# High Prevalence of Growth Hormone Deficiency in Severe Fibromyalgia Syndromes

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**Context:** Fibromyalgia (FM) is characterized by widespread pain and fatigue and is considered a syndrome with different pathogenic mechanisms. Controversial data on GH axis disturbances have been published. Some preliminary trials have shown promising effects of GH therapy on tender points and quality of life in FM.

**Aim:** The aim was to study the patterns of GH secretion/sensitivity in a cohort of severe FM patients.

**Setting:** The study was conducted in five tertiary hospitals.

**Methods:** A total of 493 FM women (1990 American College of Rheumatology criteria) recruited from five centers, having more than 16 tender points, Fibromyalgia Impact Questionnaire scores above 75, more than 1 yr of stable medication (serotonin reuptake inhibitors, amitriptyline, and opioids), and body mass index below 35 kg/m$^2$ underwent baseline IGF-I/GH determinations; an insulin tolerance test (ITT) and a modified IGF-I generation test were performed in those cases showing IGF-I of 150 $\mu$g/liter or less.

**Results:** A total of 169 of the 493 patients (34.2%) showed IGF-I of 150 $\mu$g/liter or less. Mean peak GH during ITT was 13.3 $\pm$ 9.9 ng/ml in 127 patients in which the test was performed. In 22 of 127 (17.3%), ITT peak GH was 5 $\mu$g/ml or less, and in eight of them (6.3%), the peak GH was 3 ng/ml or less. Mean baseline GH (n = 127) was 1.47 $\pm$ 2.58 ng/dl, and eight of 120 (6.8%) showed an insufficient IGF-I response ($<$50% over baseline) to the IGF-I generation test.

**Conclusion:** FM patients show a high prevalence of GH axis dysfunction. A significant number of patients show biochemical patterns of GH deficiency as well as some degree of GH resistance and might be potential candidates for substitution treatment. **(*J Clin Endocrinol Metab* 95: 4331–4337, 2010)**

Fibromyalgia (FM) is an idiopathic, chronic, nonarticular, and noninflammatory pain syndrome that is defined by a widespread increase in sensitivity in tender points and is frequently accompanied by fatigue and poor sleep (1). According to diagnosis criteria of the American College of Rheumatology (ACR), pain should involve both sides of the body both above and below the waist, including the axial skeletal system, for at least 3 months,

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Abbreviations: AGHD, Adult GH deficiency; BMI, body mass index; FIQ, Fibromyalgia Impact Questionnaire; FM, fibromyalgia; ITT, insulin tolerance test; MRI, magnetic resonance imaging; ns, not significant.

affecting at least 11 tender points among nine pairs of specified sites (1). There is still some skepticism regarding the diagnosis of fibromyalgia because the condition is not associated with specific analytical, radiological, or histological findings and because it is frequently accompanied by concomitant psychiatric symptoms (2). Due to the prevalence of FM (3–4% of the population) and its high medical costs, the medical community has made steps to implement health policies to address the needs of patients with FM (3, 4). Worldwide scientific recognition of the disorder has increased, and FM is now listed under the World Health Organization International Classification of Disease (M79.7 in the ICD-10 2007 version), but the causes of the syndrome remain heterogeneous. Because FM is defined as a syndrome with a common clinical expression rather than a single disease, subgroups of different etiology are likely to exist (5).

One pathogenic approach suggests that central nervous system hypersensitization may play a role, involving neurotransmission in the dorsal horn of the spinal cord (6) as well as abnormalities in the amygdala and hippocampus pain processing (7, 8). Microtrauma at selective tender points (tendinous insertions) have also been implicated in FM (9), and associations between FM and autoimmune disease have been reported (10).

In relation to the endocrine system, GH axis disturbances may participate in the possible pathophysiology of FM in some patients (11). Many of the symptoms described by FM syndrome include fatigue, depression, muscle weakness, low fat-free mass, cold intolerance, impaired memory, and a general feeling of poor health, very similar to those of the adult GH deficiency (AGHD) syndrome (12). In addition, low levels of IGF-I have been reported in a significant proportion of patients with FM (13). The 24-h GH profiles in patients with FM suggest that it is more likely to be the result of decreased GH secretion (14) rather than GH insensitivity, although both conditions may coexist in a given patient (15). To our knowledge, no data on the IGF-I generation test, as a biochemical proof for GH resistance, have been published so far in a large FM population.

