of 0.05 C for CBT amplitude, 100.3 pmol/L for mean melatonin level, 0.90 h for the width of melatonin secretion between crossings of the mean melatonin level, and 2.39 μg/dL for cortisol amplitude.

Results

Subject characteristics

Subject characteristics for the women with fibromyalgia and controls are detailed in Table 1. There was no significant difference between the patients and controls in age (fibromyalgia, 39.7 ± 2.2 yr; controls, 33.3 ± 2.4 yr; $P = 0.06$) or body mass index (fibromyalgia, 26.0 ± 0.8 kg/m^2; controls, 24.6 ± 1.1 kg/m^2; $P = 0.34$). Seven women with fibromyalgia had a history of a psychiatric disorder; however, only one subject with fibromyalgia had a current Axis I disorder of minor depression. The Fibromyalgia Impact Questionnaire score was significantly higher in women with fibromyalgia than in controls (70.7 ± 5.0 *vs.* 19.0 ± 5.5; $P < 0.0001$).

Habitual bedtimes were similar in women with fibromyalgia and healthy controls. However, there was a large (~5-h) variation in bedtimes among individual subjects (Table 2). This variation in habitual bedtime was accounted for by adjusting the protocol to each individual's habitual sleep-wake cycle.

Circadian rhythms in melatonin, cortisol, and CBT

Figure 1 shows the group average waveforms of melatonin, cortisol, and CBT during the constant routine. The rhythms of CBT, melatonin, and cortisol were similar in women with fibromyalgia and controls (Fig. 1) [for all three measures: group (fibromyalgia *vs.* control) effect, P = NS; time effect, $P = 0.0001$; group-time interaction effect (*i.e.* whether the pattern across time differed between groups), P = NS]. Peak and trough values of both cortisol and melatonin were similar in the two study groups during constant routine conditions. Furthermore, there was no difference in average melatonin or cortisol values in the first 24 h of the constant routine.

For each individual, circadian phase and amplitude were calculated for CBT, cortisol, and melatonin (Table 2). Circadian phase was similar in women with fibromyalgia and control women in all three markers. There were no significant differences among the three phase markers relative to each other or between the phase markers and habitual wake time (Fig. 2). There was no difference between women with and without fibromyalgia in amplitude of CBT, melatonin, and cortisol rhythms during the constant routine (Table 2 and Fig. 2).

Circadian rhythms in subjective assessments of alertness, pain, and stiffness

For subjective measures of mood, there was a similar circadian rhythm of alertness in both women with and without fibromyalgia (time effect, $P = 0.0001$; group and group-time interaction effect, P = NS; Fig. 3). The levels of pain and stiffness experienced by women with fibromyalgia were higher than those in control women (group effect, $P = 0.0001$ for pain; $P = 0.0014$ for stiffness). During the first 3 h of the constant routine, there was a significant decrease in pain in

TABLE 1. Clinical characteristics of women with fibromyalgia and control women

Age (yr)	Body mass index	Fibromyalgia Impact Questionnaire score	Disease duration (yr)[a]	History of psychiatric disorders
Fibromyalgia subjects				
35	26.9	49.1	12–16	None
40	26.5	75.7	8	None
45	27.1	83.9	2	None
34	20.1	75.0	2–14	Past: drug and alcohol abuse, panic disorder
39	27.1	80.3	8	Past: minor depression, single episode
44	28.3	61.6	2	Past: major depression, recurrent
46	26.8	44.5	5	Past: major depression, single episode
26	27.5	60.6	2–15	Past: binge eating disorder Current: mixed anxiety and depression
39	22.7	91.8	3	Past: major depression, recurrent anxiety disorder Current: mild/moderate depression
49	26.7	84.5	1–22	Past/current: posttraumatic stress disorder
Control subjects				
23	27.4	12.1	0	None
24	20.7	N/A	0	None
26	25.2	15.1	0	None
28	20.8	30.3	0	None
31	24.1	33.6	0	None
37	29.6	N/A	0	None
39	19.5	N/A	0	None
41	23.6	N/A	0	None
41	22.5	1.7	0	None
42	22.9	3.8	0	None
44	29.9	10.0	0	None
23	29.3	45.4	0	Past: major depression with acute stress disorder, single episode

N/A, FIQ score not available.

[a] A range of disease duration indicates both the number of years since diagnosis and the number of years of symptoms.

