

Growth Hormone and Insulin-like Growth Factor-1 Concentrations in Women with Fibromyalgia

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ABSTRACT. Objective. To determine activity of the growth hormone–insulin-like growth factor-1 (GH–IGF-1) axis in women with fibromyalgia (FM).

Methods. Premenopausal women with FM (n = 24) and premenopausal healthy women (n = 27) were studied. IGF-1 was measured in 23 patients with FM and 25 controls. GH was measured during a stepped hypoglycemic hyperinsulinemic clamp procedure (blood glucose decreased from 90 to 40 mg/dl every 30 min in 10 mg/dl decrements) in 12 FM and 13 control subjects.

Results. IGF-1 concentrations were similar in the FM (200 ± 71 ng/ml, mean ± SD) and control (184 ± 70 ng/ml) groups. By multiple variable analysis, IGF-1 was negatively associated with age (p = 0.0006), body mass index (BMI) (p = 0.006), and 24 h urinary free cortisol (p = 0.007) in healthy controls. Even after accounting for these factors, there was no association between FM and IGF-1. The average peak GH achieved during hypoglycemia was lower in patients with FM (range 5 to 58 ng/ml, median 13 ng/ml) versus controls (6 to 68 ng/ml, median 21 ng/ml) (p = 0.04). However, BMI was a significant predictor of average peak GH in FM (r = -0.62, p < 0.01) and control subjects (r = -0.40, p = 0.06). After considering BMI, there was no significant association between FM subjects and the average peak GH (p = 0.20).

Conclusion. In this sample of premenopausal women with FM, the activity of the GH–IGF-1 axis was similar to that of healthy controls. Increases in age and obesity were both strongly associated with lower activity of this axis, suggesting that these factors must be considered when studying activity of the GH–IGF-1 axis in FM. (J Rheumatol 2003;30:809–14)

Key Indexing Terms:

FIBROMYALGIA

GROWTH HORMONE

HYPOGLYCEMIA

INSULIN-LIKE GROWTH FACTOR-1

SOMATOMEDIN C

Fibromyalgia (FM) is a chronic, poorly understood syndrome characterized by widespread chronic musculoskeletal aches, pain, and stiffness¹. This condition can be accompanied by a variety of other symptoms including fatigue, anxiety, sleep disturbances, and irritable bowel complaints². Research into the etiology of FM has explored the hypothesis that growth hormone (GH) deficiency is a significant feature of the syndrome. This theory is predicated on the observation that adult patients with a primary pituitary defect resulting in GH deficiency have clinical features — malaise, depressed mood,

anxiety, reduced vitality and energy, reduced strength and exercise capacity, cold intolerance³ — that are also seen in patients with FM.

GH secreted by the pituitary acts on the liver and other tissues to stimulate the production of insulin-like growth factor-1 (IGF-1)⁴. The largest study of its kind involving 500 patients with FM, 26 myofascial pain patients, 52 patients with other rheumatic diseases, and 74 healthy controls found significantly low IGF-1 concentrations in the FM group⁵, supporting the conclusion of a smaller study⁶. These low IGF-1 levels raised the possibility that subjects with FM have reduced GH secretion. By contrast, studies with fewer than 20 patients and controls found no significant difference between IGF-1 levels in patients with FM versus controls^{7–9}.

Direct measurement of serum GH every 30 to 60 minutes for 24 hours revealed a significantly lower mean concentration of GH in patients with FM versus healthy controls¹⁰, with this decrease being most notable at night^{10,11}. However, another study that measured GH in 24 hour urinary collections found no difference between FM patients and healthy controls⁹.

Studies that examine the GH response to specific stimuli in FM patients have again shown variable results. FM subjects, compared to healthy controls, had a hyper-reactive GH response to hypoglycemia induced by a bolus of insulin (insulin tolerance test)¹² and a normal response to a bolus of

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GH-releasing hormone (GHRH)^{11,13}. In contrast, studies using the insulin tolerance test followed by the arginine stimulation test¹⁴ and studies using clonidine and L-dopa testing⁵ observed subnormal GH responses in FM patients compared to normative clinical values. Given these conflicting results, it remains unclear whether GH and IGF-1 are reduced in women with FM.

