Revaluation of the clinical and metabolic behavior of children with isolated growth hormone deficiency during GH treatment according to newly proposed note 39 of the Italian Medicines Agency (AIFA)

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ORIGINAL ARTICLE

Revaluation of the clinical and metabolic behavior of children with isolated growth hormone deficiency during GH treatment according to newly proposed note 39 of the Italian Medicines Agency (AIFA)

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Abstract
Purpose This study aimed at evaluating the clinical and metabolic behavior of children with isolated growth hormone (GH)-deficiency (GHD), grouped according to the new AIFA criteria for the appropriateness of use and reimbursement of GH treatment in children.
Methods The clinical and metabolic data of 310 prepubertal children (220 M, 90 F; mean age 10.8 years) grouped, according to new AIFA note 39, into Group A (No. 181 with a peak of GH <8 μg/l), Group B (No. 103 with a peak of GH ≥8 and <10 μg/l) and Group C (No. 26 with a peak of GH >10 μg/l) were retrospectively analyzed. Group A and B, diagnosed as having GHD, were treated with GH for at least 24 months, while Group C was analyzed only at baseline.
Results At baseline, Group A showed higher waist circumference than B ($p = 0.031$) and C ($p = 0.041$), while no difference in metabolic parameters was found between the three groups. After 12 and 24 months of treatment, Group B showed lower height velocity ($p < 0.001$ and $p = 0.049$, respectively) than Group A. As regards the metabolic parameters, both after 12 and 24 months of treatment, in Group B we found higher fasting glucose ($p < 0.001$ and $p = 0.020$), insulin ($p = 0.002$ and $p = 0.011$), Homa-β ($p = 0.020$ and $p = 0.015$) and Homa-IR (both $p = 0.001$) than Group A, with concomitant lower QUICKI (both $p < 0.001$) and HDL cholesterol ($p = 0.020$ and $p = 0.011$), without difference in other lipid parameters. The HbA1c levels, although always within the normal range, were found higher in Group B than Group A after 12 months ($p = 0.015$).
Conclusions According to the new AIFA criteria, the reduction of GH cut-off for GHD diagnosis can be supported by auxological and metabolic data. The real benefits from GH therapy in children with higher stimulated GH levels at diagnosis remains to be better understand.

Keywords Growth hormone deficiency · Children · Italian Medicines Agency (AIFA)

Introduction

The diagnosis of growth hormone (GH) deficiency (GHD) in childhood has been and remains object of much controversy [1–3]. The condition of GHD is established by the clinical, auxological and biochemical criteria of the GH Research Society [4]. As regards the biochemical assessment, limited and discordant data for each stimulation test exist. However, in children with appropriate clinical criteria for GHD, a peak concentration below 10 μg/L has traditionally been used to support the diagnosis, although an overlap could exist in GH peak between normal and GHD children [4]. For these reasons, in the absence of a gold standard test or cut-off, it is important to integrate clinical, auxological, radiological and biochemical criteria to diagnose GHD. In Italy, we recently had a review of the criteria of appropriateness of use and reimbursement of GH treatment in children according to the note 39 of the Italian Medicines Agency (AIFA). The critical analysis of the newly proposed note mainly focused on the cut-off of GH. As explicitly indicated in the new note, as regards the biochemical criteria, children need to show a GH peak

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<8 μg/L after two different GH provocation tests to be diagnosed as having GHD. It is noteworthy that, by applying these new criteria, a percentage of children previously diagnosed as having GHD may have received a wrong diagnosis and an unnecessary treatment, with potential clinical implications and increased healthcare spending. On the other hand, whether the under-treatment of these patients could have consequences with regard to health is not known. The aim of this study was to evaluate the clinical and metabolic behavior of GH-treated children grouped according to the new AIFA criteria.

