

COMMENTS

The Growth Hormone (GH)-Releasing Hormone - GH - Insulin-like Growth Factor-1 Axis in Patients with Fibromyalgia Syndrome*

A. LEAL-CERRO, J. POVEDANO, R. ASTORGA, M. GONZALEZ, H. SILVA,
F. GARCIA-PESQUERA, F. F. CASANUEVA, AND C. DIEGUEZ

Department of Endocrinology (A.L.-C., R.A., H.S., F.G.-P.) and Rheumatology (J.P., M.G.), Hospital Universitario "Virgen del Rocío", 15700 Sevilla; and Departments of Medicine (F.F.C.) and Physiology (C.D.), Complejo Hospitalario Universitario and Faculty of Medicine, University of Santiago, 15700 Santiago de Compostela Spain

ABSTRACT

Fibromyalgia (FM) is a painful syndrome of nonarticular origin, characterized by fatigue and widespread musculoskeletal pain, tiredness, and sleep disturbances, without any other objective findings on examination. Interestingly, some of the clinical features of FM resemble the ones described in the adult GH-deficiency syndrome. Furthermore, insulin-like growth factor (IGF)-1 levels are frequently reduced in patients with FM. To gain further insight into the mechanisms leading to dysregulation of the GH-IGF-1 axis in these patients, we assessed 24-h spontaneous GH secretion, GH responses to GHRH, and IGF-1 and IGF binding protein (BP)-3 levels before and after 4 days treatment with human (h)GH.

We found that, in comparison with controls, patients with FM exhibited a marked decrease in spontaneous GH secretion as assessed by mean GH secretion ($2.5 \pm 0.4 \mu\text{g/L}$ in controls vs. $1.2 \pm 0.1 \mu\text{g/L}$

in FM, $P < 0.05$), pulse height ($4.7 \pm 0.8 \mu\text{g/L}$ in controls vs. $2.5 \pm 0.3 \mu\text{g/L}$ in FM, $P < 0.05$), and pulse area ($4.7 \pm 1 \text{ min/mg-L}$ in controls vs. $2.3 \pm 0.3 \text{ min/mg-L}$ in FM, $P < 0.05$). In contrast, GH responses to GHRH (100 μg , iv) were similar in controls (mean peak, $13.5 \pm 2.5 \mu\text{g/L}$) and in patients with FM ($12.2 \pm 3 \mu\text{g/L}$). Finally, treatment with hGH (2 IU, sc daily), over 4 days, led to a clear-cut increase in plasma IGF-1 and IGFBP-3 levels in patients with FM.

In conclusion, our data show that patients with FM exhibited a marked decrease in spontaneous GH secretion, but normal pituitary responsiveness to exogenously administered GHRH, thus suggesting the existence of an alteration at the hypothalamic level in the neuroendocrine control of GH in these patients. Furthermore, our finding of increased IGF-1 and IGFBP-3 levels after GH treatment, over 4 days, opens up the possibility of testing the therapeutic potential of hGH in patients with FM. (*J Clin Endocrinol Metab* 84: 3378–3381, 1999)

FIBROMYALGIA (FM) is a painful syndrome of nonarticular origin, characterized by fatigue and widespread musculoskeletal pain, tiredness, and sleep disturbances, without any other objective findings on examination. It has a prevalence of 2.1–5.7% at the general practitioner's office and up to 20% at the rheumatology outpatient clinic. This disease frequently leads to a marked impairment of normal physical activity as well as work incapacity (1–8).

Although the etiology and pathogenesis of this disease are unknown, disturbed neuroendocrine function has been postulated to be present in these patients (9). Interestingly, some of the clinical features of FM are similar to the ones described in the adult GH deficiency syndrome (10–13). Shared features in these two syndromes include muscle weakness, fatigue, decreased exercise capability, and feeling of social isolation. Furthermore, insulin-like growth factor (IGF)-1 levels are frequently reduced in these patients (14–17), sug-

gesting that this could be caused by impaired spontaneous GH secretion. However the mechanisms involved in the alteration of the GH-IGF-axis are still unclear.

The aim of this study was to study whether decreased spontaneous GH secretion in patients with FM syndrome could be caused by an impairment of pituitary GH responses to GHRH. Furthermore, we investigated whether decreased plasma IGF-1 levels were associated with decreased spontaneous GH secretion as well as assessing IGF-1 and IGF binding protein (BP)-3 response to exogenously administered GH.

