

Decreased Nocturnal Levels of Prolactin and Growth Hormone in Women with Fibromyalgia*

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ABSTRACT

Fibromyalgia (FM) is a complex syndrome, primarily of women, characterized by chronic pain, fatigue, and sleep disturbance. Altered function of the somatotrophic axis has been documented in patients with FM, but little is known about nocturnal levels of PRL. As part of a laboratory study of sleep patterns in FM, we measured the serum concentrations of GH and PRL hourly from 2000–0700 h in a sample of 25 women with FM (mean, 46.9 ± 7.6 yr) and in 21 control women (mean, 42.6 ± 8.1 yr). The mean (±SEM) serum concentrations (micrograms per L) of GH and of PRL during the early sleep period were higher in control women than in patients with FM [GH, 1.6 ± 0.4 vs. 0.6 ± 0.2 ($P < 0.05$); PRL, 23.2 ± 2.2 vs. 16.9 ± 2.0 ($P < 0.025$)]. The mean serum concentrations of GH and PRL increased more after sleep

onset in control women than in patients with FM [GH, 1.3 ± 0.4 vs. 0.3 ± 0.2 ($P < 0.05$); PRL, 16.2 ± 2.4 vs. 9.7 ± 1.5 ($P < 0.025$)]. Sleep efficiency and amounts of sleep or wake stages on the blood draw night were not different between groups. There was a modest inverse relationship between sleep latency and PRL and a direct relationship between sleep efficiency and PRL in FM. There was an inverse relationship between age and GH most evident in control women. Insulin-like growth factor I levels were not different between the groups. These data demonstrate altered functioning of both the somatotrophic and lactotropic axes during sleep in FM and support the hypothesis that dysregulated neuroendocrine systems during sleep may play a role in the pathophysiology of FM. (*J Clin Endocrinol Metab* 86: 1672–1678, 2001)

FIBROMYALGIA (FM) is a complex chronic disorder characterized by symptoms of diffuse pain, fatigue, and unrefreshing sleep. In a recent prevalence study using the American College of Rheumatology diagnostic criteria (1), FM was estimated to affect 2% of the general population in one community (2). The disorder predominately affects middle-aged women. In women over 50 yr, FM is 6 times more common than in men of the same age (1).

The etiology of FM is unknown, although recent research evidence increasingly supports the involvement of altered neuroendocrine functioning at the level of the hypothalamus and/or pituitary (3, 4). An early study suggested that the hypothalamic-somatotropic [GH/insulin-like growth factor (IGF)] axis was deficient in FM (5). Subsequent research has shown that some FM patients have reduced stimulation-induced secretion of GH and low levels of one of its downstream mediators, IGF-I (6, 7). Moreover, among FM patients with low pretreatment levels of IGF-I, GH therapy increased IGF-I levels, reduced pain, and improved overall symptoms (8). Compared with controls, FM patients also have lower 24-h mean levels of GH, suggesting that GH secretion is reduced both in the daytime and at night (9, 10). Lastly, low concentrations of GH appear to be correlated with self-reported poor sleep quality in FM (9).

We also considered activity in the lactotropic-PRL axis as potentially important in FM, because the nocturnal secretion of PRL is in part, like that of GH, sleep dependent (11–17). Previous investigators have found that daytime PRL concentrations in FM were in the normal range (18–22), but data in response to stimulation were mixed (18, 21–24). For example, in one report significantly higher daytime baseline PRL levels were found, without a subsequent increase after insulin-induced hypoglycemia (18); in other studies normal baseline PRL levels were followed by increased secretion after TRH stimulation in some FM patients (22–24). These observations make it difficult to consider PRL levels abnormal in FM, yet to our knowledge there are no prior reports of basal nocturnal serum PRL levels.