Materials and methods

We retrospectively analyzed the clinical and metabolic data of 310 consecutive prepubertal children (220 males, 90 females, mean age 10.8 ± 2.9 years; range 3.7–14.0 years) with short stature consecutively admitted to the Section of Endocrinology of the University of Palermo during the years 2005–2013. All children underwent arginine test [0.5 g/kg body weight (no more than 30 g) of arginine over 30 min] and glucagon test [im administration of 30 μg/kg glucagon (no more than 1 mg)] on two different days and were divided, according to new AIFA note 39, into Group A (No. 181 with a peak of GH <8 μg/l after two tests), Group B (No. 103 with a peak of GH ≥8 and <10 μg/l) and Group C (No. 26 with a peak of GH >10 μg/l). Groups A and B, diagnosed as having GHD, were treated with GH for at least 24 months, while Group C, without GHD, was analyzed only at baseline and it was considered as a control healthy group. Among children of Group C, 15 (58 %) were diagnosed as having idiopathic short stature (ISS) and 11 (42 %) as having constitutional delay of growth. Neuroimaging, with magnetic resonance imaging (MRI) of the hypothalamic-pituitary region, was arbitrarily performed in accordance with our internal protocol only in GHD children with more severe GHD, i.e. with GH peak ≤3 μg/l (No. 43 children). Among them, six patients showed a partial empty sella and 2 a pituitary hypoplasia. We excluded children affected by multiple pituitary hormone deficiency or receiving any other kind of hormonal replacement therapy or drug and GHD children with a shorter follow-up. All children, even the older ones, were in the first or second stage (due to the presence of initial pubic hairs) of sexual development according to the Marshall and Tanner criteria [5] to avoid any interference of puberty on auxological and metabolic parameters and maintained the prepubertal hormonal status during the observation period (i.e. FSH and LH <1 mU/ml, total testosterone and 17β-Estradiol <0.50 ng/ml and <5 pg/ml, respectively, in males and females). In particular, in Groups A and B, the pubertal status was, respectively, stage I in 160/181 and 91/103 and stage II in 21/181 and 12/103 subjects at baseline, and stage I in 142/181 and 78/103, stage II in 39/181 and 25/103 subjects after 24 months of follow-up, while in the control group 21/26 children were in the stage I and 5/26 in the stage II.

The diagnosis of GHD was established by the GH Research Society criteria [4]. GHD was demonstrated by failure of GH to respond to the two stimuli (arginine and glucagon tests) with GH peaks below 10 μg/l. The GHD patients received GH once daily at bedtime with a pen injection system. During the follow-up, in line with our internal fixed protocol, in all children, regardless of GH peak, we used an initial daily dose of 0.025 mg/kg of GH with a gradual increase of 0.003–0.005 mg/kg/day every 6 months to always maintain the IGF-I levels in the normal range. In detail, from months 1 to 6 all children were maintained at a mean dose of 0.025 mg/kg/day, from months 6 to 12 at a mean dose of 0.029 mg/kg/day and from months 12 to 24 at the dose of 0.033–0.035 mg/kg/day.

Study protocol

In all GHD patients, at baseline and after 12 and 24 months of GH treatment, according to our fixed internal protocol, we measured body height (Standard Deviation, SD), body mass index (BMI) and waist circumference (WC). Blood samples were drawn after an overnight fast. Laboratory assessment included fasting glucose and insulin levels, insulin-like growth factor-I (IGF-I), glycosylated hemoglobin (HbA1c), lipid profile including total cholesterol, high-density cholesterol (HDL) and triglycerides. Low-density lipoprotein (LDL) cholesterol levels were evaluated by the formula:

$$\text{LDL cholesterol} = \text{total cholesterol} - \text{HDL cholesterol} - \text{triglycerides}/5.$$

Estimates of basal insulin secretion included fasting insulin and the homeostasis model assessment for β-cell function index (Homa-β) [6]. As surrogate estimates of insulin sensitivity we considered the homeostasis model assessment estimate of insulin resistance (Homa-IR) [6] and the quantitative insulin sensitivity check index (QUICKI) [7]. In the control subjects, this evaluation was performed only at baseline.

The institutional Ethics Committee of the University of Palermo approved this study. At the time of hospitalization informed consent for the scientific use of the data was obtained from all parents of the participants.