Subjects and Methods

All patients in this study were women. FM was diagnosed according to the classification criteria of the American College of Rheumatology (7). Forty-three patients (all female, with active FM) and 34 normal subjects participated in this study. Patients who had other concurrent medical problems or were postmenopausal were not enrolled in the study. None of these subjects were taking any medication for at least 1 month before the study or had any evidence of metabolic disease, and the diagnosis of FM was established (mean + SEM), 108 ± 27 months before the study.

GH responses to GHRH

Twenty-one patients with FM (mean age, 42.1 ± 1.7 yr) and 21 normal subjects (mean age, 35.1 ± 1.4 yr), matched by body mass index (BMI),

Received September 30, 1998. Revision received May 24, 1999. Accepted June 1, 1999.

Address all correspondence and requests for reprints to: C. Dieguez, P.O. Box 563, 15700 Santiago de Compostela, Spain. E-mail: fscadigo@uscmail.usc.es.

* This work was supported by grants from the Fondo de Investigaciones Sanitarias, Spanish Ministry of Health, and the Xunta de Galicia.

underwent this study. After obtaining a basal sample, GHRH (100 µg, iv) was administered; and sampling was continued at 15, 30, 60, and 120 min post-GHRH administration.

Spontaneous GH secretion

Fourteen patients with FM [mean age, 44.5 ± 2.5 yr (range, 23–51 yr); mean BMI, 24.8 ± 1.1 (range, 19–31)] and 13 normal subjects [mean age, 43.5 ± 3.2 yr (range, 21–48 yr); mean BMI, 26.3 ± 1.3 (range, 22–31.3)], matched by age and BMI, were enrolled in this study. Participants were admitted to the hospital the evening before the study and then underwent blood sampling at 20-min intervals for 24 h beginning at 0900 h. Subjects were permitted to ambulate, were given 3 eucaloric meals per day, and were not permitted to nap or sleep until 2300 h. Basal IGF-1 levels in this group of patients with FM (125.9 ± 12.6 µg/L) were decreased, in comparison with the group of control subjects (211.3 ± 19 µg/L).

IGF-1 and IGF-BP3 generation test

Eight patients with FM (mean age, 40.7 ± 2.9 yr) underwent this study. IGF-1 and IGF-BP3 were measured before and after 4 days of treatment with human (h)GH (2 IU/day, sc; Genotonorm, Pharmacia & Upjohn, Inc., Stockholm, Sweden).

Informed consent was obtained from each subject, and the study was approved by the Bioethical Committee. Participants were admitted to the hospital, and blood was drawn through an iv catheter placed in a forearm vein.

Plasma GH was measured by an immunoradiometric assay (Biomerieux, Madrid, Spain) with a sensitivity of 0.1 µg/L and with intrassay coefficients of variation (CVs) of 6.3% and 4.4% for GH concentrations of 2.2 µg/L and 24 µg/L, respectively. GH secretory profile was analyzed using the PULSAR program (18). The program identifies secretory peaks by height and duration from a smoothed baseline, using the assay SD as a scale factor. The assay CV was calculated from duplicates of pooled serum across the assay range, as described. The cut-off characteristics G1–5 were set to 3.6, 2.4, 1.4, 1.0, and 0.7 times the intrassay SD. The smoothing time was set to half of the total profile time. The splitting time parameter was set to 2.7, and the weight assigned to peaks was 0.05.

IGF-1 was determined by a commercially available RIA (Nichols Institute Diagnostics, San Juan Capistrano, CA). The sensitivity of the assay was 0.02 µg/L. The mean intra- and interassay CVs were 2.4% (110 µg/L), 3.0% (338 µg/L), and 3.8% (562 µg/L); and 5.2% (121 µg/L), 6.5% (371 µg/L), and 6.8% (641 µg/L), respectively. IGF-BP3 was measured using a commercially available RIA (Mediadiagnostic, GmbH; Tübingen, Germany). The intrassay CVs were 2.8 (2.2 mg/L) and 3.0% (4.3 mg/L) and the interassay CVs were 4.8% (2.6 mg/L) and 5.9% (4.5 mg/L).

Data are expressed as mean ± SEM. Statistical comparison was carried out with the Mann-Whitney test. Significance was set at *P* < 0.05.

Results

Basal GH levels were similar in patients and controls (0.5 ± 0.1 µg/L vs. 0.3 ± 0.1 µg/L). After GHRH administration (Fig. 1), a similar increase in plasma GH levels was observed in controls (mean peak, 13.5 ± 2.5 µg/L) and in patients with FM (12.2 ± 3 µg/L).