We examined the activity of the GH-IGF-1 axis in premenopausal patients with FM who had discontinued their medications versus healthy premenopausal women. We determined IGF-1 levels in 23 FM patients and 25 controls. In addition, considering that hypoglycemia is an excellent stimulus for GH secretion, we analyzed for GH stored blood samples obtained during stepped hypoglycemic hyperinsulinemic clamps performed in 12 of the subjects with FM and 13 of the controls.

MATERIALS AND METHODS

Subjects. Adult women who met the 1990 American College of Rheumatology criteria for the diagnosis of FM¹ were recruited from the practice of one investigator (DLG), and healthy women were recruited using advertisements in local newspapers.

Exclusion criteria for both patients and controls included pregnancy or lactation, the use of glucocorticoids within the past year, or the use of estrogen or progesterone within the past 4 months. Screening of all subjects included a detailed history and examination, blood and urine chemistry tests, and thyroid function studies. Anyone with abnormal laboratory studies was excluded. No subject had any concurrent medical problems other than FM, except for one FM subject with treated hypothyroidism and normal thyroid stimulating hormone. All subjects were premenopausal, based either on menstrual history or on a confirmed premenopausal level of follicular stimulating hormone (in women who had undergone a hysterectomy). All subjects were screened for psychiatric disorders by a Structured Clinical Interview from the *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edition revised (DSM-III-R) or 4th edition (DSM-IV). Control subjects with a current psychiatric history or a history of depression were excluded.

All studies were reviewed and approved by the Committee for the Protection of Human Subjects of Brigham and Women's Hospital. Informed written consent was obtained from each subject before participation. Studies were performed at the General Clinical Research Center of Brigham and Women's Hospital.

All prescription and nonprescription medications, as well as vitamins and herbal remedies, except for levothyroxine and acetaminophen, were stopped at least 2 weeks before the study. Subjects were asked to stop taking acetaminophen 48 h before the study.

A total of 24 women with FM and 27 controls were enrolled. IGF-1 samples were obtained from 23 FM subjects and 25 controls. Twelve FM subjects and 13 controls participated in the hypoglycemic clamp study described below. Urinary free cortisol (UFC) levels were obtained from 24 FM subjects and 26 controls. UFC levels were calculated as the average of the total 24 h urinary free cortisol levels for up to three 24 h periods. To ensure that the UFC data reflected a complete urinary collection, UFC data were excluded if the creatinine for any 24 h period was < 70% of the average urinary creatinine for that subject. Twenty-two controls and 23 FM subjects also completed the Fibromyalgia Impact Questionnaire¹⁵, which consists of 10 items measuring pain, stiffness, fatigue, sleep, physical functioning, work status, depression, anxiety, and well being.

Stepped hypoglycemic hyperinsulinemic clamp study. From the cohort, a subset of 12 FM patients and 13 healthy women also participated in a stepped hypoglycemic hyperinsulinemic clamp study. In this procedure, insulin is infused intravenously at a constant rate to achieve a steady blood insulin con-

centration and the amount of an intravenous (IV) infusion of 20% dextrose is regulated to achieve the target serum glucose. The effect of hypoglycemia on the ACTH, cortisol, prolactin, and catecholamines was published previously¹⁶. All subjects consumed a 10 mEq sodium/100 mEq potassium isocaloric diet for the 4 days preceding the hypoglycemic hyperinsulinemic clamp study. Before the study, serum estradiol levels were measured from 7 FM patients and 13 controls.

