Growth hormone level at admission and its evolution during refeeding are predictive of short-term outcome in restrictive anorexia nervosa

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Abstract

The growth hormone (GH)–insulin-like growth factor-1 (IGF-1) axis is dramatically altered in patients with anorexia nervosa (AN). The aim of the present study was to investigate whether GH and IGF-1 could be predictors of outcome in patients with a restrictive form of AN. Blood levels of GH, IGF-1, adipocytokines, ghrelin, insulin, glucose, and sex and thyroid hormones were measured in eleven women inpatients with AN and in ten healthy women controls. Three stages were compared during refeeding: admission (T0), when BMI reached $16 \, kg/m^2$ (T1) and at discharge when BMI reached $17.5 \, kg/m^2$ (T2). Clinical status was assessed 6 months after discharge from hospital (T3), and remission was defined by the maintenance of a BMI $\geq 17.5 \, kg/m^2$. AN patients in remission (AN-R; n 6) had significantly higher GH levels at admission than those who relapsed (AN-NR; n 5) ($P < 0.05$). During refeeding ($\Delta = T2 - T0$), the AN-R group differed from the AN-NR group only by both GH level decrease ($P < 0.05$) and BMI increase ($P < 0.05$). In multiple regression analysis, ΔGH was associated negatively and significantly and Δleptin and Δbody fat mass levels were associated positively and significantly with BMI at T3 and explained 88% of its variability (r^2 0.88, $P < 0.05$). The present study suggests that a low GH level at admission and the absence of its decrease after weight recovery could predict short-term relapse in women suffering from a restrictive form of AN.

Key words: Anorexia nervosa: Growth hormone: Insulin-like growth factor-1: Outcomes

Anorexia nervosa (AN) is an eating disorder caused by voluntary restriction of energy intake, intensive physical exercise and/or purging behaviours, and is characterised by weight loss, mainly at the expense of adipose tissue[1,2]. These behaviours lead to multiple endocrine abnormalities commonly associated with starvation, including high ghrelin levels, hypogonadotropic hypogonadism and adipocytokine disturbances[3,4]. Most of these anomalies are corrected with the recovery of normal nutritional conditions[5].

Several studies have shown that the growth hormone (GH)–insulin-like growth factor-1 (IGF-1) axis was dramatically altered in patients with AN[6,7]. But, although Argente et al.[6] have discerned two different groups of anorexic patients, one group having hypersecretion of GH and one group with hyposecretion of GH, they were unable to distinguish these two groups regarding either physical or psychological parameters at the time of diagnosis or during the recuperation period.

In the present study, the main objective was to investigate if GH and IGF-1 levels could represent prognostic factors of outcome in restrictive AN. To test this hypothesis, we performed a prospective study on a homogeneous group of eleven patients suffering from a severe pure restrictive form of AN and submitted to the same standardised inpatient protocol treatment. GH and IGF-1 levels, as well as hormone and adipocytokine profiles, insulin sensitivity, body composition and energy expenditure, were assessed at admission and at various stages of weight recuperation.

Materials and methods

Subjects

The present study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving human patients were approved by the Research Ethics Board of Aix-Marseille University and all subjects gave verbal informed consent. Verbal consent was witnessed and formally recorded. A total of eleven women suffering from AN were recruited in our department of nutrition. All subjects met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for the restrictive form of AN. This population was homogeneously selected as every patient included in this series suffered from the short-duration (12·2 (SEM 5·0) weeks) and active (BMI loss rate: −0·2 (SEM 0·03) kg/m² per week) restrictive type of AN. Patients with relapsing AN or exhibiting binge eating–purging behaviours were excluded. The patients were referred to the inpatient unit due to the presence of at least one of the following conditions: life-threatening medical condition due to severe malnutrition, incapacity to reach weight objectives during ambulatory care or marked suicidal ideation. None of the patients used oral contraception for several weeks before the hospitalisation in our department. All patients were treated by a single team from the department of nutrition according to a structured inpatient protocol combining medical, nutritional and psychiatric supports based on widely accepted standards of practice[8,9]. Treatment was based on a weight contract (progressive return to near-normal BMI, i.e. ≥17·5 kg/m²) and consisted of medical supervision, nutritional support by a dietitian, mixed cognitive behavioural and analytical psychotherapy sessions and art therapy, both performed twice a week. The standardised feeding protocol consisted of a progressive increment of energy intake from 3350 to 8370 kJ/d.