Spontaneous GH secretion in patients with FM was decreased, in comparison with control subjects, as assessed by mean GH secretion, pulse height, and pulse area, without significant differences in frequency or pulse length (Table 1, Fig. 2). No correlation was found between GH secretion and the length of time the subjects were diagnosed for FM neither with the age of the patients or with their BMI. This decrease was most noticeable during the night (0000 h to 0800 h), a period when GH secreted in the patients (3.07 µg/L) was much lower than in controls (27.9 µg/L, *P* < 0.05).

Treatment with hGH for 4 days IGF-1 led to a clear increase

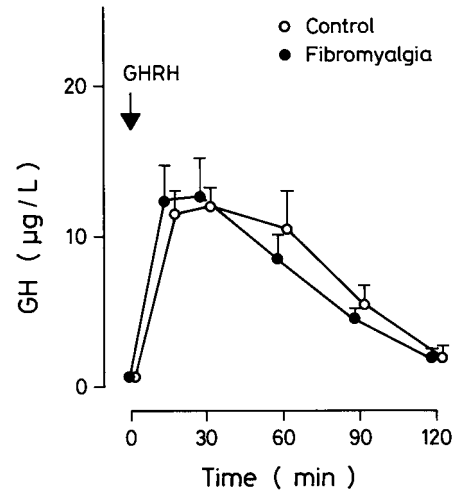


FIG. 1. Mean + SEM plasma GH levels after administration of GHRH (1 µg/kg, iv at 0 min) in control subjects and patients with FM.

TABLE 1. Mean ± SEM pulse parameters in controls (n = 13) and patients with fibromyalgia (n = 14; FM)

Parameter	Controls	FM
AUC (µg/L/24 h)	27.9 ± 8.6	8.2 ± 6.7 ^a
Mean GH secretion (µg/L)	2.5 ± 0.4	1.2 ± 0.1 ^a
Frequency (number peaks/24 h)	10.8 ± 0.5	9.0 ± 0.6
Pulse height (µg/L)	4.7 ± 0.8	2.5 ± 0.3 ^a
Pulse length (min)	90 ± 5	96 ± 5
Pulse area (min/mg · L)	4.7 ± 1	2.3 ± 0.3 ^a

AUC, area under curve.

^a *P* < 0.05.

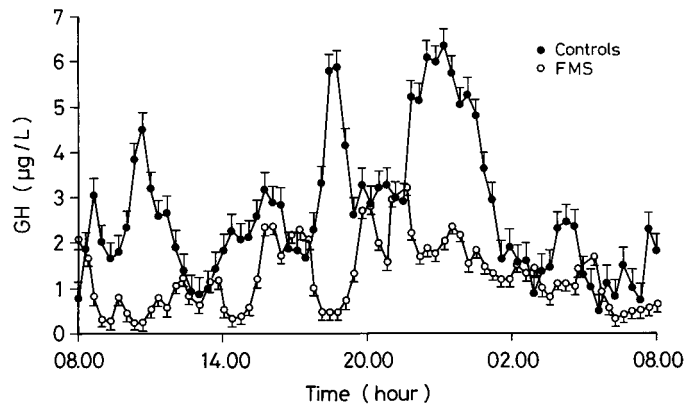


FIG. 2. Plasma GH levels (mean + SEM) over 24 h in control subjects and in patients with FM (FMS).

in plasma IGF-1 and IGF-BP3 levels in all the patients studied (Fig. 3). Mean basal IGF-1 levels (134 ± 16 µg/L) were increased after 4 days treatment with hGH (205 ± 18.8 µg/L; *P* < 0.001); the levels achieved being similar to untreated control subjects. Similarly mean basal IGF-BP3 levels (1.4 ± 0.2 mg/L) were also increased after 4 days treatment with hGH (2.2 ± 0.1 mg/L; *P* < 0.001).

