

1 **Original article:**

2 High prevalence of GH deficiency in severe fibromyalgia syndromes.

3 **Brief title:** GH/IGF-1 axis in fibromyalgia

4

5 **Key terms:** GH, IGF-1, insulin tolerance test, IGF-1 generation test, fibromyalgia, AGHD,  
6 insufficiency, GH resistance.

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16

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31

32 **Abstract**

33

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

38 Aim: To study the patterns of GH secretion/sensitivity in a cohort of severe FM patients.

39 Setting: the study was conducted in 5 tertiary hospitals

40 Methods: 493 FM women (1990 American College of Rheumatology criteria) recruited from 5  
41 centers, having >16 tender points and Fibromyalgia Impact Questionnaire >75, >1 year stable  
42 medication (serotonin reuptake inhibitors, amitriptyline and opioids), BMI<30 kg/m<sup>2</sup>,  
43 underwent baseline IGF-1/GH determinations; an insulin tolerance test (ITT) and modified  
44 IGF-1 generation test were performed in those showing IGF-1 ≤150 µg/l .

45 Results: 169 out of 493 patients (34,27%) showed IGF-1≤150 µg/l. Mean peak GH during  
46 ITT was 13,3±9,93 ng/ml in 127 patients in which the test was performed. In 22/127(17,3%)  
47 ITT peak GH was ≤5 µg/ml and in 8 of them (6,29%) , the peak GH was ≤3ng/ml. Mean  
48 baseline GH (n=127) was 1,47±2,58 ng/dl and 8/120 (6,8%) showed an insufficient IGF-1  
49 response (<50% over baseline) to the IGF-1 generation test.

50 Conclusion: Fibromyalgia patients show a high prevalence of GH axis dysfunction. A  
51 significant number of patients show biochemical patterns of GH deficiency as well as some  
52 degree of GH resistance, and might be potential candidates for substitution treatment.

53

## 54 **Introduction**

55

56 Fibromyalgia (FM) is an idiopathic, chronic, non-articular and non-inflammatory pain  
57 syndrome that is defined by a widespread increase in sensitivity in tender points, and is  
58 frequently accompanied by fatigue and poor sleep (1). According to diagnosis criteria of the  
59 American College of Rheumatology (ACR), pain should involve both sides of the body both  
60 above and below the waist, including the axial skeletal system, for at least 3 months; and  
61 affecting  $\geq 11$  tender points among nine pairs of specified sites (1). There is still some  
62 scepticism regarding the diagnosis of fibromyalgia, because the condition is not associated with  
63 specific analytical, radiological or histological findings, and because it is frequently  
64 accompanied by concomitant psychiatric symptoms (2). Due to its prevalence (3-4% of the  
65 population) and high medical costs, the medical community has made steps to implement health  
66 policies to address the needs of patients with fibromyalgia (3,4). Worldwide scientific  
67 recognition of the disorder has increased and FM is now listed under the WHO International  
68 Classification of Disease (M79.7 in the ICD-10 2007 version, but the causes of the syndrome  
69 remain heterogeneous. Since FM is defined as a syndrome with a common clinical expression  
70 rather than a single disease, subgroups of different etiology are likely to exist (5).

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

76 In relation to the endocrine system, GH axis disturbances may participate in the possible  
77 pathophysiology of FM in some patients(11). Many of the symptoms described by fibromyalgia  
78 syndrome include fatigue, depression, muscle weakness, low fat-free mass, cold intolerance,  
79 impaired memory and a general feeling of poor health – very similar to those of the adult  
80 growth hormone deficiency syndrome (AGHD) (12). In addition, low levels of insulin-like