Subjects were supine and fasted from midnight until the completion of the hypoglycemic hyperinsulinemic clamp. The hypoglycemic hyperinsulinemic clamp study was initiated at 10:00 am. Insulin and glucose were infused through an IV line, which was placed in an antecubital vein. Blood samples were obtained through a second IV line inserted in a retrograde fashion in a hand vein. This hand was warmed to 60°C (140°F) to arterialize the venous blood¹⁷. Insulin (2 mU/kg/min; Humulin®, Eli Lilly and Co., Indianapolis, IN, USA) was infused continuously for 3 h. Serum glucose levels were measured at 5 min intervals. The rate of a 20% dextrose infusion was adjusted to maintain serum glucose levels consecutively at 90, 80, 70, 60, 50, and 40 mg/dl, each for 30 min¹⁸. Blood samples were drawn at 0, 30, 60, 90, 120, 150, and 180 min. Samples were analyzed for insulin, GH, and glucose.

Laboratory tests. IGF-1 was measured using the Nichols Advantage 2-site chemiluminescence immunoassay for IGF-1 (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA). The assay was 95% sensitive to a lower limit of 6 ng/ml; the intraassay coefficient of variation (CV) varied from 4.4% to 5.2%. Human growth hormone was measured using the Nichols Advantage 2-site chemiluminescence immunoassay for growth hormone. The assay was 95% sensitive to a lower limit of 0.1 ng/ml; the intraassay CV varied from 4.2% to 8.0%. Serum glucose levels were measured using a Beckman Glucose Analyzer II (Beckman, Brea, CA, USA); the lower limit of detection was 6 µmol/l and the intraassay CV was 3%. Insulin levels were measured using the Insulin Coat-A-Count kit (Diagnostic Products Corp., Los Angeles, CA, USA), with lower limit of detection of 3 µU/ml. Urinary free cortisol was measured using the Cortisol Coat-A-Count radioimmunoassay kit (Diagnostic Products Corp.). The lower limit of detection for this assay is 0.2 µg/dl (95% confidence); intraassay CV ranged from 3.0% to 5.1%. Estradiol was measured using the Estradiol Double Antibody radioimmunoassay kit (Diagnostic Products Corp.); lower limit of detection (95% confidence) was 1.4 pg/ml, and intraassay CV ranged from approximately 5% to 16%.

To convert: glucose from mg/dl to mmol/l, multiply by 0.055; IGF-1 from ng/ml to nmol/l, multiply by 0.131; growth hormone from ng/ml to µg/l divide by 1.00; insulin from µU/ml to pmol/l divide by 0.1394; urinary free cortisol from µg/dl to nmol/l, multiply by 27.59; estradiol from ng/dl to pmol/l, divide by 0.0272.

Statistical methods. Statistical analyses were performed using SAS version 8.2. Results were reported as mean ± SD. Wilcoxon rank sum analysis was used to compare characteristics between the control and FM groups. Spearman correlation was used to determine the association between IGF-1 and age. The natural log transform was applied to normalize the distribution of the mean peak GH (average of GH at times 150 and 180 min) during the hyperinsulinemic hypoglycemic clamp. Stepwise regression was used to analyze the significance of body mass index (BMI), age, 24 h urinary free cortisol, and diagnosis of FM in the prediction of mean peak GH and IGF-1. Analysis of covariance was used to compare slopes.

RESULTS

There was no significant difference in IGF-1 concentrations between FM (200 ± 71 ng/ml) and control subjects (184 ± 70 ng/ml) (Table 1). In both groups there was a similar negative correlation between IGF-1 and age ($r = -0.59$ and -0.57 for FM and controls, respectively, $p = 0.003$ for each, $p = 0.79$ for comparison of slopes) (Figure 1). Multiple variable analysis showed that IGF-1 was significantly negatively associated with age ($p = 0.0006$), BMI ($p = 0.006$), and urinary free cor-

Table 1. Selected characteristics of patients with FM and healthy control subjects.

	FM Patients N = 24	Control Subjects N = 27	p Value ^a
Age, yrs	38 ± 8	37 ± 8	0.54
BMI, kg/m ²	25 ± 4	25 ± 4	0.36
Severity of disease (FIQ)	66 ± 17 ^b	10 ± 13 ^c	< 0.0001
Disease duration, yrs	6 ± 6	N/A	N/A
IGF-1, ng/ml	200 ± 71 ^c	184 ± 70 ^d	0.39
24-h UFC, µg/total volume	78 ± 40	76 ± 34 ^c	0.62

^a p value for comparison between the 2 groups. ^b n = 22, ^c n = 23, ^d n = 25, ^e n = 26.