In a recent study in which responses to GHRH-arginine testing were evaluated, 17% of patients with FM and low IGF-I levels failed to respond (16). Similarly, stimulation testing with pyridostigmine as well as exercise testing failed to increase GH levels in patients with FM, suggesting a high somatostatinergic tone (17). Response to the insulin tolerance test (ITT) has been reported to be normal in many patients with FM (18, 19); however, approximately one third of patients appear to show a suboptimal GH response in other studies with a small number of patients (20, 21).

Considering most of the data generated up until now, although the majority of patients with FM do not seem to present abnormalities in the somatotropic axis, a significant subset of them may have different disturbances, either of a secretory nature or of GH action. It is unknown whether these disturbances may contribute to the generation of FM symptoms or are the consequence of a chronic stress process. Treatment trials with recombinant human GH in some of these patients with proved GH disturbances would seem a rationale approach (22, 23).

The aim of this paper is to present descriptive data on GH secretion and GH sensitivity in a homogeneous cohort of patients with severe FM.

## Patients and Methods

A large cohort of severely affected FM patients including 493 women [mean age, 50 ± 9.4 yr; mean body mass index (BMI), 27.2 ± 4.1 kg/m$^2$] were screened (recruited between 2005 and 2009) to include them in the CT27560 trial, a multicenter trial conducted in Spain in five tertiary hospitals from different regions. Severe FM was diagnosed according to ACR criteria (1). To be eligible for the trial, patients had to be more than 18 yr old, with a confirmed diagnosis of FM for more than 1 yr with more than 16 tender points, and with a Fibromyalgia Impact Questionnaire (FIQ) score above 75 (24). All patients had to have received stable doses of intensive treatment including amitriptyline 10–50 mg/d, selective serotonin reuptake inhibitors 10–40 mg/d, and tramadol 100–400 mg/d for at least 1 yr before the study. BMI was less than 35 kg/m$^2$. Postmenopausal women were not on hormonal replacement therapy. Cortisol and TSH values should be normal. No head trauma was recorded in any of the screened subjects.

Baseline GH and IGF-I determinations were measured in the local laboratories of each center using an automated chemiluminescent immunoassay from a commercial source (IMMULITE 2000; Diagnostic Products Corp., Los Angeles, CA). The interassay coefficients of variation of the GH and IGF-I assays were 4.52 and 3.04%, respectively. The functional sensitivity of GH and IGF-I assays were 0.05 and 25 ng/ml, respectively.

IGF-I was considered low when 150 $\mu$U/ml or less, corresponding to −2 SD in a previously published FM population (13). In those patients in which IGF-I was 150 $\mu$g/ml or less, an ITT was performed according to previously published methods (25). Following guidelines of the American Academy of Clinical Endocrinology and The Endocrine Society, a peak GH of 3 ng/ml or less was considered as a highly deficient GH state, and a peak of 5 ng/ml or less was considered a state of partial GH deficiency (26). A glucagon test for GH secretion (27) was performed alternatively in those cases in which ITT was not valid (interrupted because of severe hypoglycemia or insufficient hypoglycemia). The same cutoffs (3 and 5 ng/ml or less, respectively) were used to define GH deficiency with this test. To explore the IGF-I response to GH administration and assess GH sensitivity, a modified IGF-I generation was used (28), due to previous data indicating an insufficient stimulatory effect with the GH dose of 0.2 mg for 4 consecutive days of the classic IGF-I generation test (29). In this modified test, sc administration of 2 mg of GH (Saizen;

**TABLE 1.** CT 27560 results of basal GH, IGF-I, peak GH value after ITT, and IGF-I after generation test in a cohort with severe fibromyalgia

| | GH (ng/ml) | IGF-I ($\mu$U/ml) | Peak GH (ITT) (ng/ml) | Δ% IGF-I (generation test) | BMI (kg/m$^2$) |
|---|---|---|---|---|---|
| Mean | 1.47 | 118.21 | 13.30 | 104.46 | 27.21 |
| SD | 2.58 | 42.36 | 9.93 | 63.82 | 4.10 |
| n | 133 | 222 | 127 | 118 | 115 |

Age-adjusted IGF-I: 36–40 yr olds, 115–284 ng/ml; 41–50 yr olds, 109–252 ng/ml; and 51–60 yr olds, 101–225 ng/ml.