81 growth factor-I (IGF-I) have been reported in a significant proportion of patients with FM (13).  
82 Twenty-four hour GH profiles in patients with FM suggest that it is more likely to be the result  
83 of decreased GH secretion (14) rather than GH insensitivity, although both conditions may  
84 coexist in a given patient (15). To our knowledge, no data on IGF1 generation test, as a  
85 biochemical proof for GH resistance, has been published so far in a large FM population.  
86 In a recent study, in which responses to GHRH-Arginine testing were evaluated, 17% of  
87 patients with FM and low IGF-I levels failed to respond (16). Similarly, stimulation testing with  
88 pyridostigmine (suggesting higher somatostatinergetic tone) as well as exercise testing, failed to  
89 increase GH levels in patients with FM (17). Response to an insulin tolerance test (ITT) has  
90 been reported to be normal in many patients with FM (18,19). However, around one-third of  
91 patients appear to show a sub-optimal GH response in other studies with a small number of  
92 patients (20,21).  
93 Considering most of the data generated up until now, there is an indication that the majority of  
94 patients with FM do not present abnormalities in the somatotropic axis, although a significant  
95 subset of them may have different disturbances, either of secretory nature or of GH action.  
96 Whether these may contribute in part to FM symptoms or are the consequence of a chronic  
97 stress process is unknown. Treatment trials with recombinant human GH in some of these  
98 patients would seem a rationale approach (22, 23).

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

101

## 102 **Materials and Methods**

103 A large cohort of severely affected FM patients including 493 women (Mean age was 50±  
104 9.4 years and mean BMI was 27.2±4.1 Kg/m<sup>2</sup>) were screened in order to include them in the  
105 CT27560 trial, a multicenter trial conducted in Spain in 5 tertiary hospitals from different  
106 regions. Severe FM was diagnosed according to ACR criteria (1). In order to be eligible for the  
107 trial, patients had to be aged >18 year-old, to have had a confirmed diagnosis of FM for >1 year,

108 with >16 tender points and FIQ (Fibromyalgia Impact Questionnaire) score >75 (24). All  
109 patients had to have been receiving stable doses of intensive treatment including amitriptyline  
110 10–50 mg/day, selective serotonin reuptake inhibitors 10–40 mg/ day and tramadol: 100–400  
111 mg/day for at least 6 months prior to the study. BMI was <35 kg/m<sup>2</sup>.

112 Baseline GH and IGF-1 determinations were measured in the local laboratories of each  
113 center using an automated chemiluminescent immunoassay from a commercial source  
114 (IMMULITE® 2000, DPC, Los Angeles, CA). The interassay coefficient of variation of GH  
115 and IGF-1 assays was 4.52% and 3.04%, respectively. The functional sensitivity of GH and  
116 IGF-1 assays were 0.05 ng/ml and <25 ng/ml, respectively.

117 IGF-1 was considered low when  $\leq 150$   $\mu\text{U/ml}$ , corresponding to -2SD in previously  
118 published fibromyalgia population (13). In those patients in which IGF-1  $\leq 150$   $\text{ug/ml}$ , an insulin  
119 tolerance test (ITT) was performed according to previously published methods (25). Following  
120 the American Academy Clinical Endocrinology and Endocrine Society guidelines, a peak GH  
121  $\leq 3$   $\text{ng/ml}$  was considered as a highly deficient GH state, and a peak  $\leq 5$   $\text{ng/ml}$ , a state of partial  
122 GH deficiency (26). A glucagon test for GH secretion (27) was performed alternatively in those  
123 cases in which ITT was not valid (interrupted because of severe hypoglycemia or insufficient  
124 hypoglycaemia). The same cut-off  $\leq 3$  and  $\leq 5$   $\text{ng/ml}$  were used to define GH deficiency with this  
125 test. A modified IGF-1 generation was used (29) in order to explore the IGF-1 response to GH  
126 and assess the GH sensitivity, if due to previous data there are indications of an insufficient  
127 stimulatory effect with the GH dose 0.2 mg for 4 consecutive days of classic IGF-1 generation  
128 test (28). In this modified test, administration of 2 mg of GH s.c. (Saizen®, Merck Q, Spain)  
129 was administered and the cut-off for a normal IGF-1 response was an increase >50% over  
130 baseline IGF-1. In those in which GH  $\leq 3$   $\text{ng/ml}$ , a second secretion test different from the first  
131 one, was performed and consisted mainly in a glucagon test (27). MRI of the hypothalamus-  
132 pituitary region was done in order to rule out other causes of AGHD. In those patients with  
133 basal GH  $\geq 5$   $\text{ng/ml}$ , GH was measured after a 75g oral glucose load, and a pituitary MRI was  
134 performed to rule out the possibility of a misdiagnosed acromegaly.