Hormone and biochemical assays

All biochemical data were collected after overnight fasting. Glycemia and HbA1c were measured in the centralized accredited laboratories with standard methods. Serum insulin was measured by ELISA (DRG Instruments GmbH,

Germany). The sensitivity of the method was 1 IU/ml. The normal insulin range (IU/ml) was 5–19. Throughout the follow-up, GH levels were assayed by immunoradiometric assay (Radim, Pomezia, Italy) and the sensitivity of the assay was 0.05 µg/l. The intra and inter-assay coefficients of variation (CV) were 2.5–3.9 and 3.8–5.0 %, respectively. Serum total IGF-I was assayed in the same laboratory with the ELISA method (OCTEIA IGF-I kit, IDS Inc., Fountain Hills, AZ, USA). The sensitivity of the method was 1.9 µg/l. The inter- and intra-assay CV values were 7–7.1 and 2.3–3.5 %, respectively, at IGF-I levels of 90.7–186 and 66.7–120.9 µg/l, respectively. The normal ranges (males and females combined) of total IGF-I levels (µg/l) were 12–108 (0–1 years); 13–100 (1–3 years); 26–280 (3–6 years); 85–230 (6–9 years); 98–404 (9–12 years); 142–525 (12–15 years); 146–415 (15–20 years).

Statistical analysis

The Statistical Packages for Social Sciences (SPSS) version 17 was used for data analysis. Baseline characteristics were presented as mean ± standard deviation (SD); rates and proportions were calculated for categorical data. The normality of distribution of the quantitative variables was assessed with the Kolmogorov–Smirnov test. Only the M value did not show a normal distribution. The differences between the three groups of children at baseline were evaluated by ANOVA univariate post hoc test analysis. The differences between the two groups of GHD children (Group A and Group B) were evaluated by the Student's *t* test for the data with a normal distribution and by Mann–Whitney *U*-test (non-parametric test) for continuous variables without normal distribution (M value). Differences in metabolic parameters were corrected for BMI through a logistic regression model. A p value of <0.05 was considered statistically significant.

Results

The clinical and biochemical features of all children, grouped according to cut-off of GH, are shown in Tables 1 and 2.

No difference was found for age between the three groups of children (Table 1). At baseline, Group A showed higher waist circumference (63.3 ± 11.1 cm) than B (58.6 ± 11 cm; $p = 0.031$) and C (58.6 ± 8.2 cm; $p = 0.041$), while no difference in metabolic parameters was found between the three groups. As expected, Group C showed a better height (−1.70 ± 0.35 SD) than A (−2.04 ± 0.72 SD; $p = 0.002$) and B (−2.06 ± 0.86 SD; $p = 0.010$), with concomitant higher IGF-1 levels ($p = 0.013$ and 0.015, respectively) (Table 1).

After 12 and 24 months of treatment, Group B showed lower height velocity (7.4 ± 2.2 vs. 8.6 ± 2.5 cm; $p < 0.001$ and 5.8 ± 1.2 vs. 7.7 ± 8.7 cm; $p = 0.049$, respectively) than Group A, with a concomitant lower, although not statistically significant, height SD and without difference in BMI, WC and IGF-1 levels (Table 2).

As regards the metabolic parameters, after 12 months of treatment both in Groups A and B we found a significant increase in fasting glucose (both $p < 0.001$), fasting insulin (both $p < 0.001$), Homa-IR (both $p < 0.001$), Homa-β (both $p < 0.001$) and HbA1c (both $p < 0.001$), with a concomitant decrease in QUICKI (both $p < 0.001$), without further significant change after 24 months. No significant difference was found in total and HDL-cholesterol and triglycerides in both groups from baseline to 24 months, while a significant decrease in LDL-cholesterol was found from baseline to 12 months only in Group A ($p = 0.010$) (data not shown).