The hypothesis that complaints of unrefreshing sleep and fatigue could be related to altered neuroendocrine function during sleep was derived from evidence of a nonrestorative sleep electroencephalogram (EEG) pattern in FM (5, 25). In the daily 24-h cycle, the largest pulse of GH secretion occurs just before or with the onset of sleep (17), and the greatest amount of PRL is secreted during the sleep period (15, 16). Reduced serum concentrations of GH and PRL occur in sleep-deprived subjects (17, 26–28), and nocturnal awakenings are associated with reduced secretory rates of GH (17) and PRL (15). We and others have observed increased non-rapid eye movement (NREM) stage 1 sleep (a transition stage between wakefulness and sleep) and wakefulness, most evident in the first half of the night, in women with FM compared with controls (29, 30). Given that nocturnal levels of GH and PRL are sleep dependent and that increased wake-

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fulness after sleep onset is common in FM, levels of both GH and PRL could be reduced during sleep.

In this study a sample of middle-aged women with and without FM completed questionnaires, a structured psychiatric interview, and polysomnography and had blood sampled throughout the nighttime hours. We addressed the main question of whether nocturnal concentrations of GH and PRL were reduced in women with FM after sleep onset compared with those in healthy women and explored factors (body composition, physical activity, estrogen levels, and depression) that could influence these hormone levels. We also measured IGF-I levels in both groups of women.

Subjects and Methods

Subjects

Twenty-five women with FM from an academic referral clinic devoted to the evaluation of fatigue and 21 healthy women from the local community were studied. Women with a diagnosis of FM based on published criteria (1) were identified from the clinic database, contacted by telephone, and invited to participate in the study. Control women from the community were recruited from advertisements placed on bulletin boards and in neighborhood newspapers. Approval for the study was obtained from the human subjects review committee of the University of Washington, and all women gave informed consent.

Information on age, height, weight, and medical history were obtained during the initial telephone interview and were used as part of the screening procedures. Women were excluded if they 1) were less than 25 or more than 60 yr old, 2) had a body mass index (BMI) greater than 40, 3) did shift work, or 4) had a history of major physical illness or sleep disorder. Additional eligibility criteria were established to enable the comparison of FM women with moderate and high pain intensity to a control group of women of similar age but without pain or poor sleep quality. We anticipated that patients with FM would report low levels of physical activity, and therefore control women with low levels of physical activity were selected for this study (see below).

Additional screening procedures

Information on self-rated pain [1 (no muscle aches and pain) to 10 (worst muscle aches and pain you can imagine)] was obtained at the initial telephone screening interview and later verified in daily symptom diary reports. On the basis of the initial phone screen, women with FM were excluded for current pain below a score of 4; control women were excluded for self-rated current pain above a score of 3. Women who met the initial study criteria completed a daily diary of symptoms for 1 month before the laboratory study. Symptoms were rated from 0 (not present) to 4 (extreme). Seven items from the diary related to pain (*i.e.* right and left arm and right and left leg muscle pain, upper and lower back pain, and joint pain) were used to further screen the women. The total number of days that any of these seven pain items were rated 3 or 4 were summed for each woman. In addition, the number of days these seven items were rated 2, 3, or 4 were summed for the control women. Women with FM were withdrawn from the study if the sum of the seven pain items rated 3 or 4 was less than 7 days. Control women were withdrawn from the study if the sum of pain items rated 3 or 4 was more than 2 days, or if the sum of items rated 2, 3, or 4 was more than 6 days.

Physical activity

Information on physical activity was obtained during the initial telephone interview and later verified from daily diary entries. Energy expenditure was calculated from the kilocalories expended weekly in various self-reported physical activities (beyond those associated with typical activities of daily living) by a locally developed computer program based on items (*e.g.* number of stairs climbed, blocks walked, and time spent in vigorous activities) from the Paffenbarger Physical Activity Questionnaire (31, 32). Control women with a calculated energy expenditure of 1500 Cal/week or more were excluded based on results from

the initial phone screening or were withdrawn from the study based on diary entries.