135 The SPSS statistical software package (version 12.0) was used for statistical analysis.  
136 Student *t* test was used to assess differences between groups and Spearman's test to assess  
137 correlations between different basal data. Values are expressed as mean  $\pm$ SD.

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

139 The study was conducted in accordance with the Declaration of Helsinki and received the  
140 local institutional review boards and Spanish Drug Agency (n°27560) approvals. The trial has  
141 been registered (NCT00933686) at Clinical Trials.gov. All patients gave written informed  
142 consent prior to their inclusion in the study.

143

## 144 **Results**

145 Among the 493 patients evaluated, 169 (34.2 %) showed low levels of IGF-1 ( $\leq$ 150  
146  $\mu$ g/ml). In 133 patients of these 169, GH secretion was evaluated. In 127 patients in which ITT  
147 were performed, mean peak GH value was  $13.3 \pm 9.93$  ng/ml (Table 1). Eight out of 127 patients  
148 had a GH stimulation after ITT  $\leq 3$  ng/ml (6.3%), 22 out of 127 had a peak GH value after ITT  
149  $\leq 5$  ng/ml (17.3%) (Table 2). Six other patients underwent a glucagon test, and all of them  
150 showed a normal GH stimulation  $\geq 3$  ng/ml at peak value. Five patients were retested after  
151 amytriptiline withdrawal for 1 month due to inconclusive results of the previous tests, and 1  
152 normalized the GH response using glucagon testing while in the other 4 GH peak persisted  $\leq 3$   
153 ng/ml. No correlation was observed between baseline IGF-1 and GH peak after ITT ( $r = -0.02$ ) in  
154 the 127 patients in which this test was performed (Figure 1).

155 Mean baseline GH (n=133) was  $1.47 \pm 2.58$  ng/dl (Table 1); 26/133 patients had basal GH  
156  $\geq 1$  ng/ml (19.5%) and 12/133 patients had baseline GH  $\geq 5$  ng/ml (9%). In these 12 cases, GH  
157 values after glucose load showed normal suppression.

158 In 8/118 (6.8%) an insufficient response to the modified IGF1 generation test was  
159 observed ( $\leq 50\%$  baseline IGF-1 ) (Figure 1). No correlation was found between baseline GH  
160 and IGF-1 after generation test ( $r=-0.1$ ), but patients with low GH at ITT ( $n=22$ ) showed  
161 normal IGF-1 generation test response in all cases (Table 2).

162 No correlations were found between IGF-1 ( $n=169$ ) ( $r=0.22$ ,  $p=ns$ ), baseline GH ( $n=133$ )  
163 ( $r=-0.23$   $p=ns$ ), peak GH after ITT ( $n=127$ ) ( $r=0.11$   $p=ns$ ), IGF-1 after generation test ( $n=118$ )  
164 ( $r=-0.27$ ,  $p=ns$ ) and severity of FM (total FIQ score). No correlation between peak GH after  
165 ITT or glucagon test and BMI was found ( $r=-0.37$ ,  $p=ns$ ).

166 Among the 8 GH highly-deficient patients (cut-off  $\leq 3$  ng/ml), 2 showed multiple  
167 hormone deficiency and 3 an empty sella at MRI. All partial insufficient responses (cut off  $\leq 5$   
168 ng/ml but  $\geq 3$  ng/ml) showed isolated GH deficiency and no abnormal findings at MRI (Figure  
169 1).