Methods

Patients were studied at three stages of care: at admission (T0), when BMI reached 16 kg/m² (T1), and at discharge, when BMI reached 17·5 kg/m² (T2). The diet of each patient was estimated by a dietitian at admission (T0) before refeeding. Clinical status was assessed 6 months after discharge from hospital (T3). Short-term remission was defined by the maintenance of a BMI ≥17·5 kg/m² at 6 months after discharge. A BMI ≥17·5 kg/m² was chosen to define remission because the diagnostic criteria for AN from the DSM-IV include a BMI ≤17·5 kg/m²[10]. The weight achieved to reach a BMI ≥17·5 kg/m² at discharge was defined as the 'target weight' in the present study. In all, six patients exhibited remission (AN-R group) and five patients were characterised by a quick relapse, being unable to maintain their weight objective (AN-NR group). It was impossible to take into account 'the healthy weight' defined by the weight at the loss of menstruation because most of the patients (four of six patients in the remission group (AN-R group) and four of five in the not in remission group (AN-NR group)) were taking oral oestroprogestogenic treatment. In addition, ten normal-weight healthy women were recruited as controls after a medical interview and a physical examination by a physician specialised in nutrition. None of them had any history of eating disorders or other psychiatric illness.

Blood samples were obtained between 07.00 and 08.00 hours after an overnight fast. Plasma glucose was measured using the hexokinase oxidase method (Beckman Coulter®) and plasma insulin levels were determined by electrochemiluminescence (Roche Diagnostics®). Insulin resistance was estimated using homeostasis model assessment-insulin resistance (HOMA-IR = fasting insulin (mIU/l) × fasting glucose (mmol/l)/ 22·5). Alanine aminotransferase and aspartate aminotransferase were determined by Synchron-CX automate (Beckman Coulter®). GH and IGF-1 were measured using immunoradiometric assays (DiaSorin®). Testosterone and oestradiol were measured by electrochemiluminescence (Roche Diagnostics®). Specific ELISA kits were used to measure serum levels of leptin (active human leptin, DSL Systems), adiponectin (Quantikine human adiponectin, R&D Systems), resistin (Quantikine human resistin, R&D Systems) and ghrelin (human unacylated ghrelin enzyme immunoassay kit, Biovendor).

Body composition was assessed by dual-energy X-ray absorptiometry (Lunar iDXA, GE Healthcare): body fat mass (BFM), body lean mass and fat-free mass compartments were considered. Resting energy expenditure was measured by indirect calorimetry (Quark-RMR-Cosmed®) in the morning after an overnight fast. Total, resting and active energy expenditure were evaluated using a wearable multisensor armband (SenseWear® Pro2 Armband SWA, BodyMedia, Inc.)[11].

Statistical analysis

Statistical analysis was carried out using SPSS software (Statistical Package for the Social Sciences, Inc., version 15.0). The results are presented as mean values with their standard errors. The paired Wilcoxon test and the Mann–Whitney *U* test were used for comparisons between groups. Spearman's correlation was used to test the association among anthropometric, biochemical, hormonal, body composition and energy metabolism parameters in AN patients at T0, T1 and T2. Before the multivariate analyses, variables with skewed distributions were logarithmically transformed to normalise the distributions. Associations were evaluated by linear regression and multiple interactions by stepwise regression and by exhaustive check of all possible multivariate models. The structure of the covariance matrix for each variable was taken into account in all analyses to ensure the most adequate statistical fit and power. A $P < 0.05$ was considered statistically significant.