Depression

The structured Diagnostic Interview Schedule (DIS; C-DISR version, C-DIS group, Ottawa) that yields diagnoses based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R) (33) was used to screen control women for past history of or current psychiatric diagnoses. The DIS was used to screen women with FM for current psychiatric diagnoses, except for depression. In addition to the psychiatric interview, women completed the Beck Depression Inventory (BDI) at the time of the laboratory study. The original BDI is a 21-item questionnaire designed to assess affective, cognitive, motivational, vegetative, and psychomotor aspects of depressed mood (34). We used the 13-item short form of the BDI because it reflected psychological aspects of depressed mood after somatic symptom items were removed (35). The maximum possible score on the BDI short form is 39. Scores of 0–4 indicated none or minimal depression, 5–7 indicated mild depression, 8–15 indicated moderate depression, and 16 or more indicated severe depression.

Medications

Control women were not eligible for the study if they were unwilling to discontinue taking medications or herbal supplements for a minimum of 2 weeks before and during the laboratory study. Women with FM were weaned from antidepressant, hypnotic, or psychotropic medications and were drug free for at least 2 weeks before and during the laboratory study (as monitored by daily diary entries). For medications such as nonsteroidal antiinflammatory drugs and antihistamines, subjects were permitted to take these medications until five half-lives before the first night of the laboratory study. Women with FM were withdrawn from the study if they were unable to discontinue sedative, hypnotic, or psychotropic medications. Women were permitted to remain on birth control pills or hormone replacement therapy (HRT) during the study.

Polysomnographic (PSG) sleep recordings

All women slept in the University of Washington Sleep Research Laboratory in temperature-controlled, sound-attenuated rooms for 3 consecutive nights. They carried out their usual daytime activities, except they were requested not to take naps and to avoid food and beverages that contained caffeine or alcohol after 1300 h. They reported to the sleep laboratory in the early evening hours, were permitted to go to bed at their usual time, and were awakened at 0700 h. The first night was considered as adaptation to the laboratory, and the data were used for screening all women for sleep apnea (index of ≥ 5 events/h). The second night was used for baseline sleep data and to score periodic leg movements associated with PSG evidence of arousal (index of ≥ 5 events/h) (36, 37) in all women. In addition to sleep, during the third night hourly blood samples were obtained. Women with menstrual cycles were recorded during days 5–10 postmenses.

Electrodes for recording the EEG, the electrooculogram, and the electromyogram were placed according to standards established by Rechtschaffen and Kales (38). To screen subjects for sleep apnea, transducers to measure airflow (Easyflow, Newlife Technologies, Midlothian, VA) and upper airway obstruction (Opti-Flex, Newlife Technologies) were placed under the nose and at the sternal notch, respectively. Electrodes to measure periodic leg movements were placed on the tibialis anterior muscle of one leg. Electrophysiological signals were amplified and conditioned on a Grass model 7 polygraph (Quincy, MA). The EEG signals were filtered with the low pass at 0.3 Hz and the high pass at 1.0 kHz. All PSG data were recorded and digitized with the Oxford Sleep Acquisition Computer system (SAC version 847, model 700 board, Clearwater, FL) on a desktop computer (Zenith 486, model Z, station 500).

Sleep stage scoring and variables

The SAC system (software version 9.3) was used to first score sleep and wake stages in 30-s epochs. Each SAC-scored sleep record was rescored manually by a sleep technologist according to standard criteria (38). An interrater agreement greater than 90% was maintained for all

scored records. Sleep variables were computed for each woman with a locally developed software program based on previously published definitions (39). The variables calculated included the following: time in bed (lights out to final arising), sleep period time (time from the beginning of NREM stage 2 until final awakening on the EEG), total sleep time (total time in NREM stages 1–4 and REM), sleep efficiency (total sleep time per time in bed), sleep latency to NREM stage 2 (time from lights out to onset of NREM stage 2 sleep), time spent awake (after sleep onset), and time in NREM (stages 1, 2, 3, and 4) and REM sleep as a percentage of the sleep period time. As a measure of sleep continuity we calculated a fragmentation index per h based on the number of changes from one sleep stage to another or to awakening. Sleep onset time was defined as the onset of NREM stage 2 sleep, and awakening time was defined as the final awakening on the EEG.