Merck Farma y Química, Barcelona, Spain) was administered, and the cutoff for a normal IGF-I response was an increase greater than 50% over baseline IGF-I. In those patients in which peak GH was 3 ng/ml or less at ITT, a second secretion test different from the first one was performed and consisted mainly of a glucagon test (27). Magnetic resonance imaging (MRI) of the hypothalamus-pituitary region was done to rule out other causes of AGHD. In those patients with basal GH of at least 5 ng/ml, GH was measured after a 75-g oral glucose load, and a pituitary MRI was performed to rule out the possibility of a nondiagnosed acromegaly.

The SPSS statistical software package (version 12.0; SPSS Inc., Chicago, IL) was used for statistical analysis. Student *t* test was used to assess differences between groups, and Spearman's test was used to assess correlations between different basal data. Values are expressed as mean ± SD.

Patients with uncompleted data or invalid dynamic testing were excluded for analysis.

The study was conducted in accordance with the Declaration of Helsinki and received approval from the local institutional review boards and the Spanish Drug Agency (no. 27560). The trial has been registered (NCT00933686) at ClinicalTrials.gov. All patients gave written informed consent before their inclusion in the study.

## Results

Among the 493 patients evaluated, 169 (34.2%) showed low levels of IGF-I (≤150 $\mu$g/ml). In 129 of these 169 patients (and four additional patients with IGF-I <170), GH secretion was evaluated. In 127 patients in which the ITT was performed, mean peak GH value was 13.3 ± 9.9 ng/ml (Table 1). Eight of the 127 patients (6.3%) had a GH after ITT of 3 ng/ml or less, and 22 of 127 (17.3%) had a peak GH value after ITT of 5 ng/ml or less, values confirmed after a glucagon test (Table 2). Six other patients with invalid ITT data also underwent a glucagon test, and all of them showed a normal GH stimulation of at least 5 ng/ml at peak value. Five patients were retested after amitriptyline withdrawal for 1 month due to inconclusive results of the previous tests, and one normalized the GH response using glucagon testing, whereas in the other four, GH peak persisted at 3 ng/ml or less. No correlation was observed between baseline

**TABLE 2.** Basal data and dynamic tests of the 22 patients with AGHD (GH <5 ng/ml)

| CT screening no. | GH (ng/ml) | GH peak ITT (ng/ml) | Time (min) (max GH peak) | IGF-I ($\mu$U/ml) | IGF-I after generation test ($\mu$U/ml) | Δ% IGF-I (generation test) | Age (yr) | BMI (kg/m$^2$) |
|---|---|---|---|---|---|---|---|---|
| 0120 | 0.33 | 3.09 | 60 | 112 | 246 | 119.64 | 46 | 24.72 |
| 0121 | 0.05 | 3.05 | 60 | 110 | 229 | 108.18 | 39 | 35.06 |
| 0130 | 0.05 | 4.65 | 45 | 60.8 | 106 | 74.34 | 56 | 31.16 |
| 0115 | 0.3 | 2.9 | 60 | 123 | 187 | 52.03 | 42 | 37.63 |
| 0108 | 0.29 | 4.02 | 90 | 121 | 251 | 107.44 | 45 | 22.58 |
| 0101 | 0.1 | 2.2 | 45 | 92.5 | ND | ND | 54 | 22.27 |
| 0105 | 1.46 | 0.69 | 30 | 72 | ND | ND | 51 | 20.83 |
| 0112 | 1.73 | 3.43 | 90 | 78 | ND | ND | 44 | 21.51 |
| 0102 | 0.25 | 2.86 | 60 | 302 | 355 | 17.55 | 39 | 21.60 |
| 0110 | 0.05 | 2.18 | 60 | 222 | 204 | −8.11 | 37 | 25.20 |
| 0209 | 3.03 | 3.66 | 45 | 135 | 209 | 54.81 | 39 | 26.72 |
| 0217 | 0.89 | 2.5 | 90 | 128 | 212 | 65.63 | 47 | 30.16 |
| 0231 | <0.1 | 3 | 90 | 88 | 227 | 157.95 | 57 | 32.25 |
| 0241 | 0.32 | 3.19 | 60 | 127 | 340 | 167.72 | 49 | 24.77 |
| 0245 | 0.05 | 4.6 | 60 | 132 | 316 | 139.39 | 43 | 30.47 |
| 0257 | 0.89 | 2.3 | 60 | 66 | 213 | 222.73 | 59 | 26.86 |
| 0263 | 0.18 | 3.51 | 60 | 97.7 | 313 | 220.37 | 58 | 27.55 |
| 0267 | 3.7 | 4.75 | 45 | 173 | 250 | 44.51 | 43 | 25.14 |
| 0501 | 1.7 | 3.4 | 30 | 161 | 285 | 177.02 | 41 | 27.64 |
| 0503 | 0.1 | 3.7 | 60 | 120 | 292 | 243.33 | 51 | 35.09 |
| 0504 | 1.5 | 3.8 | 90 | 121 | 266 | 219.83 | 39 | 25.81 |
| 0403 | 0.2 | 4.3 | 45 | 105 | 202 | 192.38 | 52 | 25.39 |