Results

Comparison between control women and anorexia nervosa women patients at admission (T0)

The mean ages of the AN patients and control subjects were similar at admission. As expected, BMI was significantly lower in the AN group ($P < 0.05$) (Table 1) .

Table 1. Anthropometric, biochemical, hormonal, body composition and energy metabolism parameters of control (C) women and patients with anorexia nervosa (AN) at admission and during refeeding

(Mean values with their standard errors)

	C (n 10)		AN-T0 (n 11)		AN-T1 (n 11)		AN-T2 (n 11)	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
Age (years)	24·6	0·17	21·9	0·36				
BMI (kg/m²)	22·3	0·16	13·1*	0·07	16·1†	0·02	17·8‡	0·02
ASAT (U/l)	15·4	0·42	17·2	0·53	21·1	0·34	24·2	0·24
ALAT (U/l)	22·5	0·39	28·1	0·51	26·3	0·25	27·8	0·23
Glucose (mmol/l)	4·5	0·04	3·9*	0·05	4·5†	0·03	4·9‡	0·04
Insulin (mIU/l)	7·7	0·49	3·0*	0·24	7·3†	0·40	9·5	0·36
HOMA-IR	1·5	0·06	0·5*	0·05	1·4†	0·09	2·1‡	0·10
GH (mIU/l)	8·7	0·65	24·5*	0·64	1·64†	0·15	1·3	0·11
IGF-1 (nmol/l	26·3	0·46	13·7*	0·75	27·2†	0·49	31·5‡	0·63
TSH (mIU/l)	1·5	0·10	2·0	0·10	2·2	0·08	2·6	0·08
FT4 (pmol/l)	13·9	0·15	12·7	0·14	11·9	0·33	12·6	0·14
FT3 (pmol/l)	4·9	0·06	2·4*	0·11	5·0†	0·12	4·3	0·15
Oestradiol (pmol/l)	257	10·50	57·1*	4·40	154†	10·40	226	14·30
Testosterone (nmol/l)	1·03	0·04	1·6	0·07	0·9†	0·03	0·9	0·02
Adiponectin (μg/ml)	10·9	0·52	6·7*	0·37	17·1†	0·51	15·1	0·55
Resistin (ng/ml)	11·8	0·38	13·1	0·80	12·5	0·48	10·0	0·32
Leptin (ng/ml)	11·6	0·35	0·4*	0·01	3·1	0·38	8·0‡	0·56
Ghrelin (pg/ml)	305·0	9·60	490·6*	21·2	274·5†	14·9	229·0	10·5
BFM (kg)	ND		3·5	0·13	8·2†	0·19	11·8	0·14
BLM (kg)	ND		32·3	0·38	37·2†	0·29	35·9	0·27
FFM (kg)	ND		34·1	0·37	39·3	0·25	37·9	0·30
REE (kJ/d)	ND		2840·1	66·1	4404·9†	62·8	4792·4‡	70·3
TEE (kJ/d)	ND		5314·9	80·3	6364·3†	71·9	6439·6	236·9
AEE (kJ/d)	ND		419·7	40·6	865·7†	45·2	1603·7	96·2

T0, admission (baseline); T1, BMI reached 16 kg/m²; T2, discharge when BMI reached 17·5 kg/m²; ASAT, aspartate aminotransferase; ALAT, alanine aminotransferase; HOMA-IR, homeostasis model assessment-insulin resistance; GH, growth hormone; IGF-1, insulin-like growth factor-1; TSH, thyroid-stimulating hormone; FT4, free thyroxine; FT3, free tri-iodothyronine; BFM, body fat mass; ND, not determined; BLM, body lean mass; FFM, fat-free mass; REE, resting energy expenditure; TEE, total energy expenditure; AEE, active energy expenditure.

* Mean value was significantly different for C from that of the AN group before refeeding (AN-T0) ($P<0.05$; Mann–Whitney U test or Wilcoxon test).