UFC: urinary free cortisol.

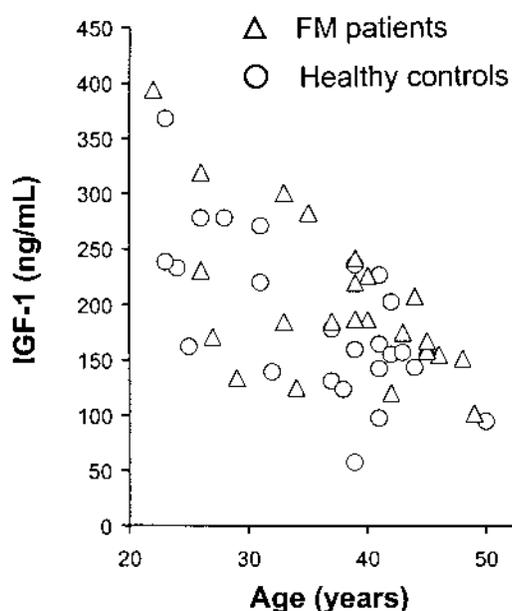


Figure 1. IGF-1 as related to age in FM patients and controls. A similar inverse correlation between IGF-1 and age was observed in FM patients and controls.

tisol ($p = 0.007$) in controls. Even after taking these factors into account, the presence of FM was not a significant predictor of IGF-1.

Growth hormone response to hypoglycemia. In the subgroup of subjects who participated in the hypoglycemic clamp protocol, there were no significant differences in age, BMI, baseline estradiol, or IGF-1 between FM and control subjects (Table 2).

Baseline glucose, insulin, and growth hormone levels measured at time zero were similar in FM and control subjects (Table 2). With the insulin infusion, insulin levels rose in both FM patients and controls to average levels of 175 ± 47 and 163 ± 35 ng/ml, respectively ($p = 0.41$). The decrease in serum glucose did not differ significantly between the study groups. Serum glucose fell from 94 ± 8 to 43 ± 1 mg/dl in the FM

Table 2. Selected characteristics for subset of subjects participating in hypoglycemic hyperinsulinemic clamp study.

	FM Patients N = 12	Control Subjects N = 13	p Value ^a
Age, yrs	39 ± 7	40 ± 7	0.81
BMI, kg/m ²	26 ± 5	24 ± 4	0.46
Severity of disease (FIQ)	66 ± 18	4 ± 7	< 0.0001
Disease duration, yrs	8 ± 7	N/A	N/A
Estradiol, pg/ml	101 ± 110 ^b	58 ± 39	0.61
IGF-1, ng/ml	176 ± 47 ^c	148 ± 60 ^c	0.10
24-h UFC, µg/total volume	107 ± 30	104 ± 25	0.50
Insulin at baseline, ng/ml	7 ± 4	6 ± 1	0.51
Glucose at baseline, mg/dl	94 ± 8	95 ± 4	0.34
Growth hormone at baseline, ng/ml	2 ± 2	4 ± 4	0.20

^a p value for comparison between the 2 groups. ^b n = 7, ^c n = 11.

UFC: urinary free cortisol.

group and from 95 ± 4 to 43 ± 2 mg/dl for the control group ($p = 0.50$) (Figure 2).

In both groups, growth hormone rose in response to hypoglycemia plateauing at target serum glucose levels of 40–50 mg/dl (Figure 2). For each individual the average peak GH (average of the GH response at target serum glucose levels of 40–50 mg/dl) was determined. The mean peak GH was significantly reduced in FM subjects compared to controls ($p = 0.04$). However, there was marked variation in average peak GH secretion between individuals in both the control group (range 6 to 68 ng/ml, median 21 ng/ml) and the FM group (range 5 to 58 ng/ml, median 13 ng/ml).

