

RESEARCH

GH deficiency in patients with spinal cord injury: efficacy/safety of GH replacement, a pilot study

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Abstract

Objective: Growth hormone (GH) was shown to stimulate proliferation, migration and survival of neural cells in animal models. GH deficiency (GHD) was reported following traumatic brain lesions; however, there are not available data in spinal cord injury (SCI) patients. The aim of the study was to evaluate (1) the frequency of GHD in chronic SCI population; (2) the efficacy/safety of GH replacement in patients with SCI and suboptimal GH secretion.

Design and methods: Nineteen consecutive patients with chronic thoracic complete SCI (AIS-A) were studied. Patients with low GH secretion were randomized in a double-blind, placebo-controlled study to receive either subcutaneous placebo injections or GH combined with physical therapy, for 6 months. Baseline cranial MRI, AIS motor and sensory scale, quality of life (spinal cord impact measurement) and modified Ashworth spasticity scale, quantitative sensory testing and neurophysiological exploration were assessed at baseline, 1, 3 and 6 months following treatment.

Results: Thirteen had GH deficiency. Seven received GH, five placebo and one dropped out. Both groups were similar according to clinical and demographical data at baseline, except for greater GH deficiency in the GH treatment group. At 6th month, patients treated with GH showed a significant improvement in SCIM-III score and in electrical perception threshold up to the 5th level below SCI, on both sides compared to baseline.

Conclusions: GHD seems to be frequent in traumatic SCI and GH replacement is safe without side effects. GH combined with physical therapy can improve quality of life of SCI patients and, strikingly, the sensory perception below lesion level.

Key Words

- ▶ growth hormone
- ▶ GH deficiency
- ▶ spinal cord injury
- ▶ physical therapy
- ▶ safety

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Introduction

Growth hormone deficiency (GHD) has been studied in neurological disorders affecting central nervous systems, such as multiple sclerosis to amyotrophic lateral sclerosis (1, 2). Because of the direct impact to the pituitary area, transient GHD was reported following traumatic brain injury and subarachnoid hemorrhage. Around 25%

of traumatic brain injury (TBI) patients remain with persistent GHD after 1 year, and this accounts for their cognitive and rehabilitation outcomes (3). Some case report was published (7) and the work done in transitional rodent models (8, 9, 10) focused our attention on the potential of GH for neurologic improvement in SCI.

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However, in humans, very little is known about GH deficiency in spinal cord injury (SCI) (4, 5) despite having a high social impact since they mostly involve young people (61.4% between 14 and 44 years of age). Their incidence in Spain is considered around 2.5/100,000 persons/year, road accidents being the main cause (43.7%). Male/female ratio stands at 3.9/1, tetraplegia (cervical lesions) accounts for 38.5% of the cases and complete injuries affect 56.7% of the patients (6).

As known, GH mediates its action mainly on the liver acting through IGF1 synthesis and partially through IGF2 (bone) or MGF (muscle), on an endocrine pathway. Nevertheless an important paracrine effect has also been described, particularly in the central nervous system (2), and this has been hypothesized to be a potential action for pain modulation in GH-deficient fibromyalgic patients (11). Endogenous GH secretion depends on peptides such as somatostatin or GHRH, acting as neurotransmitters, but closing a negative feedback loop, GH and IGF1 may also act as neurotransmitters in a paracrine manner. There is evidence of blood-brain barrier crossing and GH/IGF1 receptors have been described in all neurologic cells (neurons, oligodendrocytes, astrocytes) and neuronal stem cells (both in hippocampal glial precursors and spinal ependymal precursors) (12). GH was shown to stimulate proliferation, differentiation, migration and survival of astrocytes and oligodendrocytes in animal models. This could be in part because of a GH-mediated neuronal anti-apoptotic effect (Akt signaling pathway) both in animals and humans, as seen *in vitro* (13).

In order to assess (1) frequency of GHD in chronic SCI patients and (2) the efficacy and safety of GH replacement therapy in SCI patients with GH deficiency, we designed a prospective, phase II, double-blind, placebo control study.

Subjects and methods

Fifty-one consecutive outwards patients from specialized Neurorehabilitation Hospital were screened. Nineteen patients were finally included in this study (Fig. 1) (14). They all had complete (AIS-A) spine cord injury (SCI) (15), exclusively affecting thoracic neurological level, and a time-lapse spent from the lesion between 1 until 2 years (chronic SCI). The exclusion criteria were acute or subacute SCI; lumbar lesion, incomplete SCI (AIS-B or C or D), concomitant TBI, pressure sores, articular limitation or unstable medical condition.