† Mean value was significantly different for the first step of refeeding (AN-T1) from that of before refeeding (AN-T0) ($P<0.05$; Mann–Whitney U test or Wilcoxon test).

‡ Mean value was significantly different for the first step of refeeding (AN-T1) from that of the second step of refeeding (AN-T2) ($P<0.05$; Mann–Whitney U test or Wilcoxon test).

Plasma GH and serum ghrelin levels were higher in AN patients compared with controls ($P<0.05$ for both). Plasma levels of IGF-1, oestradiol, free tri-iodothyronine, leptin and adiponectin were significantly lower in patients with AN compared with control subjects ($P<0.05$ for all). Plasma levels of glucose, insulin and HOMA-IR were significantly lower in patients with AN than in control subjects ($P<0.05$ for all).

Comparison between admission (T0) and first stage of refeeding (T1) in anorexia nervosa patients

The first stage of refeeding (T1) was reached after a mean of 14·1 (SEM 3·3) weeks of hospitalisation (Table 1). As expected, an improvement in body composition was observed after this first period of refeeding. BFM and body lean mass both increased significantly and resting energy expenditure, active energy expenditure and total energy expenditure also increased significantly during this stage ($P<0.05$ for all).

A significant decrease in GH, ghrelin and testosterone levels and an increase in IGF-1, free tri-iodothyronine and oestradiol concentrations were observed ($P<0.05$ for all). Concerning adipocytokine levels, a significant increase was only seen

with adiponectin ($P<0.05$). There was a significant increase in glucose, insulin and HOMA-IR levels ($P<0.05$ for all).

In Spearman's correlation analysis at T1, there was a significant negative association between GH and plasma glucose levels and between GH levels and active energy expenditure ($r -0.7$, $P=0.04$ and $r -0.8$, $P=0.02$, respectively).

Comparison between first stage (T1) of refeeding and discharge (T2) in anorexia nervosa patients

The second stage of refeeding (T2) was reached after a mean hospitalisation of 3·7 (SEM 1·2) weeks from the first stage of refeeding (T1) (Table 1). During this second stage, BFM was the only body composition parameter to increase, but non-significantly. Resting energy expenditure increased significantly ($P<0.05$).

There was a significant increase in IGF-1 and leptin levels ($P<0.05$ for both). Glucose and HOMA-IR levels increased significantly ($P<0.05$ for both).

In Spearman's correlation analysis at T2, plasma GH levels were negatively and significantly associated with leptin levels ($r -0.8$, $P=0.03$).