BMI was a significant predictor of the mean peak growth hormone achieved during hypoglycemia in FM subjects ($r = -0.62$, $p < 0.01$) and controls ($r = -0.4$, $p = 0.06$) (Figure 3). The relationship between BMI and mean peak GH was not significantly different in the FM versus the control group ($p = 0.35$). After taking BMI into account there was no significant additional predictive value for the diagnosis of FM ($p = 0.20$). Estradiol, age, and 24 h urinary free cortisol did not provide significant predictive value for the GH response to hypoglycemia.

To determine if the relationship between peak GH and BMI was specific we examined the correlation between peak prolactin response to hypoglycemia and BMI. Prolactin levels during the hypoglycemic hyperinsulinemic clamp were reported in our earlier report on the study population¹⁶. There was no significant ($p = 0.35$) correlation between the peak prolactin response to hypoglycemia and BMI in either FM subjects or controls.

DISCUSSION

Using a precise hypoglycemic challenge, we found that women with FM as well as healthy women have growth hormone responses that correlated inversely with BMI. After taking into account BMI, the GH response to hypoglycemia was

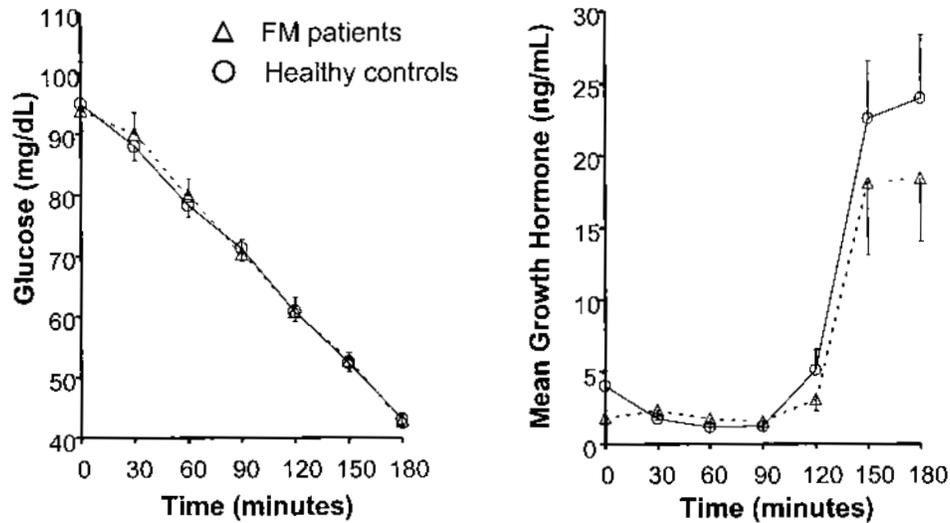


Figure 2. Glucose (left) and growth hormone (GH, right) during hypoglycemic hyperinsulinemic clamp procedure in 12 FM patients and 13 healthy controls. Mean \pm SD of glucose at time 0 and the average of glucose measured every 5 min for each 30 min block. A similar decrease in glucose over time was observed in both groups. In both groups the GH response plateaued at time 150 to 180 min. GH at time 150 and time 180 min was averaged to determine the mean peak GH response.

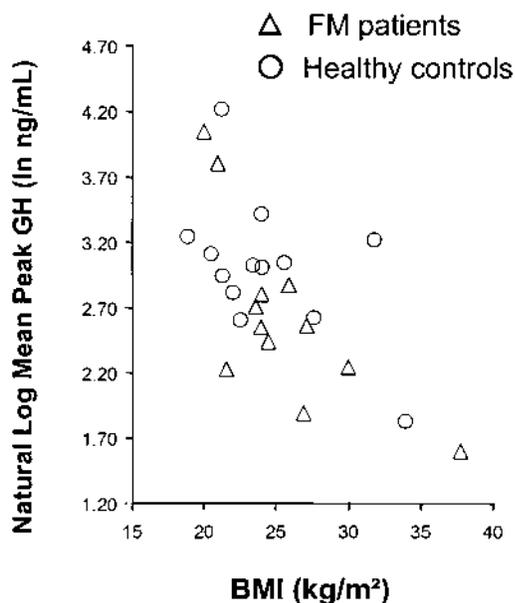


Figure 3. The natural log of the mean peak GH compared to BMI in FM patients and controls. BMI was found to be a significant predictor of GH. After considering BMI, there was no significant additional predictive value for the diagnosis of FM ($p = 0.20$) in determining the average peak GH.