Protocol of GHD analytical assessment

All MRI done at the onset of SCI were reviewed to confirm pituitary integrity. GH secretion was performed with intramuscular glucagon test for under standardized procedure during 180min. Peak GH at any point more than 10ng/mL was considered as a normal response, and less than 3ng/mL as the cut-off for severe deficiency, following current guidelines (16, 17).

GH was measured in a central laboratory using an automated chemiluminescent immunoassay from a commercial source (IMMULITE 2000; Diagnostic Products Corp., Los Angeles, CA, USA). The inter-assay coefficient of variation of the GH assays was 4.52%. The functional sensitivity of GH assays was 0.05 ng/mL. Baseline cortisol and TSH as well as basic blood analysis including glucose, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, liver, renal parameters and blood count, were performed at baseline (T0) and at 3 months of treatment (T3).

Clinical assessment

BMI, waist circumference, lower and upper limbs diameter were registered at T0, T3 and T6 time point. For SCI assessment, we used ASIA (American Spine Injury Association) Scale (AIS) (international standards for neurological classification of spinal cord injury) for sensory perception and motor score (18), SCIM-III (Spinal Cord Impact measurement) to evaluate the quality of live and functional recovery (19), modified Ashworth scales for spasticity (20) and neurophysiological tests (Motor (MEPs) and somatosensory evoked potentials (SEPs) to evaluate motor and somatosensory conduction and electrical perception (EPT) and electrical pain perception threshold (EPPT) to evaluate small changes in sensory and pain perception) were assessed (21, 22, 23). For the assessment of MEPs of tibialis anterior, and abductor hallucis (AH) muscles bilaterally, single magnetic stimuli were generated by a magnetic stimulator (Magstim super-rapid, Magstim Company, Spring Gardens, Whitland, UK) and delivered through a double cone coil centered over the vertex at rest or performing or imagining bilateral foot dorsiflexion during stimulus delivery with maximum stimulator output. We realized 4 single recordings, filtered between 10Hz and 10kHz and amplified with a gain of 0.1 mV/div. SEPs (Cz-Fz) were obtained following retro-maleolar tibial nerve electrical stimulation of 1ms duration delivered at a 3Hz rate with a maximal intensity of



CONSORT 2010 Flow Diagram

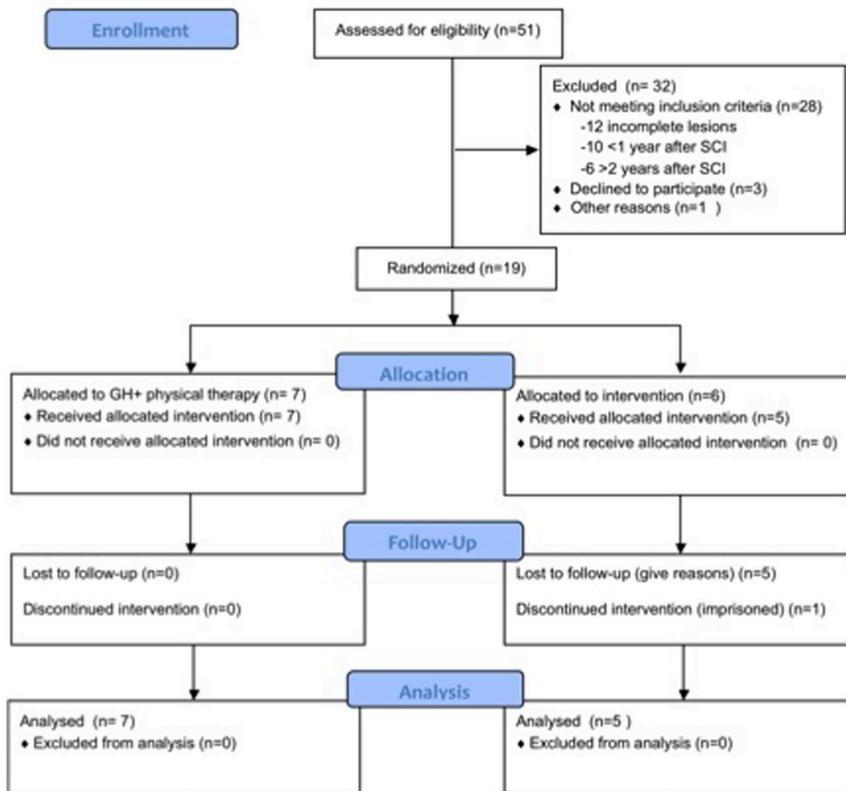


Figure 1
Consort 2010 flow diagram of the study.