Blood specimens

On the third study night, an iv catheter was inserted in a forearm vein, and 1 L normal saline with 1000 USP units heparin were infused at a continuous rate (15 gtts/min). The iv solution bag with an extension line were passed through a conduit in the wall to a double stopcock and syringe in the adjoining equipment room. A water-filled heating pad (Gaymar Industries, Inc., Buffalo, NY) set at a temperature of 36.5°C was used to warm the arm with the iv catheter during the night.

Blood specimens for hormone measurements were drawn each hour from 2000–0700 h. Our intent in this study was to describe the average nocturnal serum concentrations of GH and PRL over 11 nighttime h, not to determine secretory pulse patterns. After initial processing, all serum and plasma samples were frozen and kept at –70°C until assayed.

Hormone measurements

GH and PRL were measured from serum obtained from 5 mL blood collected and placed in a clean glass tube, kept at room temperature, allowed to clot, and centrifuged. Blood samples from FM and control women were assayed in sets (two FM and one control or one FM and two controls per assay plate) and run on the same day to avoid refreezing samples. All samples were assayed in duplicate. Two or three external controls with known concentrations were included in every assay. Serum GH and PRL were assayed with enzymatically amplified two-step sandwich-type enzyme-linked immunosorbent assay kits (Diagnostics Systems Laboratories, Inc., Webster, TX). The absorbency of chromogen was measured by dual wavelength at 450 and 620 nm. The intraassay variations for GH were 12.6% and 6.9%, and the interassay variations were 20.2% and 6.99% for assays run with 0.5 and 1.5 ng/mL as standard, respectively. The published lower detection limit was 0.03 ng/mL. The intraassay variations for PRL were 5.98% and 4.1%, and the interassay variations were 9.5% and 14.4% for assays run with 7.5 and 18 ng/mL as standard, respectively. The published lower detection limit of the assay was 0.14 ng/mL.

IGF-I was measured from plasma obtained from a blood sample drawn at 0600 h, placed in an ethylenediamine tetraacetate-coated tube, kept on ice, and centrifuged. IGF-I was measured with an amplified one-step sandwich-type enzyme-linked immunosorbent assay kit (Diagnostics Systems Laboratories, Inc.). IGF-I was extracted from its binding protein with an ethanol-HCl solution. The absorbency of chromogen was measured by dual wavelength at 450 and 620 nm. The intraassay coefficient of variation was 5.0%, and the interassay coefficient of variation was 6.7%. The published lower detection limit of the assay was 0.03 ng/mL.

As estrogen is known to modulate GH and PRL levels (40–42), we measured plasma estradiol in all of the women. Estradiol was measured in plasma obtained from an additional blood sample drawn at 0700 h, placed in an ethylenediamine tetraacetate-coated tube, kept on ice, and centrifuged. Estradiol was measured by a third generation ¹²⁵I-labeled estradiol, double antibody RIA kit (Diagnostics Systems Laboratories, Inc.). The lower detection limit of the assay was 0.75 pg/mL. The plasma estradiol intraassay coefficient of variation was 1.6%, and the interassay coefficient of variation was 6.5%.

Statistical analyses

The main outcome measures in this study were the serum concentrations of GH and PRL during sleep. The largest increase in the noc-

turnal concentration of GH occurs during the first few hours of sleep (17), and the concentration of PRL rises shortly after sleep onset and remains elevated during sleep (12, 15). As mean sleep onset times were similar in both groups, measures for GH from 2400–0200 h and for PRL from 2400–0400 h were averaged for each group and defined as postsleep hours for each hormone, respectively. To determine whether there were group differences in how much the concentrations of GH and PRL increased after sleep onset, the mean concentration for each hormone from the presleep hours (2000–2300 h) was subtracted from the mean for the postsleep hours. Occasionally, a blood sample was missed because of an inability to obtain it from the iv line and the desire to refrain from awakening the subject. Of 252 possible samples in control women, 5 samples were not obtained; of 300 possible samples in women with FM, 19 samples were not obtained. To be certain that these missed samples did not influence the mean concentrations of GH and of PRL during pre- or postsleep hours, data from women with more than 1 missed sample were excluded from the statistical analysis (see footnotes to Table 1).