When we analyzed the difference between the two groups of GHD children, both after 12 and 24 months of treatment in Group B we found higher fasting glucose (5.18 ± 0.40 vs. 4.86 ± 0.55 mmol/L; $p < 0.001$ and 5.07 ± 0.35 vs. 4.89 ± 0.50 mmol/L; $p = 0.015$), fasting insulin (12.9 ± 5 vs. 9 ± 6.2 IU/ml; $p = 0.002$ and 12.7 ± 4.4 vs. 9.6 ± 5.3 IU/ml; $p = 0.011$), Homa-β (46.2 ± 1.9 vs. 33.4 ± 2.4 %; $p = 0.020$ and 47.8 ± 1.6 vs. 36.4 ± 2.2 %; $p = 0.015$) and Homa-IR (3.02 ± 1.22 vs. 2.02 ± 1.48; $p = 0.001$ and 3.01 ± 0.96 vs. 2.08 ± 1.15; $p = 0.001$) than Group A, with concomitant lower QUICKI (0.32 ± 0.01 vs. 0.36 ± 0.04; $p < 0.001$ and 0.32 ± 0.01 vs. 0.35 ± 0.03; $p < 0.001$) and HDL cholesterol (54.5 ± 11.4 vs. 58.8 ± 13 mgdl; $p = 0.020$ and 53.1 ± 11.7 vs. 59.4 ± 12.2 mg/dl; $p = 0.011$), without difference in other lipid parameters. The HbA1c levels, although always within the normal range, was found higher in Group B than Group A after 12 months of treatment (5.3 ± 0.3 vs. 5.1 ± 0.3 %, $p = 0.015$), but not after 24 months (Fig. 1; Table 2)

When we performed the same analysis by grouping all children according to gender, we did not found significant difference between males and females (data not shown).

Discussion

Although recombinant human GH has been available since 1985, there are several unanswered questions related to its use. To date a clear benefit-risk profile in some specific groups of treated children, i.e. in the milder forms of GHD or in ISS, is still not well defined. Children with ISS are distinguished from GHD children by an arbitrary cut-off in peak stimulated GH secretion and the ISS indication is approved in the USA and not in Europe [8]. Despite the GH Research Society has well established the clinical,

Table 1 Baseline clinical and biochemical features of all children grouped according to cut-off of GH after stimulation test (Group A: peak of GH <8 µg/l; Group B peak of GH ≥8 and <10 µg/l; Group C peak of GH >10 µg/l)

	GHD Group A (No. 181)	GHD Group B (No. 103)	Controls Group C (No. 26)	*p**	*p***	*p****
	Subjects (%)	Subjects (%)	Subjects (%)			
Gender						
Males	136 (75)	72 (70)	12 (46)	0.413	0.004	0.041
Females	45 (25)	31 (30)	14 (54)			
	Mean ± SD	Mean ± SD	Mean ± SD	*p**	*p***	*p****
Age (years)	10.7 ± 2.9	10.8 ± 2.8	11.3 ± 2.9	0.746	0.331	0.432
Height (SD)	−2.04 ± 0.72	−2.06 ± 0.86	−1.70 ± 0.35	0.935	0.040	0.010
Height velocity (cm/year)	3.7 ± 1.5	4.2 ± 1.2	4.1 ± 1.7	0.098	0.122	0.745
BMI (kg/m^2)	17.7 ± 3.3	17.3 ± 3.2	16.6 ± 3.1	0.352	0.102	0.295
WC (cm)	63.3 ± 11.1	58.6 ± 11	58.6 ± 8.2	0.031	0.041	0.991
IGF-1 (µg/l)	119 ± 68.7	121 ± 64	199 ± 108	0.829	<0.001	0.015
GH peak[a] (µg/l)	3.4 ± 1.6	8.5 ± 1.8	14.2 ± 5.4	<0.001	<0.001	<0.001
Fasting glucose (mmol/L)	4.45 ± 0.57	4.57 ± 0.68	4.28 ± 0.60	0.159	0.152	0.057
Fasting insulin (IU/ml)	4.9 ± 4	5.7 ± 8.1	3.8 ± 2.8	0.586	0.231	0.292
HbA1c (%)	4.9 ± 0.4	4.9 ± 0.5	5.2 ± 0.3	0.477	0.060	0.140
Homa-β (%)	18.7 ± 1.7	24.9 ± 5	15 ± 1.3	0.468	0.343	0.348
Homa-IR	1 ± 0.88	1 ± 1.42	0.72 ± 0.54	0.697	0.152	0.238
QUICKI	0.42 ± 0.10	0.44 ± 0.13	0.46 ± 0.13	0.452	0.189	0.581
Total cholesterol (mg/dl)	163.3 ± 30.5	156.6 ± 29.2	164.5 ± 30.2	0.118	0.857	0.259
HDL cholesterol (mg/dl)	58.2 ± 13.4	56.2 ± 13.2	63.2 ± 14.5	0.284	0.104	0.055
LDL cholesterol (mg/dl)	92.2 ± 27.5	87.8 ± 29.2	87.6 ± 24.8	0.352	0.839	0.384
Triglycerides (mg/dl)	66.7 ± 34	62.6 ± 24.5	68.3 ± 35.2	0.277	0.453	0.972