similar in FM subjects and controls. Similarly, IGF-1 levels were similar in FM and control subjects, even after taking into account the effects of age, cortisol, and BMI on IGF-1. Therefore, based on the GH response to hypoglycemia and on IGF-1 levels we found no evidence for abnormal regulation of the GH-IGF-1 axis in premenopausal women with FM.

Our findings are consistent with studies showing a decrease in IGF-1 with age^{5,19}, and confirm that this relationship is apparent even in premenopausal women. The observation that IGF-1 levels were similar in subjects with FM and healthy controls is consistent with results of several studies⁷⁻⁹, but does not support the one large study showing reduced IGF-1 levels in 500 women with FM⁵. However, this latter study, while taking age into account, did not consider obesity in the analysis of IGF-1 levels in FM. Low IGF-1 levels are associated with indices of obesity such as BMI in women in the current study, BMI in men only¹⁹, and visceral fat mass in women and men²⁰ and in men only²¹. Thus, the finding of lower IGF-1 levels in the study by Bennett and colleagues⁵ may be related to increased obesity, particularly abdominal obesity, in the FM population and/or to other factors that influence GH secretion such as physical activity^{22,23} and estrogen status^{24,25}.

The marked variability in the peak GH response to hypoglycemia observed in both study groups was strongly attributable to an inverse correlation between GH response to hypoglycemia and BMI. Several other studies have also shown blunting of the GH response to hypoglycemia in obese subjects compared to lean controls²⁶⁻²⁸. Further, this impairment in GH release is reversible, since weight loss is associated with an increase in the GH response to hypoglycemia^{27,29}. Our ability to detect this relationship between GH and BMI in the present study is likely related to the strict control of hypoglycemia during the clamp technique that obviates differences in insulin sensitivity associated with obesity. Careful control of blood glucose levels and accounting for obesity may explain the difference between the current results and previ-

ous studies, showing either an increased GH response to hypoglycemia in FM subjects versus controls¹² or a reduced GH response to hypoglycemia in one-third of women with FM as compared to published clinical standards¹⁴. Both these studies used an acute injection of insulin to induce hypoglycemia, a technique that relies on a decrease in glucose to 40 mg/dl or lower to activate the counterregulatory response, but does not accurately control the depth or duration of hypoglycemia.

BMI and in particular abdominal adiposity^{29,30} also appear to be correlated with lower GH levels under basal conditions and in response to other stimuli, including exercise^{22,23}, GHRH^{26,31,32}, L-dopa^{32,33}, arginine^{28,32}, and GH secretagogue L-692,429³⁴. Thus, obesity may again partially account for the variable reports of low or normal GH levels in FM under resting conditions and in response to stimuli (arginine, clonidine, or GHRH)^{5,10-12}. Finally, since estrogen stimulates GH release^{24,25}, restricting the present study to premenopausal women may have controlled for another modifier of GH secretion.

Our studies suggest that regulation of the GH-IGF-1 axis is similar in premenopausal women with fibromyalgia and premenopausal healthy women. Our study design does not allow us to rule out the possibility that altered regulation of this axis may occur with aging or menopause. Further, while decreased activity of the GH-IGF-1 axis is not required for the presence of FM, those individuals with low levels could be more susceptible to development of FM. Alternatively, low GH-IGF-1 axis activity may exacerbate some of the symptoms of FM. Due to the negative effects of age and obesity on the GH-IGF-1 axis, older and heavier patients with FM are most likely to have reduced activity of this axis.

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