30mA. Two sets of 300 responses were averaged with 100 ms of sweeps, at 3 Hz and 3000 Hz of filters, and at a gain of 1 $\mu\text{V}/\text{div}$.

Electrical perception and electrical pain perception threshold

To investigate subclinical differences, we performed a sensory responsiveness quantification using electrical perception threshold (EPT) and EPPT at baseline (T0), T1, T3 and T6 (1, 3, 6 months). They were done in seven dermatomes bilaterally: at the neurological level (0) and at the first, second and fifth dermatomes rostral (1+, 2+, 5+) and caudal (1-, 2-, 5-) to the neurological level. The participants were in a supine position on a bed in a quiet room throughout the test.

Pediatric ECG electrodes (cathode) with a diameter of 18mm (3M Red Dot™, type 2248) were attached over the AIS sensory key points. A ground inactive electrode attached to the ankle joint. The fifth dermatome rostral

to the lesion was tested first, so that the patient was able to experience the stimulation in a dermatome with intact sensation. Then, each of the subsequent lower dermatomes was tested.

For every dermatome tested, the stimulus intensity was manually increased (increased the current in steps of 0.1 mA for EPT and 0.3 mA for EPPT) until the participant first reported the sensation (ascending) under the cathode. A stimulus of 0.5 ms duration delivered at 3 Hz (maximum stimulation applied: 40 mA) (21).

Experimental procedure

Those with abnormal GH secretion ($n=13$, 12 males 1 female) were randomized (computer-based) in a double-blind, placebo-controlled study. They received identical subcutaneous injections of either placebo ($n=5$) or GH (Nutropin Aq) (0.0125 mg/kg/day) ($n=7$) 6 days a week together with rehabilitation, for 6 months.



Table 1 Individual clinical data.

Age	Sex	Time since SCI (months)	AIS	Injury level	SCI etiology	Peak GH (Glucagon test) (ng/mL)	Low GH secretion	Treatment group allocation
37	F	17	A	Th 11	Bicycle accident	16	No	No
24	M	13	A	Th 11	Traffic accident	4.3	Yes	GH
43	F	12	A	Th 4	Work accident	6.8	Yes	Placebo
39	M	18	A	Th 4	Traffic accident	1.9	Yes	GH
27	M	24	A	Th 4	Traffic accident	7.4	Yes	Placebo
24	M	16	A	Th 5	Falling from three	2.6	Yes	GH
63	F	13	A	Th1	Traffic accident	14	No	No
41	F	23	A	Th 1	Traffic accident	24	No	No
51	M	23	A	Th 7	Bicycle accident	4.5	Yes	Placebo
34	M	13	A	Th 1	Gun shot	0.2	Yes	GH
43	F	12	A	Th 8	Falling from height	16	No	no
24	M	20	A	Th 6	Traffic accident	5.4	Yes	Placebo
46	M	23	A	Th 1	Falling from horse	0.3	Yes	GH
25	M	18	A	Th 11	Work accident	4.3	Yes	Placebo
50	M	13	A	Th 1	Falling from height	0.9	Yes	GH
45	M	21	A	Th 6	Traffic accident	3	Yes	Placebo
52	F	14	A	Th 4	Traffic accident	21	No	No
27	M	13	A	Th 5	Work accident	11	No	No
42	M	22	A	Th 1	Traffic accident	2.4	Yes	GH

GH dosage was titrated according to physiological IGF1 levels measured at T1 and T3 (un-blind investigator). A paired up or down-titration was also done in the placebo group. IGF1 was measured at T1 and T3, using the same chemiluminescent assay. The inter-assay coefficient of variation of IGF-1 was 3.04% and the sensitivity of IGF-1 assay was <25 ng/mL (IMMULITE 2000; Diagnostic Products Corp.).

Physical therapy consisted of 2h a day for 5 days a week for 6 months in a specialized program, done both in the GH and placebo groups.