170

## 171 **Discussion**

172 Since FM is no longer considered as a unique entity, but a syndrome characterized by  
173 common signs and symptoms (pain and fatigue) with possible different pathogenic factors,  
174 efforts over the last decade have been aimed at investigating the pathogenesis of this syndrome  
175 which have included extensive research into potential disturbances of the endocrine system.  
176 Various reports indicate that in some patients with severe FM, an impairment of GH secretion  
177 due to an altered neurosecretory regulation of the somatotrophic axis may be present in some  
178 patients (11,13,14,16); conversely, an impaired action of GH at different peripheral tissues  
179 indicating some degree of GH resistance has also been postulated (15). In most of the reported  
180 series, the majority of FM patients have shown a normal GH/IGF-1 axis when analyzed through  
181 GH releasing tests (18, 19). In our study, we evaluated the GH/IGF-1 axis trying to detect GH  
182 deficiency and resistance situations in patients that may eventually be included in a clinical trial

183 where GH add-on treatment would be used. Our cohort of patients with FM, a very  
184 homogeneous rheumatic cohort (>16 tender points, >75 FIQ score), is the largest published so  
185 far explored using ITT/glucagon and IGF-1 generation tests.

186 In our study, mean GH value after ITT was also normal for the whole cohort, but when  
187 stratification according to response category of ITT and glucagon test was done, a significant  
188 17,3% of patients appeared to have an insufficient capacity of GH secretion confirmed by a  
189 second provocative testing procedure. Moreover, there was a significant 6.3% of patients in  
190 which the degree of GH deficiency was very severe, as they showed a peak GH value even  
191 lower than 3 ng/ml. In this highly GH deficient group, only 2 patients showed multiple hormone  
192 deficiencies, and 3 an empty sella, indicating that in some patients with organic pituitary  
193 disturbances FM may be the clinical expression. A very recent report described by Yuen et al  
194 studying GH secretion with GHRH-Arginine in a low IGF1 fibromyalgia population (16) has  
195 found a similar number of GH deficient patients (17%). Insulin tolerance test has been  
196 considered the gold-standard dynamic testing for GH secretion, although hypoglycemia only  
197 activates GHRH through the adrenergic system; arginine inhibits also somatostatinergic tone,  
198 which has been proposed to be hyperactivated in fibromyalgia, and more over, GHRH/arginine  
199 has compared well with the ITT test (25).

200 BMI or estrogenic status might be important confounders in GH provocative testing  
201 results, either ITT or glucagon (27,30), but in our patients no morbid obese subjects were  
202 included in the study and no significant correlation between BMI and peak GH values was seen,  
203 thus it is unlikely that GH insufficiency in these cases maybe influenced by overweight.

204 So far only studies with limited number of ITT testing has been done, all of them showing a  
205 normal GH secretory pattern in the majority of FM patients, however all these studies were  
206 done in a limited number of patients (18,19). Dinser et al reported suboptimal GH responses  
207 (<10 ng/ml) in 45 women and 15 men (20). The study by McCall-Hosenfeld et al, in a group of  
208 24 FM patients, also found lower GH values during hypoglycemia compared to controls

209 (stepped hypoglycemic hyperinsulinemic clamp procedure), although BMI was a major  
210 confounder, since their patients were mainly obese (21). In relation to other factors that may  
211 modify the somatotrophic axis activity, antidepressive drugs taken by these patients for long  
212 periods of time have not been shown to affect GH axis (13, 22) and opioids seem to stimulate  
213 GH secretion rather than diminish it (31). Some of our patients showing low stimulated GH  
214 were retested after triple treatment withdrawal with no change in the GH response (data not  
215 shown). It seems then unlikely that pharmacological factors could explain a depressed  
216 somatotrophic axis in our FM patients.

217         If this unexpected quite high prevalence of GH deficiency found (17,3%) is confirmed by  
218 other groups, as some data in literature suggests (16), severe FM cohorts may hide a significant  
219 pool of GH deficient patients, susceptible to be treated with GH. These data are similar to those  
220 of hypopituitarism seen in traumatic brain injury, which has had much of our attention in recent  
221 years (32).