* *p* difference between Group A and B

** *p* difference between Group A and C

*** *p* difference between Group B and C

[a] Mean GH peak after glucagon and arginine test

auxological and biochemical criteria for the diagnosis of GHD [4], many questions remain about the proper diagnosis in children [9]. Many different stimuli are currently used to induce GH secretion, but to date no stimulation test is completely reliable. The provocative tests are poorly reproducible, the GH cut-off is quite arbitrary and the GH peak response could be influenced by many factors, such as age, BMI, adiposity or pubertal status [10–13]. Some years ago Kristrom et al. demonstrated that the growth response in ISS was similar to GHD children, despite the first required higher dose of GH [14], while other authors have demonstrated that there is no benefit in treating these groups of children [15, 16]. In addition, similar proportions of poor responders to treatment have been found in ISS and GHD children, which probably indicates that there is not a different underlying pathology in most of these patients, except for those with severe GHD with a GH peak <3 µg/l [17]. Despite that pharmacological tests are not completely reliable and are burdened by poor specificity because they test the GH-IGF-I axis in a non-physiological manner [18–20], measuring GH secretion after provocative tests is necessary to regulate the use of GH and is still considered the gold standard in the diagnosis of GHD, according to the well-established criteria. To date the cut-off <10 µg/l after two tests has commonly used [4]. However, there is little evidence to support this classically suggested cut-off, set rather arbitrarily and without adjusting for the above mentioned factors. This may lead to misdiagnosis GHD. Indeed, up to 85 % of short children who were diagnosed as having GHD with peak GH <10 µg/l in two provocative tests had a normal GH response when retested a few months later [21]. Despite this, the cut-off level for the diagnosis of GHD has not yet been revised [22].

In Italy, the criteria of appropriateness of use of GH treatment in children have been recently revised and the cut-off of GH after a stimulation test to make a diagnosis of

Table 2 Clinical and biochemical features of children grouped according to cut-off of GH after stimulation test (Group A: peak of GH <8 μg/l; Group B peak of GH ≥8 and <10 μg/l) after 12 and 24 months of GH treatment