Student's *t* test (one-tailed) was used to make between-group comparisons of the hormone concentrations. The significance level was set at $P < 0.05$. Subsequently, we used the Mann-Whitney U test to examine differences in group-subject characteristics (age, BMI, depressed mood, estradiol, and physical activity) and sleep variables that might provide alternative explanations for the observed differences in hormone levels during sleep. The significance level for these tests was also set at $P < 0.05$ to protect against a type 2 error. We used the Pearson product-moment correlation test to explore the extent of relationships between the mean concentrations of GH and PRL during postsleep hours and measurements of sleep quality during the first half of the sleep period (*e.g.* sleep efficiency, sleep latency, and fragmentation index) and age, BMI, depressed mood, and physical activity, which have been shown to affect the concentrations of GH and PRL (42–50).

Results

Sample characteristics

Sample characteristics are summarized in Table 1. There were no significant differences in age or BMI between women with FM and control women. Four women with FM (16%) met DSM-III criteria for current depression. The mean scores on the BDI short form were significantly higher in the FM compared with the control group. The BDI scores indicated mild to moderate depressed mood in FM (34) and minimal depressed mood in control women. Although mean calculated energy expenditures in kilocalories derived from self-reported physical activity were similar between the groups, it was significantly higher in control women compared with FM women. More women with FM were postmenopausal and receiving HRT than control women; more control women were premenopausal and taking birth control pills than women with FM. Most of the women in both groups were Caucasian.

Hormone levels

As shown in Table 1 and Fig. 1, mean serum concentrations of GH and PRL were significantly lower during sleep in women with FM than in control women. Presleep hormone levels were equivalent in the two groups. The mean concentrations of GH and PRL increased significantly more after sleep onset in the control women than in the women with FM. Mean IGF-I and estradiol levels were similar in both groups (Table 1). Because some women with FM were premenopausal and others were postmenopausal, we compared GH and PRL concentrations during sleep between these two subgroups of women. None of the premenopausal women

TABLE 1. Demographic data clinical features, and hormone assay results

Variable	Women with fibromyalgia	Control women
Demographic data		
Age (mean yr)	46.9 ± 1.5	42.6 ± 1.8
Race (% Caucasian)	84	85.7
Clinical features		
Body mass index (kg/m ²)	26.7 ± 1.1	24.9 ± 0.8
Beck Depression Inventory ^a	7.0 ± 1.1	0.8 ± 0.2
Physical activity (calculated Cal) ^b	516 ± 152	611 ± 78
Premenopause		
On estrogen ^c	0/10	15/16
Not on estrogen	10/10	1/16
Postmenopause		
On estrogen ^d	11/15	1/5
Not on estrogen	4/15	4/5
Hormone assays		
Estradiol (pg/mL)	45.7 ± 5.8	39.2 ± 4.8
PRL (μg/L), presleep h	7.3 ± 0.9	7.8 ± 0.7
PRL (μg/L), postsleep h ^e	16.9 ± 2.0	23.2 ± 2.2
PRL (μg/L), postminus presleep h ^f	9.7 ± 1.5	16.2 ± 2.4
GH (μg/L), presleep h	0.4 ± 0.1	0.5 ± 0.1
GH (μg/L), postsleep h ^g	0.6 ± 0.2	1.6 ± 0.4
GH (μg/L), postminus presleep h ^h	0.3 ± 0.2	1.3 ± 0.4
Insulin-like-growth factor I (ng/mL) ⁱ	110.9 ± 14.7	124.55 ± 14.4

Data are the mean ± SEM or the percentage of the group sample unless otherwise indicated.

^a $z = 5.01$; $P < 0.00$.

^b $z = 2.02$; $P < 0.05$.

^c Premenopause = still having periods and taking birth control pills.