Statistical analysis

SAS version 9.4 was used for statistical analysis. Because of the low number of patients included (n=13) and non-normally distributed data, we used non-parametric analysis. Mann-Whitney U test was used to compare the data between the GH and placebo groups and Wilcoxon-t test to compare the changes in the same group in comparison to baseline. The comparison between groups of categorical variables (sex, BMI categories, SCI etiology groups, presence of previous spasticity, presence of previous rehabilitation) was performed using Fisher's exact or chi-square tests, values expressed as mean±s.d. The mean and standard deviation (s.d.) of EPT and EPPT value for each dermatome were calculated from three values at different time point evaluation (at baseline, T0, T1, T3 and T6). Changes in EPT and EPPT values at T1, T3 and T6 were tested using the Wilcoxon-t and Friedman tests in comparison to T0 (22, 23). EPT and

EPPT comparisons between groups were analyzed, in each side, using a mixed linear model.

The study was approved by the 'Hospital Quiron-Teknon' independent Ethical Committee. The trial has been registered (EudraCT 2011-005377-23) and approved by the Spanish Drug Agency. It was conducted in accordance with the Declaration of Helsinki and all patients gave written informed consent before their inclusion in the study.

Results

13/19 patients showed a suboptimal GH secretion and were randomized (7 received GH+physical therapy and 6 placebo+physical therapy). One patient dropped out from the study (prisoned). Results are then expressed

Table 2 Statistical similarity of placebo and GH-treated groups.

	Placebo	GH	P-Value
Sex (M/F)	5M 1F	7M	1
Age (year)	35.8 (±13.4)	37.0 (±10.7)	1
BMI (kg/m²)	25.5 (±3.0)	26.6 (±3.8)	0.71
Abd perimeter (cm)	101.8 (±5.8)	105.5(±11.2)	0.76
Time from injury (months)	19.6 (±5.0)	16.9 (±9.0)	0.82
IGF1 (ng/mL)	218±56.5	189.1±53.5	0.34
Peak GH (ng/mL)	5.3 (±2.4)	1.8 (±2.0)*	0.034
Cortisol (µg/dL)	10.6 (±3.7)	11.7 (±3.3)	0.79
TSH (µIU/mL)	1.7 (±0.4)	2.2 (±1.1)	0.34

Values expressed as mean±s.d.
*P<0.05.



Electrical perception threshold

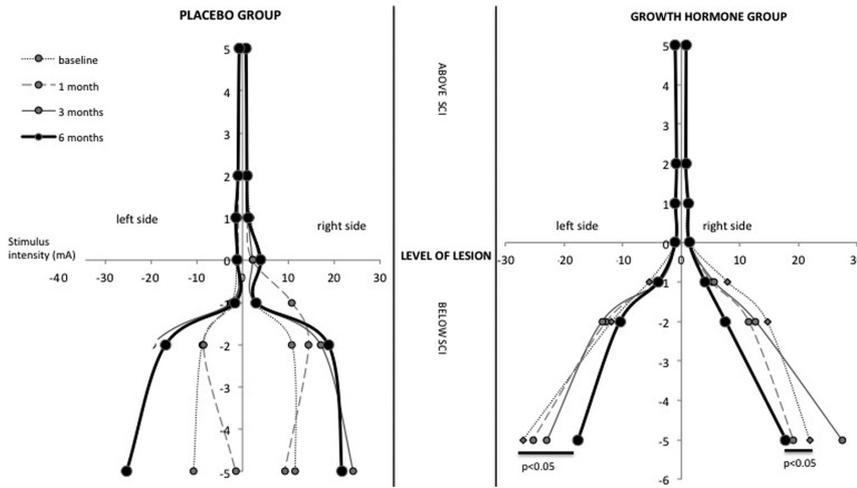


Figure 2 Electric perception threshold (EPT) diagram. Intra-individual assessment. X: electric amperage (mA) needed for inducing sensorial perception. Y: mean values drawn at +5, +2 and +1 levels above, at level (0), and at -1, -2 and -5 levels below the neurological level of injury. Mean values are presented for baseline and 1, 3 and 6 months after initiation of treatment. $P \leq 0.05$, according to Wilcoxon *t* test.

for 12 patients who completed the study (7 GH and 5 placebo) (Fig. 1).

7/12 showed a peak GH <3ng/mL indicating severe deficiency. Individual clinical data are shown on Table 1.