TABLE 2. Mean ± SEM of circadian measures

Measure	Control	Fibromyalgia	*P* value, by *t* test
Habitual bedtime (clock time in hours)	23:34 ± 0:26 (21:30–2:40)[a]	23:26 ± 0:22 (22:10–1:40)[a]	0.83
CBT fit minimum (clock time in hours)	4:52 ± 0:29	4:23 ± 0:31	0.50
CBT fit minimum (hours posthabitual bedtime)	5:19 ± 0:19	4:57 ± 0:33	0.56
CBT amplitude (C)	0.27 ± 0.02	0.28 ± 0.02	0.82
Cortisol fit maximum (clock time in hours)	9:46 ± 0:35	9:58 ± 0:28	0.79
Cortisol fit maximum (hours posthabitual bedtime)	10:13 ± 0:23	10:32 ± 0:20	0.53
Cortisol amplitude (μg/dL)	5.1 ± 0.2	4.6 ± 0.6	0.49
Melatonin phase (clock time in hours)	3:16 ± 0:31	3:12 ± 0:23	0.91
Melatonin phase (hours post habitual bedtime)	3:43 ± 0:19	3:46 ± 0:13	0.90
Melatonin mean amplitude (pmol/L)	108.7 ± 12.5	126.2 ± 23.9	0.50
Duration of melatonin secretion between crossings of mean amplitude (h)	9:15 ± 0:09	9:10 ± 0:13	0.75

[a] Range is in *parentheses*.

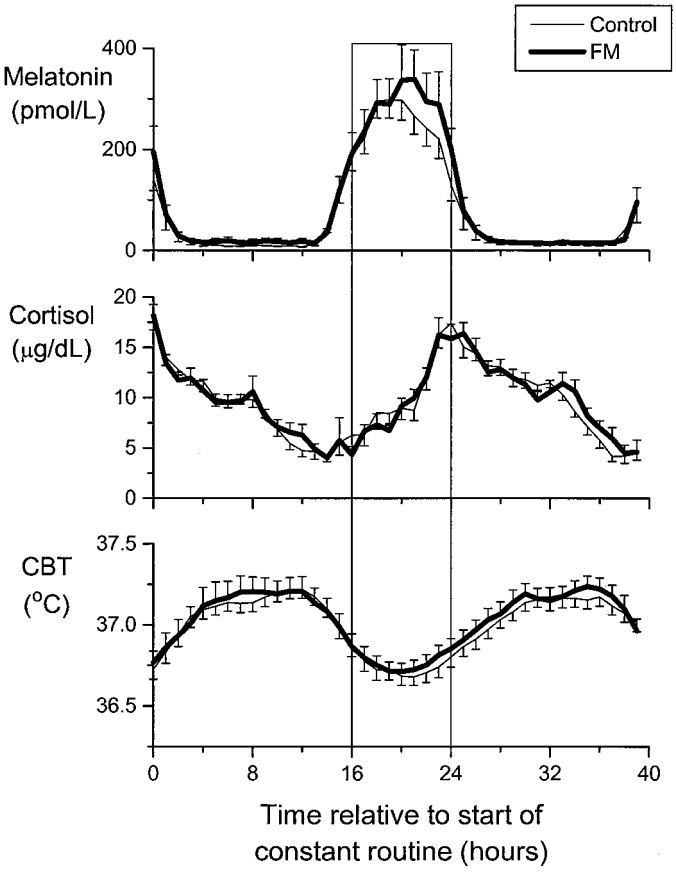

FIG. 1. Mean ± SEM of melatonin, cortisol, and CBT in 1-h bins referenced to the start of the constant routine. A constant routine begins at habitual waketime. The *heavy line* represents the women with fibromyalgia; the *light line* represents the control healthy women. The *open box* indicates the time of habitual sleep, although individuals were continuously awake during the 40-h constant routine.

the women with fibromyalgia ($P = 0.03$), but not in the control group of women ($P = 0.11$). Over the same 3 h, there was a trend toward decreased stiffness in both groups of women (fibromyalgia, $P = 0.08$; control, $P = 0.09$). During the constant routine, there was a progressive increase in stiffness, but not pain (time effect, P = NS for pain and $P = 0.0225$ for stiffness; group-time interaction effect, P = NS for both pain and stiffness). However, this change was progressive across the 40 h and was not indicative of a circadian rhythm.