^d Postmenopause = no longer having periods and taking hormone replacement.

^e PRL Postsleep hours (2400–0400 h). $t = 2.1$; $P < 0.025$, by one-tailed test. FM = 23; control = 21 subjects.

^f PRL postsleep hours minus presleep hours (2000–2300 h). $t = 2.3$; $P < 0.025$, by one-tailed test. FM = 21; control = 19 subjects.

^g GH postsleep hours (2400–0200 h). $t = 2.0$; $P < 0.05$, by one-tailed test, unequal variance assumed. FM = 25; control = 21 subjects.

^h GH postsleep hours minus presleep hours (2000–2300 h). $t = 2.0$; $P < 0.05$, by one-tailed test, unequal variance assumed. FM = 22; control = 19 subjects.

ⁱ $n = 13$ in each group.

with FM were receiving estrogen therapy, but a majority of the postmenopausal women were receiving HRT. There were no differences in the mean concentrations of GH and PRL during sleep in women with FM between those who were premenopausal [GH, 0.7 ± 0.3 μg/L ($n = 10$); PRL, 14.9 ± 3.4 μg/L ($n = 9$)] vs. postmenopausal [GH, 0.6 ± 0.3 μg/L ($n = 15$); PRL, 18.1 ± 2.5 μg/L ($n = 14$)].

Sleep measures

Sleep variables derived from PSG data recorded during the same night as blood samples were obtained are summarized in Table 2. There were no differences in sleep and wake stages as a percentage of sleep period time or in indicators of sleep quality and continuity between women with FM and control women.

Correlation of GH and PRL with sleep and clinical variables

Relationships that showed a correlation of 0.4 or more of GH and of PRL with sleep and clinical variables in either the FM or control group are listed in Table 3. There was an inverse relationship between nocturnal GH and age in control women, but this relationship was not as strong in women with FM.

In women with FM we found an inverse relationship between PRL and sleep latency and a direct relationship between PRL and sleep efficiency. In control women we found

a positive correlation between PRL and sleep period time and fragmentation index.

Discussion

We measured nocturnal hormone levels of GH and PRL in a sample of women with FM and found reduced levels of both of these hormones during sleep compared with levels in healthy sedentary women. To our knowledge this is the first study to report low levels of nocturnal PRL in FM. Our finding of lower nocturnal GH is consistent with the reported reduction in GH secretion during a 24-h period in patients with FM (9, 10). Taken together these findings provide further evidence for altered neuroendocrine functioning at the level of the hypothalamus and/or pituitary during sleep in FM.

Nocturnal PRL levels were differentially related to selected sleep variables in women with FM and control women, although there were no significant differences in sleep variables between the two groups. Sleep efficiency both in women with FM and control women during night 3 was lower than we have reported for night 2 in a previous study of women with and without FM symptoms (29). Compared with sleep efficiency scores on night 2 (data not shown), the lower sleep efficiency on the blood draw night probably represents increased amounts of wakefulness after sleep onset, most likely secondary to blood-sampling procedures as other investigators have reported (51). However, these pro-

FIG. 1. Mean \pm SEM nocturnal (2000–0700 h) serum concentrations of GH (A) and PRL (B) during 11 nighttime h. Δ , Controls (n = 21); \blacksquare , FM (n = 25). The dark bar represents the sleep period. For all women mean sleep onset was 2318 h, and mean awakening time was 0700 h.