Prediction of short-term clinical outcome

At 6 months after discharge from hospital with a BMI $\geq 17 \cdot 5$ kg/m^2, the AN-R group maintained this objective (BMI 18·08 (SEM 0·2) kg/m^2), whereas the AN-NR group did not (BMI 17·28 (SEM 0·2) kg/m^2). At admission, there were no differences in the total energy intake or in the nutrient intake between the AN-R and the AN-NR groups (2495 (SEM 177) *v.* 2215 (SEM 134) kJ/d for total energy intake; 30·4 (SEM 2·2) *v.* 37·0 (SEM 4·0) g (20·6 (SEM 1·2) *v.* 25·6 (SEM 2·1) %) for protein intake; 73·0 (SEM 7·9) *v.* 61·2 (SEM 4·9) g (46·6 (SEM 2·5) *v.* 49·8 (SEM 5·0) %) for carbohydrate intake; and 20·8 (SEM 1·2) *v.* 15·6 (SEM 2·5) g (32·8 (SEM 1·5) *v.* 24·4 (SEM 3·4) %) for fat intake). In univariate analysis, the AN-R group differed from the AN-NR group at admission only by GH levels (39·8 (SEM 1·2) *v.* 5·9 (SEM 0·8) mIU/l; $P < 0 \cdot 05$) (Fig. 1(a)), but not by IGF-1 levels (14·4 (SEM 1·2) *v.* 13·9 (SEM 1·5) nmol/l, $P = 0 \cdot 65$) (Fig. 1(b)) or by the other anthropometric, biochemical, hormonal, body composition and energy metabolism parameters. GH levels were higher in the AN-R group compared with the control group, but not different between the AN-NR and the control groups (Fig. 1(a)).
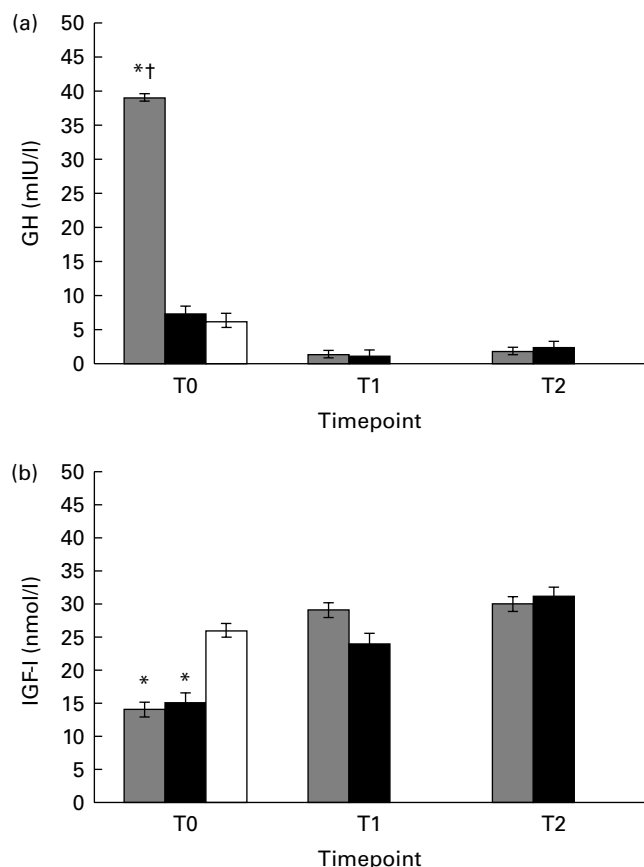
IGF-1 levels were lower in the AN-R and AN-NR groups compared with the control group (Fig. 1(b)).

During refeeding, ($\Delta = $ T2 − T0), the AN-R group differed from AN-NR group only by both GH level decrease (− 15·3 (SEM 2·10) *v.* − 3·6 (SEM 1·84) mIU/l, $P < 0 \cdot 05$) and BMI increase (5·6 (SEM 0·3) *v.* 3·8 (SEM 0·2) kg/m^2; $P < 0 \cdot 05$) (Table 2). When we compared the GH level in relation to weight at admission (T0), at T1 and at discharge (T2), we found a higher mean ratio in the AN-R group *v.* the AN-NR group at T0 ($P < 0 \cdot 05$), but no difference at T1 and T2 between the two groups and a significant decrease of this mean ratio only in the AN-R group between T0 and T1 ($P < 0 \cdot 05$) and between T0 and T2 ($P < 0 \cdot 05$). The mean ΔGH (T2 − T0) in relation to the 'target weight' at T2 was significantly lower in the AN-R group *v.* the AN-NR group ($P < 0 \cdot 05$) (Table 3). The difference in BMI increase between the two groups was explained by a non-significant lower BMI in the AN-R group at admission (Table 4) and by a non-significant higher BMI in the AN-R group at discharge.

In an additional stepwise multivariate analysis of BMI at 6-month follow-up (T3), carried out for all the patients and adjusted for ($\Delta = $ T2 − T0) Δglucose, Δinsulin, ΔHOMA-IR, ΔGH, ΔIGF-1, ΔTSH, ΔFT4, Δfree tri-iodothyronine, Δoestradiol, Δtestosterone, Δadiponectin, Δresistin, Δleptin, Δghrelin, ΔBFM, Δbody lean mass and Δfat-free mass, we found that ΔGH was associated negatively and significantly with the variability of BMI (β − 0·89; $P < 0 \cdot 05$) and that Δleptin and ΔBFM were associated positively and significantly with the variability of BMI (β 0·11; $P < 0 \cdot 05$ and β 0·39; $P < 0 \cdot 05$, respectively).