Discussion

Over the past few years, considerable attention has been given to the possibility that decreased plasma IGF-1 levels could be of relevance to the etiology of some of the clinical

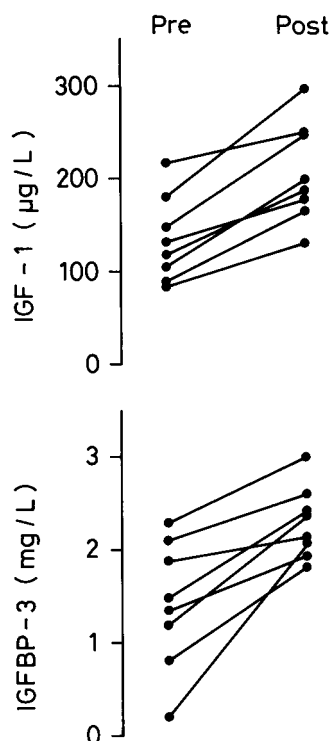


FIG. 3. Serum IGF-1 and IGFBP-3 levels in eight patients with FM before (pre) and after 4 days treatment (post) with hGH (2 IU/day, sc).

features exhibited by patients with FM. The possibility that decreased IGF-1 levels could be caused by depression, concomitant medication, poor aerobic condition, obesity, or pain level was ruled out (17). Therefore, low IGF-1 levels could be caused by reduced GH secretion. Although 24-h urinary GH secretion in patients with FM has been reported to be no different from controls, these patients exhibited much larger nocturnal diuresis than controls. Because urinary GH secretion is mainly dependent on the renal tubular resorptive function, this may well explain the lack of differences observed in such a study (19). Also, some workers have reported normal basal GH levels in patients with FM (16). However, it should be noted that GH levels were only measured at individual time points during the day (e.g. 0800 h). Taking into account that GH secretion is highly pulsatile, the failure to find any differences between patients and controls, using this approach, is not surprising. Furthermore, maximal GH secretion occurs during stage 4 sleep, and this stage is reduced in patients with FM (3–8). In fact, we and others have previously found a marked decrease in spontaneous GH secretion at night in association with reduced length of stage III-IV of sleep (20–21). In keeping with this possibility, in the present work, we found a marked impairment in 24-h spontaneous GH secretion in patients with FM, in comparison with control subjects, which was largely caused by decreased GH pulse amplitude rather than frequency.

Next, and to clarify whether decreased GH secretion could be caused by an alteration at hypothalamic or pituitary levels, we assessed GH responses to exogenously administered GHRH. We found a similar GH response to GHRH in patients and in control subjects. These data imply the existence

of normal pituitary responsiveness to GHRH and that pituitary GH reserve is largely preserved in patients with FM. In support of an alteration at hypothalamic level is the fact that the alterations in this condition seem to be global, involving the pain system, the CRH neuron, and the autonomic system (22). Furthermore, it has been postulated that patients with FM exhibited abnormalities in some signals involved in the control of GH secretion, namely, serotonin, NPY, and CRF, among others (9). Also, blunted GH responses to L-dopa and clonidine have been reported in FM (17). Low adrenergic stimulation of the GH axis could explain the decreased secretion of this hormone and its sequellae (22). However, the lack of data in control subjects in these studies, together with the fact that GH response to these secretagogues in normal subjects is usually very poor, does not allow us to reach firm conclusions regarding these findings. Further studies are now needed to characterize the implications of these alterations in the neuroendocrine control of GH in these patients.

Taking into account that decreased GH secretion in patients with FM could contribute to symptoms such as reduced exercise tolerance, impaired vitality, cold intolerance, muscle weakness, and a feeling of social isolation, a beneficial effect of treatment with hGH in patients with FM has been postulated (17, 20–21). However, the possibility of the presence of peripheral GH insensitivity in these patients has not been ruled out. We found that treatment with hGH for 4 days led to a clear increase in plasma IGF-1 and IGF-BP3 levels, reversing their declining levels in patients with FM. These data indicated the feasibility of testing the therapeutic potential of hGH in patients with FM. Indeed, it has been recently reported that a randomized, double-blind, placebo-controlled study, of 9 months treatment with GH, in patients with FM, showed an improvement in their overall symptomatology and number of tender points (23).

In conclusion, our data show that patients with FM exhibited a marked decrease in spontaneous GH secretion but normal pituitary responsiveness to exogenously administered GHRH, thus suggesting the existence in these patients of an alteration at hypothalamic level in the neuroendocrine control of GH secretion. Furthermore, our finding of increased serum IGF-1 and IGFBP-3 levels, after 4-days treatment, in these patients, indicates that GH-receptor-mediated responsiveness at target tissues is preserved.