Except for sex (12 male, 1 female), both groups were statistically similar according to time from injury, 19.6 months (± 5.0) vs 16.9 months (± 9.0); age, 35.8 (± 13.4) vs 37.0 (± 10.7); BMI, 25.5 (± 3.0) kg/m² vs 26.6 (± 3.8) kg/m²; waist circumference, 101.8 (± 5.8) cm vs 105.5 (± 11.2) cm or baseline IGF1 levels, 218 \pm 56.5 ng/mL vs 189.1 \pm 53.5 ng/mL, respectively in the placebo and the GH-treated groups (Table 2). These results are in accordance with the published SCI Spanish population characteristics (24, 25).

No biochemical differences were observed comparing lipid profile or glucose levels. Only peak GH was lower in the GH-treated group: 1.8 (± 2.0) ng/mL vs 5.3 (± 2.4) ng/mL in the placebo group (Mann–Whitney *U*; $P = 0.0348$), even after multiple adjustment, suggesting a higher degree of GH deficiency in the GH-treated group. All patients showed normal cortisol and TSH values.

Empty sella was observed in one patient, at baseline MRI.

Changes in the SCI assessment

We did not observe any change in motor or sensory AIS scale between groups (Mann–Whitney test, $P > 0.05$).

When analyzing SCIM-III results, no differences were observed between treatment groups at any visit (Mann–Whitney test, $P > 0.05$). However, in the GH group, the change at T6 was statistically significant compared to baseline (Wilcoxon sign-rank test, $P = 0.031$).

There were not significant changes in modified Ashworth scale (spasticity), neither in doses of anti-spastic treatment throughout the study and no significant GH-related adverse events (carpal tunnel syndrome, headache, maleolar edema) were described.

MEPs and SEPs

MEPs in all recorded muscles and SEPs were absent bilaterally at baseline in all patients and remained absent at 6 months of treatment in both group.

Changes in EPT and EPPT over time

The intra-individual analysis of EPT (Friedman test) improved during GH treatment and the differences reached significant level at the 5th level below the lesion, bilaterally, within the first 6 months of GH treatment with respect to baseline condition ($P = 0.04$). Here, the electric intensity (mA) needed to induce electric perception on the patient was significantly smaller at T6 compared with baseline intensity. At T6 within the placebo group, EPT did not show significant improvement at any level of SCI ($P > 0.05$; Fig. 2).

EPT was statistically different comparing GH compared to placebo group (mixed linear model analysis), $P = 0.023$ for left side at T6, and $P = 0.031$ for right side at T6 (Table 3).

Changes in EPPT were not significant at any level of SCI within any treatment group ($P > 0.05$ for each comparison with respect to baseline in GH and placebo group; Fig. 3), neither between groups.

Table 3 Statistical differences in EPT between GH and placebo groups.

Level	Side	Placebo						GH						P*
		Month 0	Month 1	Month 3	Month 6	Month 0	Month 1	Month 3	Month 6					
5	R	0.76±0.15	0.71±0.08	0.73±0.19	0.89±0.08	0.86±0.15	0.90±0.15	0.85±0.13	0.83±0.23	0.023				
5	L	0.86±0.32	0.72±0.20	0.79±0.21	0.81±0.07	1.00±0.12	1.03±0.16	1.00±0.23	1.04±0.63	0.031				
2	R	0.95±0.21	0.92±0.27	0.95±0.24	0.97±0.23	0.78±0.17	0.82±0.23	0.82±0.26	0.76±0.23	0.185				
2	L	1.05±0.45	0.94±0.21	0.96±0.29	0.98±0.36	0.85±0.28	0.84±0.09	0.91±0.25	0.84±0.22	0.585				
1	R	1.73±0.83	1.01±0.44	1.24±0.56	1.24±0.66	0.99±0.44	1.03±0.40	0.99±0.31	1.15±0.64	0.180				
1	L	1.19±0.34	0.92±0.37	1.22±0.43	1.49±1.03	0.96±0.21	0.93±0.32	0.95±0.18	1.01±0.18	0.023				
0	R	3.47±2.94	2.14±1.06	2.15±1.97	3.97±4.51	1.43±0.84	1.43±0.46	1.37±0.52	1.34±0.66	1.000				
0	L	1.26±0.34	1.00±0.24	1.14±0.35	1.12±0.58	1.05±0.37	1.00±0.27	1.03±0.25	1.02±0.29	0.028				
-1	R	2.81±2.88	10.77±15.88	2.71±2.93	3.03±1.89	7.91±8.15	5.16±5.63	5.62±5.79	4.07±3.50	0.155				
-1	L	2.34±1.41	1.55±0.60	2.50±1.88	1.61±0.40	5.57±5.27	4.29±3.91	3.77±3.36	3.97±3.54	0.050				
-2	R	10.85±9.28	14.46±10.94	17.07±13.09	18.74±8.25	14.66±12.74	11.54±6.62	12.73±7.88	7.57±5.78	0.670				
-2	L	8.76±5.82	8.48±5.70	19.78±16.96	16.76±12.66	11.89±10.17	12.84±10.97	13.58±11.76	10.53±9.44	0.168				
-5	R	11.54±5.95	9.18±10.21	24.17±14.47	21.70±0.99	21.92±5.11	19.14±3.57	27.43±17.26	17.87±8.26	0.871				
-5	L	10.67±0.00	1.47±0.00	-	25.30±0.00	27.07±8.46	25.41±6.23	22.95±8.70	17.68±8.83	1.000				