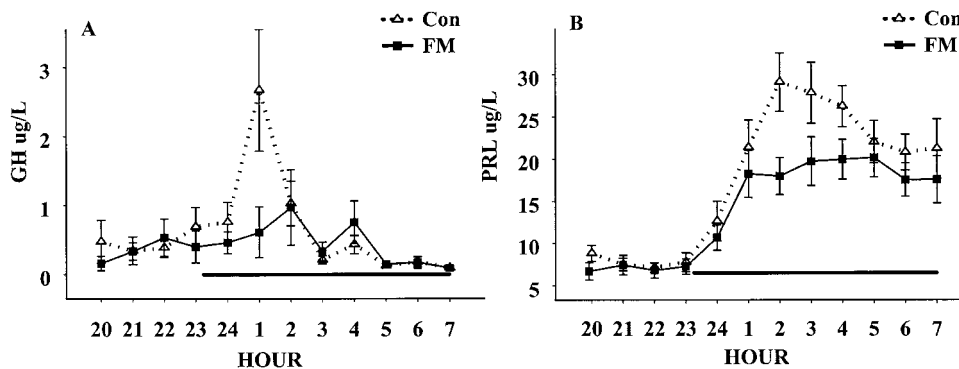


TABLE 2. Sleep variables in fibromyalgia and controls during the blood draw night

Sleep variables	Fibromyalgia	Control
Sleep onset (h \pm min)	2318 \pm 66	2318 \pm 48
Morning awakening (h \pm min)	0700 \pm 18	0700 \pm 12
Time in bed (min)	483 \pm 61.5	475 \pm 52.8
Sleep period time (min)	445 \pm 70.4	447 \pm 52.7
Total sleep time (min)	359 \pm 67.4	370 \pm 52.6
Sleep efficiency index ^a	74.4 \pm 12.1	78.3 \pm 11.3
Sleep latency, stage 2 (min)	27.4 \pm 30	18.3 \pm 13.3
Wake (%; after sleep onset)	19.1 \pm 9.5	16.7 \pm 11.5
NREM stage 1 (%)	11.5 \pm 3.9	9.5 \pm 3.9
NREM stage 2 (%)	40 \pm 9.4	42.2 \pm 10.4
Slow wave sleep ^b	10.4 \pm 8.5	12.2 \pm 5.8
REM (%)	19.1 \pm 5.6	19.3 \pm 6.6
Fragmentation index ^c	8.2 \pm 3.1	8.0 \pm 3.1

Data are the mean \pm SD.

^a Sleep efficiency index = total sleep time/time in bed.

^b NREM stages 3 and 4.

^c Index of number of stage changes to wakefulness or NREM stage 1/h.

cedures had similar effects on sleep efficiency as an indicator of sleep quality and on the fragmentation index as an indicator of sleep stability in both groups. Women with FM had mean PRL concentrations that were inversely related to the time it took them to fall asleep (sleep latency) and directly related to sleep efficiency. Thus, once women with FM were able to fall asleep, the PRL serum concentration increased somewhat and was positively related to sleep quality. In control women, PRL levels were directly related to both the sleep period time, a measure of sleep duration, and the sleep fragmentation index, a measure of sleep disruption. These potentially contradictory findings could reflect intact sleep-dependent (13) and sleep-independent circadian regulation of the increased PRL levels in control women (52–54). In this regard, reduced nocturnal PRL levels have been associated with increased wakefulness at night in elderly men (55), but others have found that sleep quality did not adversely impact PRL levels in men until sleep efficiency was reduced more than 50% (15). In FM, lowered nocturnal PRL could reflect altered sleep-dependent regulation (13, 15, 16) or sleep-independent circadian regulation of PRL secretion (52–54). Further studies of PRL secretory profiles in FM are needed to determine whether lower nocturnal levels are related to altered sleep-dependent or circadian regulation of PRL.

PRL secretion from the pituitary is mainly under tonic inhibition from dopaminergic cells in the hypothalamus (55).

TABLE 3. Correlations of GH with age and PRL with sleep quality

	Fibromyalgia	Control
GH ^a		
Age	–0.08	–0.49 ^b
PRL ^a		
Sleep efficiency, night 3	0.42 ^b	–0.14
Sleep latency	–0.48 ^b	0.40
Sleep period time	0.03	0.44 ^b
Fragmentation index/h	–0.07	0.54 ^c

^a GH postsleep hours (2400–0200 h) and PRL postsleep hours (2400–0400 h) were correlated with sleep variables calculated for the first half of the sleep period.

^b $P < 0.05$.

^c $P < 0.02$.