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

227 Another pathogenic mechanism involved in FM syndromes is GH insensitivity. Denko et al.  
228 described increased levels of serum GH in a small cohort (n=32) of FM patients with different  
229 degrees of severity (15). The fact that a majority of FM patients stand with normal-low IGF-1  
230 but normal secretion test (11,13,14,16), suggests a certain degree of GH insensitivity in this  
231 disorder. Our data show an important number patients had increased serum GH levels, as 21,6%  
232 had  $\text{GH} \geq 1$  ng/ml and 10%  $\text{GH} \geq 5$  ng/ml, and mean baseline serum GH was  $1.47 \pm 2.5$  ng/dl.  
233 Concomitant low IGF-1 and oral glucose overload with normal suppression of GH excluded the  
234 possibility of a misdiagnosis of acromegaly in our cases (33). In the 2 previous trials with rhGH

235 as an add-on treatment in low IGF-1 FM population, the average dose used was 0,125  
236 mg/kg/day, reaching in some individuals dosages above 1 mg/day, highlighting the clinical GH  
237 resistance in these patients (22, 23).

238 High GH levels in FM patients suggest GH insensitivity, possibly reflecting an adaptive  
239 neuroendocrine response to chronic stress. An initial hyperactivated anterior pituitary function  
240 may be detected which can lead in the long term to an exhaustion of the somatotrophic cell  
241 response to provocative tests, as seen in other chronically stressed models (34) and other  
242 rheumatic diseases as hyperostosis and osteoarthritis (35,36).

243 One of our aims was to explore the GH sensitivity of FM patients with a specific dynamic  
244 test. Classic IGF-1 generation test used for the diagnosis of Laron syndrome (28) did not  
245 showed any increase in IGF-1 values in the first 8 patients tested (data not shown). Since a  
246 positive IGF-1 response was hypothesized to be necessary for assessing GH treatment efficacy,  
247 a modified version of the IGF-1 Generation test was used. A protocol using 2 mg of  
248 subcutaneous GH in a single dose overnight was used, in which, for a matter of safety, the dose  
249 was lowered in comparison to the 7 mg originally established by Gleeson and Shallet (29).  
250 With this procedure we found a 6.8% of subnormal IGF1 increase (<50% over baseline) in our  
251 patients, indicating that some FM cases show quite an intense GH insensitivity that make the  
252 interpretation of GH/IGF1 axis disturbances in FM syndromes even more complex. Estrogens  
253 and BMI have been associated to subnormal IGF-1 generation test responses due to lower IGF-1  
254 hepatic production, but in our cohort no correlation between serum basal GH or peak IGF-1  
255 after the generation test regarding to pre or post menopausal status or BMI (37).

256 In summary, GH axis disturbances are present to some extent in a considerable subset of  
257 FM patients. Whether they are causally related to FM or are just an epiphenomenon reflecting  
258 the stress caused by maintained pain on the hypothalamic-pituitary axis, i.e. through  
259 hyperactivating corticotrophin releasing factor leading to an enhanced somatostatinergetic tone or  
260 other mechanisms, remains uncertain. However, from an endocrinological point of view, the

261 detection in patients where their clinical condition is associated to a GH response as low as < 3  
262 ng/ml is of relevance and suggest a link between AGHD of secretory origin and fibromyalgia,  
263 by virtue of which some cases of true AGHD maybe clinically expressed as FM. We would  
264 therefore recommend to perform GH secretion dynamic tests as a part of the biological work-up  
265 in low IGF-1 FM patients.

266

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380 **Tables and Figures**

381

382 Table 1:

383 CT 27560 results of basal GH, IGF1, peak GH value after ITT, and IGF1 after generation test, in a  
384 cohort with severe fibromyalgia

385

386 Table 2:

387 Basal data and dynamic tests of the 22 patients with AGHD (Gh<5 ng/ml)

388

389 Figure 1:

390 Screening procedures flowchart: summary of GH/IGF1 axis results

391 MPHD: multiple pituitary hormone deficiency

392

393 Figure 2:

394 A possible overlap between fibromyalgia syndromes, GH deficiency and GH resistance

395

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	<b>GH (ng/ml)</b>	<b>IGF1 (μU/ml)</b>	<b>Peak GH (ITT) (ng/ml)</b>	<b>Δ% IGF-1 (Generation test)</b>	<b>BMI (Kg/m<sup>2</sup>)</b>
<b>Mean</b>	1,47	118,21	13,30	104,46	27,21
<b>SD</b>	2,58	42,36	9,93	63,82	4,10
<b>Conf. inter</b>	0,44	5,98	1,69	11,42	0,75
<b>n</b>	133	222	127	118	115