*Mixed linear model P value.
L, left side; R, right side; Y, +5 to -5 from level of injury (0).

IGF1 values (ng/mL) were higher at 1st, 291.5 (±106.9) vs 200.6 (±55.9); 3rd, 296.4 (±128.4) vs 206.0 (±46.9) and 6th months, 265.0 (±90.4) vs 207.6 (±36.5), comparing GH-treated group to placebo, but these differences were not statistically significant. No correlation between changes in IGF1 values (final vs baseline, and 1st/3rd month vs baseline) and clinical changes was found.

Discussion

Although assessed in a small number of patients, our study shows that long-term GH suboptimal secretion seems to be quite frequent (13/19) following traumatic complete SCI and that GH replacement therapy improves quality of life and, strikingly, sensory deficit below SCI.

Insulin tolerance test (ITT) should have been the gold standard method to assess GH deficiency, but glucagon test (GHRH+Arg being not available in Spain) was considered the safer diagnostic tool by our Ethics Committee due to the seizures' risk by inducing hypoglycemia with ITT in patients with a very compromised mobility.

Although 13/19 patients had a peak <10ng/mL after glucagon test, suggesting a suboptimal pituitary GH secretion, only 7/12 patients had a peak GH <3ng/mL, accepted cut-off value for the diagnostic of severe GH deficiency (16). Recent data suggest an even lower cut-off point for GH in overweight/obese people (a frequent condition in SCI population) (25) using glucagon test (17). Only 3/12 patients of our cohort showed that degree of severity (peak GH <1ng/mL). Any other pituitary deficiencies (including diabetes insipidus) were not detected in our cohort at baseline, suggesting that the somatotroph axis is the most sensible one following trauma injuries. This has already been reported in GH-associated TBI. However, our prevalence seems higher than published TBI cohorts using similar methods (25% of patients remaining GH-deficient after 1 year) (3).

It is difficult to understand how dorsal spinal damage may influence pituitary secretion much more than direct cranial traumatism. We may wonder they have received a simultaneous brain impact, and this may partially affect their GH secretion capacity.

However in our cohort, TBI was an exclusion criteria, low Glasgow score was not reported in any of the reviewed clinical histories at onset and all initial cranial MRI were described as normal. Some of the screened patients had SCI from fire shot, falling from horse or bicycle without any direct brain trauma (Table 1). Therefore our study supports the idea that there should be another connection between SCI and low GH secretion.