Fig. 1. (a) Plasma levels of growth hormone (GH) and (b) insulin-like growth factor-1 (IGF-1) in control subjects (control, □) and in patients with anorexia nervosa in remission (AN-R, ▨) and not in remission (AN-NR, ■) 6 months after discharge. At admission (T0), at BMI ≥ 16 kg/m^2 (T1) and at BMI $\geq 17 \cdot 5$ kg/m^2 (T2). * Mean value was significantly different from that of the control group ($P < 0 \cdot 05$; Mann–Whitney *U* test). † Mean value was significantly different from that of the AN-NR group ($P < 0 \cdot 05$; Mann–Whitney *U* test).

Table 2. Anthropometric, biochemical, hormonal and body composition changes during refeeding (between admission (T0) and discharge (T2)) in anorexia nervosa (AN) patients in remission (AN-R) and not in remission (AN-NR) 6 months after discharge

(Mean values with their standard errors)

ΔT2 − T0†	AN-R (*n* 6)		AN-NR (*n* 5)	
	Mean	SEM	Mean	SEM
ΔBMI (kg/m^2)	5·6	0·30	3·8*	0·20
ΔGlucose (mmol/l)	1·0	0·03	1·2	0·02
ΔInsulin (mIU/l)	6·1	0·08	6·2	0·07
ΔHOMA-IR	1·5	0·03	1·6	0·07
ΔGH (mIU/l)	− 15·3	2·10	− 3·6*	1·84
ΔIGF-1 (nmol/l)	9·2	0·88	17·2	0·94
ΔTSH (mIU/l)	0·8	0·08	0·9	0·06
ΔFT4 (pmol/l)	1·6	0·23	1·4	0·66
ΔFT3 (pmol/l)	2·9	0·08	2·3	0·09
ΔOestradiol (pmol/l)	141·6	10·60	339·1	26·73
ΔTestosterone (nmol/l)	− 1·1	0·08	− 0·5	0·06
ΔAdiponectin (µg/ml)	9·7	0·71	8·3	0·62
ΔResistin (ng/ml)	− 8·0	1·15	− 3·6	0·62
ΔLeptin (ng/ml)	11	0·93	4·9	1·09
ΔGhrelin (pg/ml)	− 92·6	12·5	− 390	23·5
ΔBFM (kg)	10·1	0·43	6·2	0·79
ΔBLM (kg)	4·9	1·03	2·8	0·41
ΔFFM (kg)	5·7	0·55	3·4	0·50

HOMA-IR, homeostasis model assessment-insulin resistance; GH, growth hormone; IGF-1, insulin-like growth factor-1; TSH, thyroid-stimulating hormone; FT4, free thyroxine; FT3, free tri-iodothyronine; BFM, body fat mass; BLM, body lean mass; FFM, fat-free mass.
* Mean value was significantly different for AN-R from that of the AN-NR group ($P < 0 \cdot 05$; Mann–Whitney *U* test).
† T2 − T0 is between admission (T0) and discharge (T2).

Table 3. Growth hormone (GH) level in relation to weight (W) at admission (T0), at BMI reaching 16 kg/m^2 (T1) and at discharge (T2) of anorexia nervosa (AN) patients in remission (AN-R) and not in remission (AN-NR)

(Individual values and mean values with their standard errors)