398

399 **Table 1**

400

CT screening number	Initials	GH (ng/ml)	GH peak ITT (ng/ml)	time (min) (max GH peak)	IGF-1 (µU/ml)	IGF-1 after generation test (µU/ml)	Δ% IGF1 (generation test)	Height (m)	Weight (Kg)	BMI (Kg/m <sup>2</sup> )
0120	MAP	0,33	3,09	60	112	246	119,64	1,65	67,3	24,72
0121	AJM	0,05	3,05	60	110	229	108,18	1,52	81,0	35,06
0130	GDE	0,05	4,65	45	60,8	106	74,34	1,52	72,0	31,16
0115	SBC	0,3	2,9	60	123	187	52,03	1,64	101,2	37,63
0108	MM	0,29	4,02	90	121	251	107,44	1,63	60,0	22,58
0101	CBG	0,1	2,2	45	92,5	ND	ND	1,56	54,2	22,27
0105	LTR	1,46	0,69	30	72	ND	ND	1,67	58,1	20,83
0112	RIC	1,73	3,43	90	78	ND	ND	1,52	49,7	21,51
0102	ADM	0,25	2,86	60	302	355	17,55	1,64	58,1	21,60
0110	ESR	0,05	2,18	60	222	204	-8,11	1,74	76,3	25,20
0209	AMC	3,03	3,66	45	135	209	54,81	1,63	71,0	26,72
0217	TGG	0,89	2,5	90	128	212	65,63	1,55	72,0	30,16
0231	DFC	<0,1	3	90	88	227	157,95	1,57	79,5	32,25
0241	JMC	0,32	3,19	60	127	340	167,72	1,62	65,0	24,77
0245	RJP	0,05	4,6	60	132	316	139,39	1,60	78,0	30,47
0257	IFB	0,89	2,3	60	66	213	222,73	1,62	70,5	26,86
0263	PSG	0,18	3,51	60	97,7	313	220,37	1,65	75,0	27,55
0267	MGV	3,7	4,75	45	173	250	44,51	1,55	60,0	25,14
0501	YFG	1,7	3,4	30	161	285	177,02	1,58	69,0	27,64
0503	CCJ	0,1	3,7	60	120	292	243,33	1,51	80,0	35,09
0504	ACD	1,5	3,8	90	121	266	219,83	1,55	62,0	25,81
0403	JMR	0,2	4,3	45	105	202	192,38	1,73	76,0	25,39