Electrical pain perception threshold

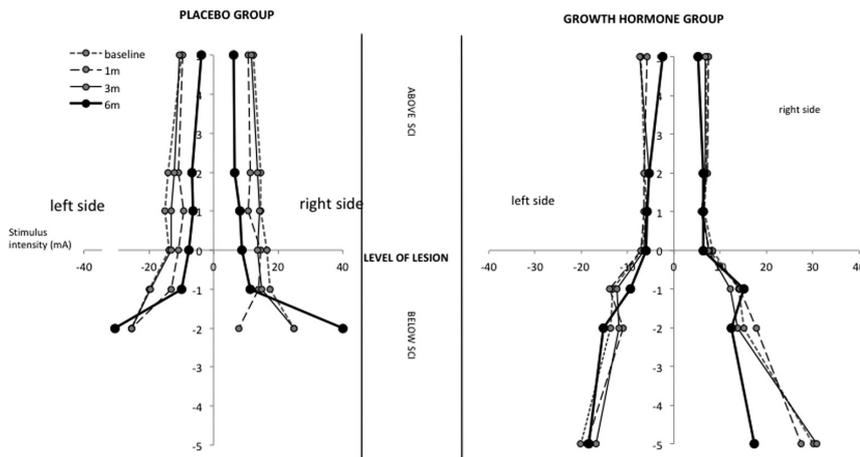


Figure 3 Electric pain perception threshold (EPPT) diagram. Intra-individual assessment. X: electric amperage (mA) needed for inducing pain. Y: mean values drawn at +5, +2 and +1 levels above, at level (0), and at -1, -2 and -5 levels below the neurological level of injury. Mean values are presented for baseline and 1, 3 and 6 months after the initiation of treatment.

To our knowledge there is no evidence in humans or animals of spinal neurological pathways acting through hypothalamic areas involved in the control of GH axis. We may wonder that lower back injuries induce a ‘hinge’ effect in the spine, which is finally driven to the pituitary stalk as a possible mechanic etiology. However, no anatomic changes were seen in the pituitary MRI, except for 1 empty sella.

This is the first pilot study done *in vivo* with complete SCI and concomitant low GH secretion levels.

It is important to highlight that our aim was to replace these patients in a physiologic manner, up and down-titrating the dosage according to IGF1 levels, rather than treating any spine lesion with GH, without knowing their pituitary status. We deeply think that this approach is particularly important in terms of safety and to avoid any expectations that could lead to un-labeled use.

Our aim was to assess the patients in the worst possible clinical situation, which is a complete AIS-A injury (motor and sensory failure) and lasting for at least 12 months (no spontaneous recovery of either motor or sensorial are supposed to happen after this time point). This approach and the limitation of our study only to thoracic lesions have certainly reduced the number of potential participants in the trial, but strengthen our results.

As expected in large time-lapse injuries, physical therapy in chronic patients did not improve functional parameters (SCIM-III) in the placebo group, enhancing the need of much more precocious rehabilitation (26). However at 6-month evaluation, GH-treated group showed a better SCIM score than baseline, suggesting a direct effect of GH in functional recovery and quality of

life. We can hypothesize it to be a neurological effect or rather a GH-driven muscular activity changes (27). In our study, no changes in spasticity (Ashworth test) or dosage of anti-spastic medication were observed and we did neither observe any change in upper or lower limbs diameter, to hypothesize direct muscular effect of GH.

Although no significant changes were seen with light touch sensorial physical examination (AIS scale examination), rejecting therefore any idea of immediate clinical recovery, those patients with GH treatment showed significant improvement in sensory perception at 5th level of injury in both sides following 6 months of treatment, when using a highly sensible quantitative sensory testing (Figs 2 and 3).

It is unclear how GH (together with intense physical therapy) may induce a partial, subclinical, sensory recovery of the nerve. It has been pointed out that intense exercise promotes activity-induced neuronal plasticity (28, 29), but GH could play a key role in enhancing this plasticity since the placebo group (which also received physical therapy sessions) did not showed any electric change in any visit. We can speculate on the direct central nervous system effect of GH-, IGF1- or GH-related peptides, such as ghrelin since receptors for these hormones have been found in all neural cell types. GH effect on proliferation, differentiation, migration and survival of astrocytes, oligodendrocytes and neural stem cells have already been proven in spine injury animal models (8, 9, 10, 12). A GH-mediated neuronal anti-apoptotic effect (via Akt signaling pathway) has been proved *in vitro* both in animal and humans cells (13). We can also hypothesize that this neurological protective effect of GH could also be driven through vascular

pathways since IGF1 is known to modify endothelial function (30).

Although it is accepted that a chronic lesion starts at 1 year after the injury, spontaneous functional recovery occurs in number of *incomplete* SCI patients as well as in animal models, with time courses ranging from months to years (31).

This is only a pilot study, done with a small number of patients. Before claiming benefits with impact on daily life, larger and complementary studies (higher dosage regime, longer time after injury, efficacy assessment in acute or incomplete (AIS-B, C or D) spine injuries) should be done. Despite some hypothesis based on transitional models, we still do not clearly understand by which physiological mechanism GH replacement combined to physical therapy might be beneficial in SCI.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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