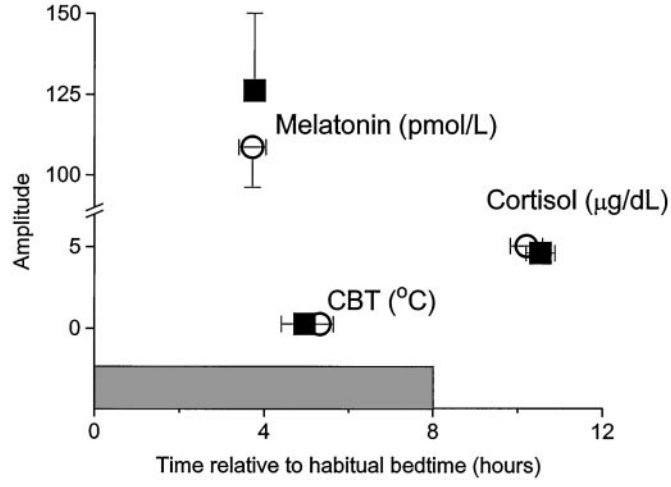

FIG. 2. The time and amplitude of each of the phase markers of the measures (CBT, melatonin, and cortisol) relative to habitual bedtime. *Closed symbols* represent the women with fibromyalgia; *open symbols* represent the control healthy women. *Error bars* represent the SEMs; they are not plotted if the *error bars* lie within the boundaries of the symbol. The *gray box* indicates the time of the habitual sleep episode, although individuals were continuously awake during the 40-h constant routine.

Discussion

To our knowledge, this is the first study of circadian phase and amplitude in women with fibromyalgia performed using an established protocol that controls for known masking effects on circadian markers. In this study we found no abnormalities in circadian phase or amplitude in women with fibromyalgia compared with healthy women based on cortisol, melatonin, and core body temperature rhythms. Furthermore, the relationships of these three markers of circadian rhythmicity to each other were similar in women with and without fibromyalgia. Patients with fibromyalgia showed the same levels and circadian rhythm in subjective alertness as control women. As anticipated, pain and stiffness were increased in fibromyalgia, but there were no circadian rhythms in either pain or stiffness symptoms. The decrease in pain that we and others (18) have shown to occur in patients with fibromyalgia after awakening appears to reflect the changes in sleep-wake state or activity patterns rather than endogenous circadian rhythms in pain percep-

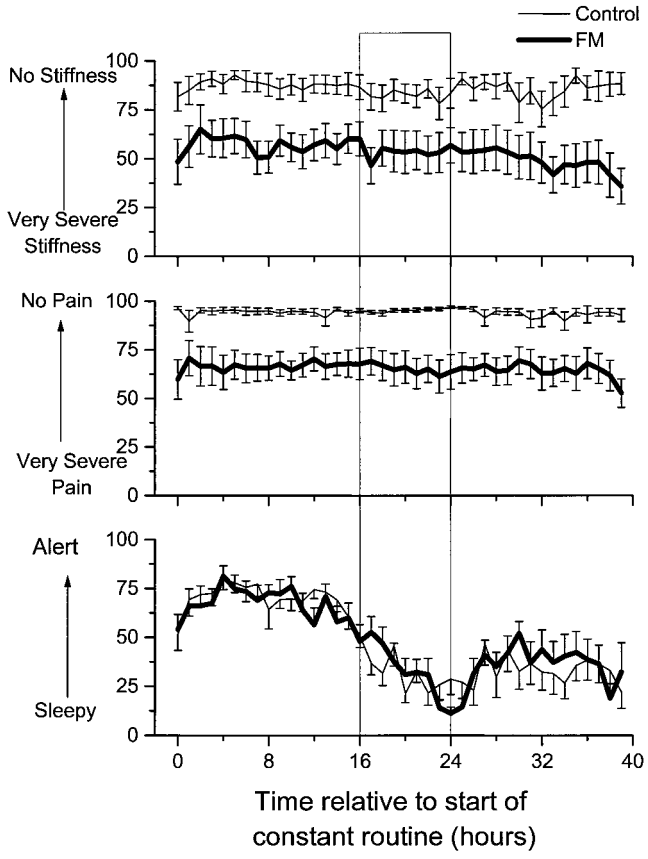

FIG. 3. Mean ± SEM stiffness, pain, and alertness in 1-h bins referenced to the start of the constant routine. A constant routine begins at habitual waketime. The *heavy line* represents the women with fibromyalgia; the *light line* represents the control healthy women. The *open box* indicates the time of habitual sleep, although individuals were continuously awake during the 40-h constant routine.

tion. These results suggest that abnormalities in circadian phase do not contribute to the pathophysiology of fibromyalgia.