	GH/W at T0 (mIU/l per kg)	GH/W at T1 (mIU/l per kg)	GH/W at T2 (mIU/l per kg)	ΔGH (T2 − T0)/W (T2) (%)§
AN-R (n 6)				
1	0·60	0·12	0·27	− 33·2
2	0·77	0·08	0·04	− 73·5
3	0·84	0·43	0·36	− 48·4
4	1·08	0·12	0·10	− 98·3
5	1·11	0·35	0·39	− 72·1
6	1·29	0·10	0·09	− 119·2
Mean	0·95*	0·18†	0·20‡	− 74·1*
SEM	0·04	0·01	0·01	5·4
AN-NR (n 5)				
1	0·21	0·17	0·15	− 6·1
2	0·27	0·14	0·13	− 14·3
3	0·61	0·27	0·24	− 35·1
4	0·19	0·13	0·17	− 5·1
5	0·16	0·10	0·14	− 2·1
Mean	0·28	0·16	0·17	− 11·2
SEM	0·03	0·01	0·01	2·0

* Mean value was significantly different for AN-R from that of the AN-NR group ($P < 0.05$; Mann–Whitney U test or Wilcoxon test).
† Mean value was significantly different for the first step of refeeding (T1) from that of before refeeding (T0) in the AN-R group ($P < 0.05$; Mann–Whitney U test or Wilcoxon test).
‡ Mean value was significantly different for the second step of refeeding (T2) from that of before refeeding (T0) in the AN-R group ($P < 0.05$; Mann–Whitney U test or Wilcoxon test).
§ ΔGH (T2 − T0) is between admission (T0) and discharge (T2).

These three parameters explained 88 % of the variance of BMI at T3 (r^2 0·88; $P < 0.05$), but ΔGH was the strongest determinant of BMI at T3, accounting for 74 % of its variability (r^2 0·74; β − 0·71; $P < 0.05$).

Discussion

The main original finding of the present study is that GH level at admission and GH evolution during refeeding may predict short-term clinical outcome after weight recuperation. Specifically, low GH levels at admission in hospital and lower amplitude of plasma GH variation between admission and discharge from hospital were strongly associated with relapse 6 months after discharge. In addition, GH at admission is an important contributor in the variability of the final BMI. It is worthy to note that, despite the small number of patients, clear-cut differences between remitters and non-remitters were observed in this particularly homogeneous population characterised by the recent-onset pure restrictive form of AN and submitted to a standardised inpatient treatment. This finding should be confirmed by larger and long-term outcome studies. The prognostic effect of GH variations occurring during refeeding was independent from concomitant IGF-1 changes associated with weight gain. Likewise, whereas higher urinary GH levels have been shown in weight-recovered eumenorrhoeic compared with underweight amenorrhoeic and weight-recovered amenorrhoeic patients, yet, serum IGF-1 levels of amenorrhoeic AN patients were significantly higher only in weight-recovered but still amenorrhoeic patients

compared with the underweight amenorrhoeic AN patients[12]. The follow-up of the present study was too short to assess the resumption of menses. Moreover, the impossibility to determine 'the healthy weight' corresponding to the weight at the loss of menstruation could represent a limitation of the study that might have an impact on its interpretation. We did not observe any link between the GH level at admission or its evolution during refeeding and any nutritional behaviour before admission or psychiatric co-morbidities. High-protein meals as well as amino acids, such as arginine, lysine, ornithine, tyrosine, glycine and tryptophan, enhance GH release in human subjects[13], and protein and energy intakes are both essential to regulate IGF-1[14]. The higher GH level in the AN-R group compared with the AN-NR group at admission cannot be explained by the nutrients, because we found no difference in energy and protein intakes between the two groups. The patients did not receive any medication susceptible to interference with the GH–IGF-1 axis.

The heterogeneity in GH secretion pattern in patients suffering from AN had already been noted by Argente et al.[6], and these authors distinguished two groups characterised by nycthemeral GH values above or below the threshold of 3 ng/ml for 24 h. However, they were unable to detect any clinical or psychological feature associated with these phenotypes. The functional coupling of GH and IGF-1 has been extensively studied in AN[15,16]. The usual pattern associating low levels of IGF-1, despite an increase of GH secretion, suggests that AN is characterised by a specific resistance state to the action of GH. Administration of supraphysiological recombinant human GH treatment to women with AN does not overcome this resistance state to GH[17]. This resistance phenomenon is specific to the GH–IGF-1 axis, as the effect of recombinant human GH on adipose tissue lipolysis is preserved as the BFM of the treated patients decreased[17]. Other authors explained the enhanced GH secretion in AN as a result of an increase in both frequency and amplitude of secretory pulses[18]. These anomalies are totally reversed after nutritional recovery[6]. Brick et al.[19] have shown that free testosterone could modulate GH secretion across the weight spectrum: AN, normal weight and obesity.