References

1. Goldenberg DL. 1987 Fibromyalgia syndrome. An emerging but controversial condition. *JAMA*. 257:2782–2787.
2. Bennet RM. 1995 Fibromyalgia: the commonest cause of widespread pain. *Compr Ther*. 21:269–275.
3. Moldofsky H, Searisbrick P, England R, Smythe H. 1975 Musculoskeletal symptoms and non-REM sleep disturbances in patients with fibrositis syndrome and healthy subjects. *Psychosom Med*. 37:341–351.
4. Moldofsky H. 1994 Chronobiological influences on fibromyalgia syndrome: theoretical and therapeutic implications. *Ballieres Clin Rheumatol*. 8:801–810.
5. Cohen ML, Quintner JL. 1993 Fibromyalgia syndrome, a problem of tautology. *Lancet*. 342:906–909.
6. Bennett RM. 1989 Confounding features of the fibromyalgia syndrome, a current perspective of differential diagnosis. *J Rheumatol*. 19:58–61.
7. Wolfe F, Smythe HA, Yunus MB, et al. 1990 The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis Rheum*. 33:160–172.
8. Wolfe F. 1996 The fibromyalgia syndrome: a consensus report on fibromyalgia and disability. *J Rheumatol*. 16:185–191.
9. Crofford LJ, Pillemer SR, Kalogeras KT, et al. 1994 Hypothalamic-pituitary-

- adrenal axis perturbations in patients with fibromyalgia. *Arthritis Rheum.* 37:1583–1592.
10. **Cuneo RC, Salomon F, McGauley GA, Sonksen PH.** 1992 The growth hormone deficiency syndrome in adults. *Clin Endocrinol (Oxf).* 37:387–397.
 11. **Rosen T, Johansson G, Johansson JO, Bengtsson BA.** 1995 Consequences of growth hormone deficiency in adults and the benefits and risks of recombinant human growth hormone treatment. A review paper. *Horm Res.* 43:93–99.
 12. **Jorgensen JOL, Pedersen SA, Thuesen L, et al.** 1989 Beneficial effects of growth hormone treatment in GH-deficient adults. *Lancet.* 1:1221–1225.
 13. **De Boer H, Blok GJ, Van der Veen E.** 1995 Clinical aspects of growth hormone deficiency in adults. *Endocr Rev.* 16:63–86.
 14. **Bennett RM, Cark SR, campbell SM, Burckhardt CS.** 1992 Low levels of somatomedin C in patients with fibromyalgia syndrome. *Arthritis Rheum.* 35:1113–1116.
 15. **Ferraccioli G, Guerra P, Rizzi V, et al.** 1994 Somatomedin C (INSULIN-LIKE GROWTH FACTOR 1) levels decrease during active changes of stress related hormones. Relevance for fibromyalgia. *J Rheumatol.* 21:1332–1334.
 16. **Buchwald D, Umali J, Stene M.** 1996 Insulin-like growth factor 1 (somatomedin C) levels in chronic fatigue syndrome and fibromyalgia. *J Rheumatol.* 23:739–742.
 17. **Bennett RM, Cook DM, Clark SR, Burckhardt CS, Campbell SM.** 1997 Hypothalamic-pituitary-insulin-like growth factor-1 axis dysfunction in patients with fibromyalgia. *J Rheumatol.* 24:1384–1389.
 18. **Merriam RG, Wacher KW.** 1982 Algorithms for the study of episodic hormone secretion. *Am J Physiol.* 243:E310–E318.
 19. **Jacobsen S, Main K, Danneskiold-Samsøe B, Skakkebaek NE.** 1995 A controlled study of serum insulin-like growth factor-1 and urinary excretion of growth hormone secretion in fibromyalgia. *J Rheumatol.* 22:1138–1140.
 20. **Bagge E, Bengtsson BA, Carlsson L, Carlsson J.** 1998 Low growth hormone secretion in patients with fibromyalgia—a preliminary report on 10 patients and 10 controls. *J Rheumatol.* 25:145–148.
 21. **Leal-Cerro A, Povedano J, Silva H, et al.** 1996 The GH-IGF-1 axis in patients with fibromyalgia syndrome. *Proc of the International Congress of Endocrinology, San Francisco, CA, 1996*, pp 1–491 (Abstract).
 22. **Pillemer SR, Bradley LA, Crofford LJ, Maldofsky H, Chrousos GP.** 1997 The neuroscience and endocrinology of fibromyalgia. *Arthritis Rheum.* 40:1928–1939.
 23. **Bennett RM, Clark SC, Walczyk J.** 1998 A randomized, double-blind, placebo-controlled study of growth hormone in the treatment of fibromyalgia. *Am J Med.* 104:227–231.