Our finding of similar melatonin levels in women with fibromyalgia compared with healthy women agrees with one report of normal urinary melatonin levels in fibromyalgia (7), but differs from two studies showing altered levels of circulating melatonin in this disorder (8, 9). Multiple factors may contribute to these differences. Melatonin is highly sensitive to suppression by light in a dose-dependent fashion (24, 25). It is suppressed by normal room levels of light and can plummet to 33% of peak values within 12 min of ocular exposure to bright light (26). Only one of the previous studies examining melatonin in women with fibromyalgia reported the light levels during the study (8); the levels reported in that study could have been sufficient to partially suppress melatonin levels.

In the absence of suppressive light levels, melatonin is usually elevated above detectable levels for approximately 12 h of the day. In the present study performed with light levels below 15 lux, a nonsuppressive light level, melatonin began to rise 2 h before habitual bedtime, reached 60% of the maximum value by bedtime, and returned to 45% of the maximum value at the habitual waketime in the healthy control subjects. If light levels were low only during the sleep episode, melatonin would be partially suppressed at all times except for the sleep episode, potentially leading to inaccurate assessments of circadian phase and amplitude with respect to this marker rhythm.

In addition, circadian phase is tightly linked to habitual sleep-wake times (27). Previously reported alterations in circadian rhythms may have been observed if timing of the sleep episode was not considered during the study. For example, it is possible to artificially create some symptoms of circadian misalignment (jet lag) by studying individuals at times different from their habitual sleep-wake times. If an individual's habitual bedtime is 2100 h, but sleep is not scheduled to begin until 2300 h during the study, the subject may appear to have a shortened sleep latency, early morning awakening, and earlier rise of cortisol and melatonin. The reverse would be true for an individual with a habitual bedtime of 0100 h and a scheduled sleep time of 2300 h. Also, if the study schedules were not adjusted for each individual's habitual sleep-wake times (and therefore light exposure), different portions of the melatonin curve would be affected by the lighting conditions of the study.

Other factors can alter the assessment of circadian phase and hormone levels. Melatonin levels can be increased by changes in posture from supine to upright (28) and decreased by β-blocker medications. Cortisol levels are affected by meals, posture, activity, and sleep-wake state (29, 30). CBT is influenced by activity levels and also by sleep-wake state. Previous studies of baseline cortisol and melatonin levels in fibromyalgia may not have adequately accounted for the masking effects of various activities on these markers and thus could have resulted in misleading conclusions.

The current finding that average serum cortisol levels were similar in females with and without fibromyalgia during the constant routine is consistent with our previous finding of normal 24-h urinary free cortisol levels in women with fibromyalgia (14). This suggests that, at least under the controlled baseline conditions present in this study, potential abnormalities in ACTH secretion (14, 15) do not translate into defects in baseline cortisol levels.

Although our study populations had statistically significant differences in the number of individuals with a history of psychiatric disorders, we do not believe that these influenced our results. The two individuals with both fibromyalgia and a current psychiatric diagnosis had circadian parameters similar to those of other individuals with fibromyalgia and to controls (data not shown). Although the women with fibromyalgia tended to be slightly older than control subjects, this difference did not reach statistical significance, and all women in both groups were premenopausal. Furthermore, within the study groups, age did not correlate with any of the measures of circadian phase relative to habitual bedtime or amplitude (data not shown). Therefore, we do not believe that the nonsignificant age difference between subject groups obscured our ability to detect alterations in circadian rhythmicity in women with fibromyalgia.

In the present study comparing women with fibromyalgia to healthy women, circadian phase was assessed using a protocol that strictly controls for variables that could affect circadian phase markers. This study was powered statistically to detect meaningful differences in circadian phase. No

differences were found in the circadian phase and amplitude of CBT, plasma cortisol, or plasma melatonin, three well known markers of the circadian system, or in alertness. Pain and stiffness were increased in women with fibromyalgia, but showed no circadian pattern in either study group. These findings suggest that abnormalities in circadian phase do not account for the reported abnormalities in neuroendocrine function or for the symptoms of fatigue, sleep disturbances, myalgias, and cognitive complaints that occur in fibromyalgia. Thus, abnormalities in circadian phase do not appear to play a role in the pathophysiology of fibromyalgia.

Acknowledgments

We thank the patients, nurses, and technicians of the Brigham and Women's Hospital General Clinical Research Center for their efforts.

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