The mechanism of this peripheral resistance to GH, mainly at the liver level, is still unknown. Some explanations based on indirect arguments have been proposed. The decrease in

Table 4. Individual weight and BMI at admission (admission (baseline) (T0)) of anorexia nervosa (AN) patients in remission (AN-R) and not in remission (AN-NR)

(Individual values and mean values with their standard errors)

	AN-R (n 6)		AN-NR (n 5)	
	Weight (kg)	BMI (kg/m^2)	Weight (kg)	BMI (kg/m^2)
	34·6	11·4	37·2	13·6
	36·5	13·7	39·4	14·5
	42·3	13·9	31·0	12·6
	36·2	13·5	33·3	11·8
	33·5	12·2	38·0	14·1
	34·6	13·2		
Mean	36·1	13·0	35·7	13·3
SEM	2·1	0·2	2·9	0·1

the circulating cleaved form of the GH receptor, GH-binding protein, in malnourished patients suffering from AN suggests that expression of GH receptor could be decreased in the target tissues and that this effect is reversible with refeeding[6,16,20,21]. Another hypothesis has recently been proposed attributing a role to the fibroblast growth factor-21 (FGF-21) secreted by the liver[22]. Indeed, FGF-21 transgenic mice are smaller than wild-type littermates and are characterised by a profound decrease of IGF-1 without a parallel decrease of GH secretion[23]. As FGF-21 is a hormone secreted during prolonged starvation in both animals and human subjects, this factor could explain the GH resistance associated with AN[24]. Two studies measuring FGF-21 in this disease lead to conflicting results. Dostalova *et al.*[25] observed a decrease of this factor in patients suffering from AN, with a subsequent reduction after 2 months of refeeding; however, it is worthy to note that they found a positive correlation between the pre-treatment level of FGF-21 and weight gain during refeeding. Fazeli *et al.*[22] observed similar FGF-21 levels in AN patients and controls before adjusting for insulin resistance and BFM; however, after adjustment for these factors, which could influence FGF-21 production, patients suffering from AN were characterised by a relative increase in FGF-21 levels. Moreover, in the Fazeli *et al.* study, FGF-21 levels were significantly and positively correlated with GH AUC and negatively with IGF-1 values, suggesting that, as in rodents, FGF-21 could be a regulator of GH sensitivity in patients with AN[22]. FGF-21 appears to be an important coordinator of the metabolic and hormonal response to prolonged starvation[24]. As IGF-1 and FGF-21 are both primarily produced in the liver, we looked for any emaciation-induced liver dysfunctions in the patients characterised by both low levels of GH at admission and poor prognosis. This hypothesis can be ruled out, as aminotransferase (alanine aminotransferase and aspartate aminotransferase) levels at admission were not different between the patients with or without remission. We could assume that the increase of GH associated with active AN could be a marker of the persistence of a correct FGF-21-mediated adapted response to the disease in some patients. Refeeding by shutting down the FGF-21 pathway in these specific patients could lead to a larger weight gain, as shown by Dostalova *et al.*[25], and to a better prognosis. In contrast, paradoxically low levels of GH in acute AN could be a signal of loss of physiological adaptation associated with poor prognosis.

In conclusion, monitoring GH levels at admission and during refeeding in patients suffering from AN has some prognostic value. The role of this factor in the disease is probably indirect, reflecting specific changes associated with the adapted response to starvation. Elucidating the pathway of this response could be useful in improving the care of patients with AN.

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