Increased secretion of PRL during sleep is postulated to involve reduced sensitivity to dopamine inhibition (15, 54), but the mechanisms that account for lower PRL secretion during sleep are unknown. Dopamine has been implicated in the regulation of wakefulness, but not sleep (15), and decreased nocturnal PRL has been associated with increased dopaminergic tone in older men (47, 56). Increased dopaminergic tone could be the basis for reduced nocturnal PRL and the increased nocturnal wakefulness that have been reported in FM (29, 57, 58).

Various chronic conditions are associated with hypoprolactinemia, but the clinical significance of this finding is unclear. Mean 24-h PRL levels are reported lower in cluster headache (59). Poorly controlled insulin-dependent diabetic men showed reduced levels of nocturnal PRL and lower amplitude of the circadian PRL rhythm (60). There is some evidence of altered PRL levels in major depression, although the findings are mixed, with evidence of increased PRL before sleep onset (46), lower nocturnal sleep-related levels (44, 48), and no significant nocturnal reduction compared with controls (43). In this study we did not find an association between depressed mood and nocturnal PRL levels in women with FM.

The data from this study showed altered functioning of the somatotrophic axis during sleep in women with FM. The reduced levels of nocturnal GH in this study are consistent with previous reports of reduced 24-h mean GH secretion (9, 10) and reduced levels of IGF-I (7, 8) in FM. In the present study the levels of IGF-I in women with FM were not different from control values, consistent with several studies, including one with more than 500 women with FM (6, 61). Activity levels

influence serum concentrations of GH and IGF-I (42), and as we recruited control women with low to moderate activity levels, this might explain the lower than expected values of IGF-I in our control sample. Reduced GH concentrations have been reported to be secondary to nocturnal wakefulness (17, 62), but unlike PRL, we did not find any relationship between sleep quality or stability and nocturnal GH in FM or control women. However, age was inversely related to nocturnal levels of GH in control women, but this relationship was not as strong in FM.

Major depression has been linked with altered hypothalamic-pituitary function (54), especially manifested in diminished concentrations of GH during the first half of the sleep period in women with recurrent depression (48). Only four women with FM in this study had depression diagnosed by a structured psychiatric interview, but as a group they manifested moderate depressed mood on the BDI. However, we did not find a relationship between depressed mood and nocturnal concentration of GH in this study. Nevertheless, depressed mood and low levels of physical activity are common in FM and may explain the reduced association between age and GH concentration.

Estrogen modulates PRL and GH secretion (40–42). Nocturnal serum levels of PRL have been reported to be higher in women than in men and also higher in young women than in postmenopausal women (41). As estradiol levels were similar in control women and women with FM, the lower nocturnal levels of PRL and GH in FM cannot be attributed to differential levels of estradiol between these groups. However, among women with FM some were premenopausal and not taking estrogen, whereas others were postmenopausal and taking HRT. Nevertheless, we did not find differences in nocturnal hormones in the women with FM based on menopausal and estrogen status. Although we could not separate out effects of menopause from those of estrogen status on nocturnal hormones in women with FM, the concentration of PRL was slightly lower in the premenopausal compared with the postmenopausal women. PRL levels in these women were still lower than those in control women.

This study has several limitations. First, the women with FM were highly selected, as they were drawn from an academic referral clinic and were willing to discontinue their medications. In addition, the study was restricted in terms of age and gender. As such, our patients might not represent the larger population of community-dwelling men and women of all ages who suffer from FM. Second, the long interval (60 min) between hormone samples did not permit us to describe the secretory profiles of PRL and GH. Without data on the 24-h temporal characteristics of PRL and GH and secretory profiles we were unable to conduct a more rigorous time-dependent analysis of the relationships between PRL and GH levels and sleep stages or compare nocturnal and daytime levels.

In summary, we observed reduced levels of PRL and GH during sleep in midlife women with FM. Our data add to the accumulating evidence that altered neuroendocrine regulation, in particular that of the lactotropic and somatotrophic axes, may have a role in the pathophysiology of FM.

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