ND, Not determined.

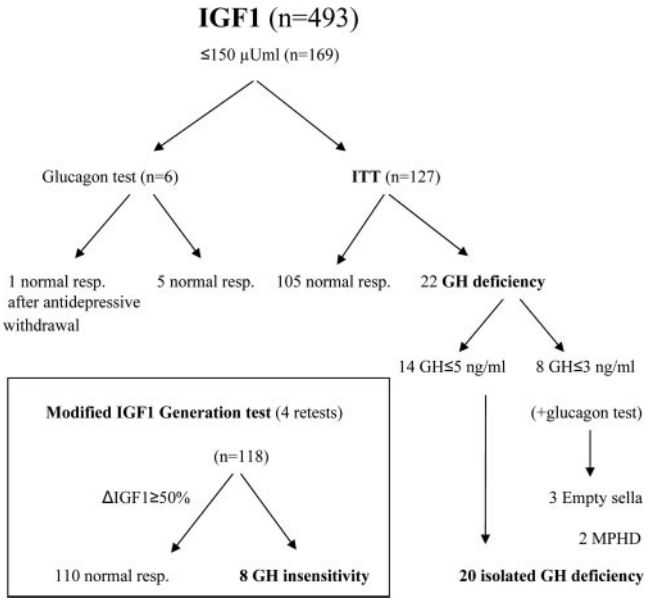


**FIG. 1.** Screening procedures flowchart: summary of GH/IGF-I axis results. MPHD, Multiple pituitary hormone deficiency.

IGF-I and GH peak after ITT (r = −0.02) in the 127 patients in which this test was performed (Fig. 1). No differences were found comparing peak GH in pre- and postmenopausal women.

Mean baseline GH (n = 133) was 1.47 ± 2.5 ng/dl (Table 1); 26 of 133 patients had basal GH of at least 1 ng/ml (19.5%), and 12 of 133 patients had baseline GH of at least 5 ng/ml (9%). In these 12 cases, GH values after glucose load showed normal suppression.

In eight of 118 patients (6.8%), an insufficient response to the modified IGF-I generation test was observed (≤50% baseline IGF-I) (Fig. 1). No correlation was found between baseline GH and IGF-I after the generation test (r = −0.1). Nineteen patients with low GH at ITT showed normal IGF-I generation test response. No correlation between baseline IGF-I and BMI was observed.

No correlations were found between the severity of FM symptoms (total FIQ score) and IGF-I (n = 169) [r = 0.22; *P* = not significant (ns)]; baseline GH (n = 133) (r = −0.23; *P* = ns); peak GH after ITT (n = 127) (r = 0.11; *P* = ns); or IGF-I after generation test (n = 118) (r = −0.27; *P* = ns). No correlation between peak GH after ITT or glucagon test and BMI was found (r = −0.37; *P* = ns).