Table 2

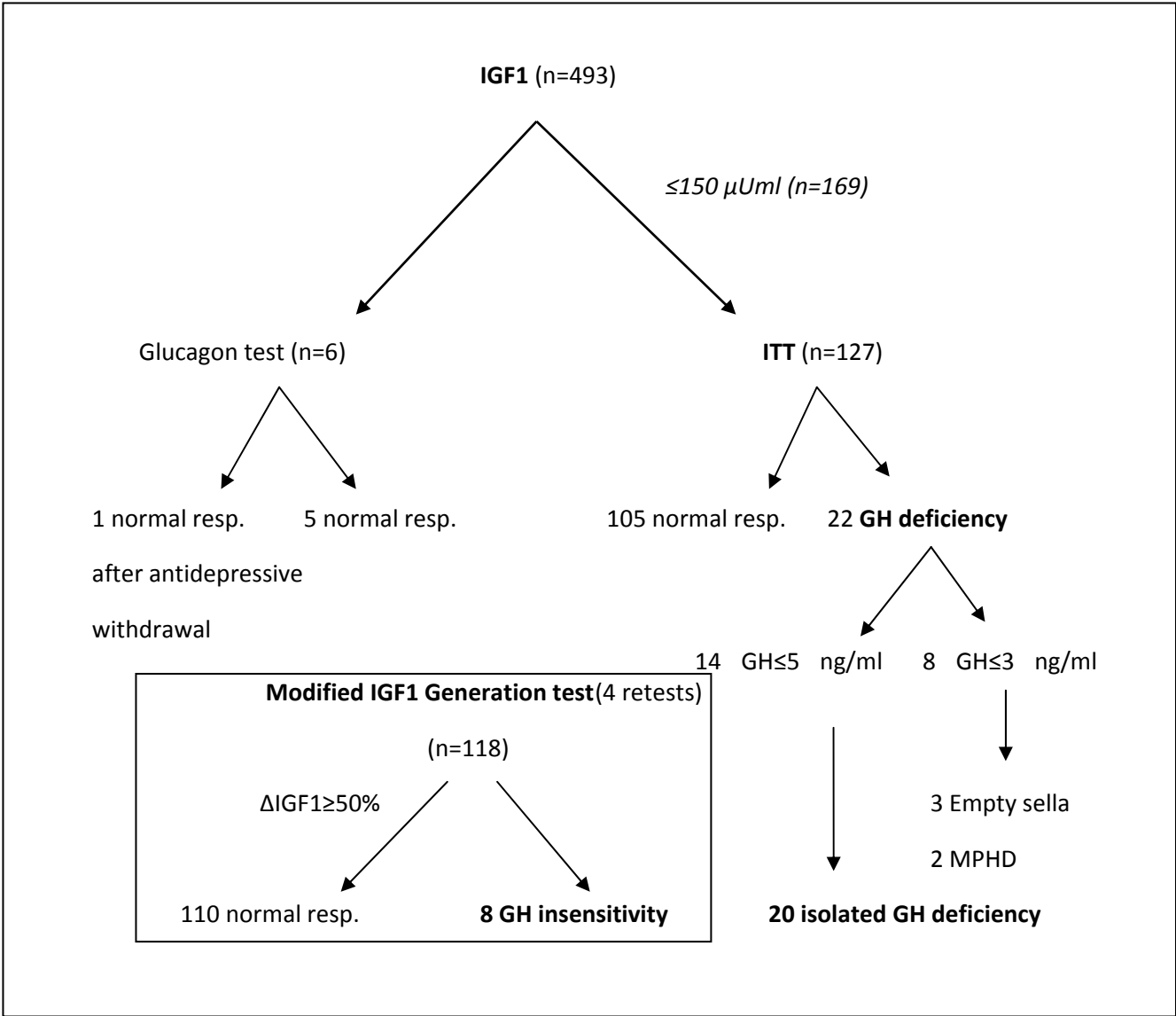


Figure 1

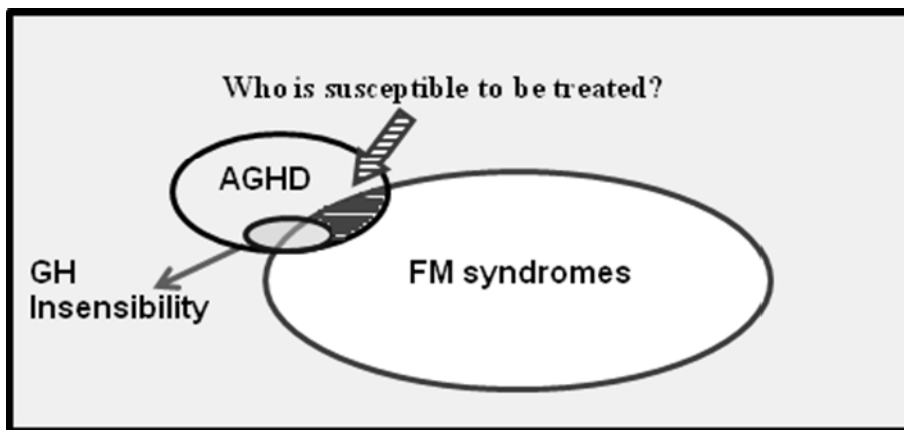


Figure 2