Among the eight highly deficient GH patients (peak GH ≤3 ng/ml), two showed multiple hormone deficiency (two LH/FSH deficiency both in unreplaced postmenopausal women), and three showed an empty sella at MRI. All partial insufficient responses (peak GH ≤5 ng/ml, but ≥3 ng/ml) showed isolated GH deficiency and no abnormal findings at MRI (Fig. 1).

## Discussion

Because FM is no longer considered as a unique entity, but rather a syndrome characterized by common signs and symptoms (pain and fatigue) with possible different pathogenic factors, efforts over the last decade have been aimed at investigating the pathogenesis of this syndrome and included extensive research into potential disturbances of the endocrine system. Various reports indicate that in some patients with severe FM, an impairment of GH secretion due to an altered neurosecretory regulation of the somatotropic axis may be present (11, 13, 14, 16); in addition, an impaired action of GH at different peripheral tissues indicating some degree of GH resistance has also been postulated (15).

IGF-I has been used as a screening tool when investigating the GH axis in FM syndromes (13, 16). It is not known whether FM patients as a whole population may behave differently from their normal controls. In our study, we used the proposed cutoff level of 150 µg/dl in other studies (13) for evaluating somatotropic axis disturbances in FM. Although IGF-I may vary in relation to different physiological and pathological situations, and although low IGF-I levels do not invariably reflect GH insufficiency, we found repeated low IGF-I levels in 34.2% of our FM cohort. Our results are in line with other previous reports (13, 16), but this high frequency of low IGF-I levels may not reflect the global FM population because our cohort showed a particularly aggressive form of the syndrome.

In most of the reported series, the majority of FM patients have shown a normal GH/IGF-I axis when analyzed through GH-releasing tests (18, 19). In our study, we evaluated the GH/IGF-I axis, trying to detect GH deficiency and resistance situations in patients that may eventually be included in a clinical trial where GH add-on treatment would be used. Our cohort of patients with FM, a very homogeneous cohort (>16 tender points, >75 FIQ score), is the largest published and so far explored using ITT/glucagon and IGF-I generation tests.

In our study, mean GH value after ITT was also normal for the whole cohort, but when stratification according to response category of ITT and glucagon test was done, a significant 17.3% of patients appeared to have an insufficient capacity of GH secretion, confirmed by a second provocative testing procedure. Moreover, there was a significant 6.3% of patients in which the degree of GH deficiency was very severe because they showed a peak GH value lower than 3 ng/ml. In this highly GH-deficient group, two patients showed multiple hormone deficiencies, and three showed an empty sella, indicating that in some patients with organic pituitary disturbances FM may

be the clinical expression. A recent report by Yuen *et al.* (16), studying GH secretion with GHRH-arginine in a low IGF-I FM population, has found the same prevalence of GH-deficient patients (17%). ITT has been considered the gold-standard dynamic testing for GH secretion, although hypoglycemia only activates GHRH through the adrenergic system; arginine also inhibits somatostatinergic tone, which has been proposed to be hyperactive in FM, and moreover, GHRH/arginine has compared well with the ITT (25). As in other studies in which low IGF-I is used for selecting in which patients GH secretory test should be performed, underestimation of the real amount of GH deficiency may occur.

BMI or estrogenic status might be important confounders in GH provocative testing results, either ITT or glucagon (27, 30). No morbid obese subjects were included in our study, and no significant correlation between BMI and peak GH values was found; thus, it is unlikely that GH insufficiency in these cases may be influenced by overweight. Similarly, no differences in peak GH were observed comparing pre- and postmenopausal subgroups.

So far, only studies with a limited number of ITTs have been done, all of them showing a normal GH secretory pattern in the majority of FM patients; however, all these studies were performed in a limited number of patients (18, 19). Dinser *et al.* (20) reported suboptimal GH responses (<10 ng/ml) in 45 women and 15 men. The study by McCall-Hosenfeld *et al.* (21) in a group of 24 FM patients also found lower GH values during hypoglycemia compared with controls using a stepped hypoglycemic hyperinsulinemic clamp procedure, although BMI was a major confounder, because their patients were mainly obese. In relation to other factors that may modify the somatotropic axis activity, antidepressive drugs taken by these patients for long periods of time have not been shown to affect GH axis (13, 22), and opioids seem to stimulate GH secretion rather than diminish it (31). Although few of our patients showing low stimulated GH were retested after triple treatment withdrawal, mainly for pain worsening and ethical compromise, we did not observe any change in the GH response. It seems unlikely then that pharmacological factors could explain a depressed somatotropic axis in our FM patients.

If this unexpected, quite high prevalence of GH deficiency found (17.3%) is confirmed by other groups, as some data in literature suggest (16), severe FM cohorts may hide a significant pool of GH-deficient patients, susceptible to being treated with GH. These data are similar to those of hypopituitarism seen in traumatic brain injury, which has had much of our attention in recent years (32, 33).

Alterations in quality of life scores, decreased well-being, and fatigue are usual symptoms in patients with AGHD in the endocrine outpatient clinics. But could pain in specific tender points be an uncommon clinical sign of AGHD? So far, only the Australian multicenter trial for the use of GH in adults with AGHD has indirectly addressed the question (12), and pain score significantly decreased after 6 months of GH treatment.

Another possible disturbance associated with FM syndrome is GH insensitivity. Denko and Malemud (15) described increased levels of serum GH in a small cohort of FM patients (n = 32) with different degrees of severity. The fact that a majority of FM patients stand with normal-low IGF-I and normal secretion test (11, 13, 14, 16) suggests a certain degree of GH insensitivity in this syndrome. Our data show that a significant number of patients (21.6%) had serum GH of at least 1 ng/ml, 10% had GH of at least 5 ng/ml, and mean baseline serum GH was 1.47 ± 2.5 ng/dl. However, the lack of correlation between baseline GH and insufficient IGF-I response to GH does not seem to support a major role for GH insensitivity in this heterogeneous syndrome. Concomitant low IGF-I and oral glucose overload with normal suppression of GH excluded the possibility of a nondiagnosed acromegaly in our cases (34). In two previous trials with recombinant human GH as an add-on treatment in a low IGF-I FM population, the average dosage used was 0.125 mg/kg · d, reaching in some individuals dosages above 1 mg/d and highlighting a possible GH resistance in these patients (22, 23). The majority of the GH-deficient patients did not show any biochemical evidence of GH insensitivity.

High GH levels in some FM patients suggest GH insensitivity, possibly reflecting an adaptive neuroendocrine response to chronic stress. An initial hyperactive anterior pituitary may lead in the long term to an exhaustion of the somatotrope cell response to provocative tests, as seen in other chronically stressed models (35) and other rheumatic diseases as hyperostosis and osteoarthritis (36, 37).

One of our aims was to explore the GH sensitivity of FM patients with a specific dynamic test. The classic IGF-I generation test used for the diagnosis of Laron syndrome (28) did not show any increase in IGF-I values in the first eight patients tested (data not shown). Because a positive IGF-I response was hypothesized to be necessary for assessing GH treatment efficacy, a modified version of the IGF-I generation test was used. A protocol using 2 mg of sc GH in a single dose overnight was used, and for a matter of safety, the dose was lowered in comparison to the 7 mg originally established by Gleeson and Shalet (29). With this procedure, we found a 6.8% of subnormal IGF-I increase (<50% over baseline) in our patients, indicating that some FM cases show quite an intense GH insensitivity that makes the interpretation of GH/IGF-I axis disturbances in FM syndromes even more complex. Estrogens

and BMI have been associated to subnormal IGF-I generation test responses due to a low IGF-I hepatic production, but in our cohort no correlation was found between peak GH regarding pre- or postmenopausal status or peak GH and baseline IGF-I after the generation test regarding BMI (38).

In summary, we found that GH axis disturbances are present to some extent in a considerable subset of severe FM patients. Whether they are causally related to FM or are just an epiphenomenon reflecting the stress caused by maintained pain on the hypothalamic-pituitary axis, *i.e.* through hyperactivating corticotropin-releasing factor leading to an enhanced somatostatinergic tone or other mechanisms, remains uncertain. However, from an endocrinological point of view, the detection of patients where their clinical condition is associated to a GH response as low as less than 3 ng/ml is of relevance and suggests a link between AGHD of secretory origin and FM, by virtue of which some cases of true AGHD may be clinically expressed as FM. We would therefore recommend performing GH secretion dynamic tests as a part of the biological workup in low IGF-I FM patients.

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