	GHD Group A (No. 181) 12 months	GHD Group B (No. 103)	*p*	*p**	GHD Group A (No. 181) 24 months	GHD Group B (No. 103)	*p*	*p**
	Mean ± SD	Mean ± SD			Mean ± SD	Mean ± SD		
Height (SD)	−1.58 ± −0.66	−1.55 ± 0.79	0.853		−1.33 ± 0.77	−1.17 ± 0.91	376	
Height velocity (cm/year)	8.6 ± 2.5	7.4 ± 2.2	0.001		7.7 ± 8.7	5.8 ± 1.2	0.049	
BMI (kg/m^2)	18 ± 3.3	17.9 ± 3.4	0.710		18.3 ± 3.3	18.1 ± 3	0.667	
WC (cm)	64.4 ± 10.2	65.5 ± 11.1	0.616		66.8 ± 11.6	69 ± 7.4	0.349	
IGF-1 (μg/l)	311 ± 181	321 ± 161	0.695		331 ± 191	352 ± 142	0.509	
Fasting glucose (mmol/l)	4.86 ± 0.55	5.18 ± 0.40	<0.001	<0.001	4.89 ± 0.50	5.07 ± 0.35	0.015	0.020
Fasting insulin (IU/ml)	9 ± 6.2	12.9 ± 5	0.001	0.002	9.6 ± 5.3	12.7 ± 4.4	0.011	0.011
HbA1c (%)	5.1 ± 0.3	5.3 ± 0.3	0.016	0.015	5.1 ± 0.3	5.2 ± 0.3	0.190	0.200
Homa-β (%)	33.4 ± 2.4	46.2 ± 1.9	0.007	0.020	36.4 ± 2.2	47.8 ± 1.6	0.014	0.015
Homa-IR	2.02 ± 1.48	3.02 ± 1.22	0.001	0.001	2.08 ± 1.15	3.01 ± 0.96	0.001	0.001
QUICKI	0.36 ± 0.04	0.32 ± 0.01	<0.001	<0.001	0.35 ± 0.03	0.32 ± 0.01	<0.001	<0.001
Total cholesterol (mg/dl)	163 ± 29	156.9 ± 28.1	0.175		160.7 ± 24.4	149.4 ± 36.7	0.093	
HDL cholesterol (mg/dl)	58.8 ± 13	54.5 ± 11.4	0.030	0.020	59.4 ± 12.2	53.1 ± 11.7	0.011	0.011
LDL cholesterol (mg/dl)	89.1 ± 26.8	89 ± 29.2	0.998		88.7 ± 24.5	81.7 ± 36.5	0.242	
Triglycerides (mg/dl)	74.2 ± 31.4	66.1 ± 27.7	0.076		62.2 ± 22.1	75.4 ± 36.7	0.054	

* *p* value corrected for BMI

GHD has been arbitrarily reduced from 10 to 8 μg/l. Retrospectively applying this new cut-off to a series of patients already diagnosed as GHD and treated with GH, we found that 36 % of children showed a GH peak between 8 and 10 μg/l. In this group of subjects, considered as affected by GHD on the basis of previous, but not current, AIFA criteria, we found a worse auxological response during 24 months of GH treatment. Indeed, these children showed a lower height velocity than children with a GH peak <8 μg/l. In addition, when the metabolic parameters were analyzed, at baseline children with lower GH peak showed higher WC than children with GH peak between 8 and 10 μg/l and this finding could be a sign of a real condition of GHD [23].

During the follow-up, the evidence that children of Group B showed a worse metabolic profile probably confirms that the previous cut-off of 10 seems to be too high. We found higher glucose and insulin levels with higher insulin resistance degree in this group of children, concomitant with higher insulin-secretion. This trend to impairment in glucose metabolism during GH treatment has often been previously demonstrated [24, 25]. It is well known that GH treatment leads to a decrease in insulin sensitivity and alteration in insulin secretion even without evident changes in glucose tolerance [26] and the current study confirms this finding. Indeed, particularly after the first 12 months of GH treatment, we found a worsening trend of insulin sensitivity, as documented by increase in fasting glucose and insulin levels, Homa-IR and HbA1c, in both groups of GHD children and this trend was greater in Group B. This finding is consistent with the data of Salerno et al. which showed in children during GH treatment that the HOMA index increased more significantly in the group with partial than those with severe GHD [27]. In addition, the children of the Group A showed a decrease in LDL cholesterol during the first 12 months of treatment and higher HDL cholesterol than Group B throughout the follow-up. These evidences could demonstrate that children with higher baseline stimulated GH levels may not fully benefit from the GH treatment as well as the children with more severe GHD. Therefore, a percentage of children previously diagnosed with GHD may have been misdiagnosed and may have received an unnecessary treatment, with potential clinical implications. These data could be confirmed during the future follow-up when children, after reaching the adult height, will be subject to retesting of GH axis. Indeed, to date, 60–85 % of patients diagnosed with GHD in childhood will have adequate GH secretion when retested in late adolescence or adulthood [28–30] and these data could reflect a wrong diagnosis of GHD. When the diagnosis of GHD in children is made with the new more selective GH cutoff proposed by AIFA, probably the percentage of GHD children not confirmed by retesting in the transition period may be reduced.

A limit of this study is likely represented by the use of similar doses of GH in the two groups of children. Indeed, discordant data exist about the different metabolic effects of

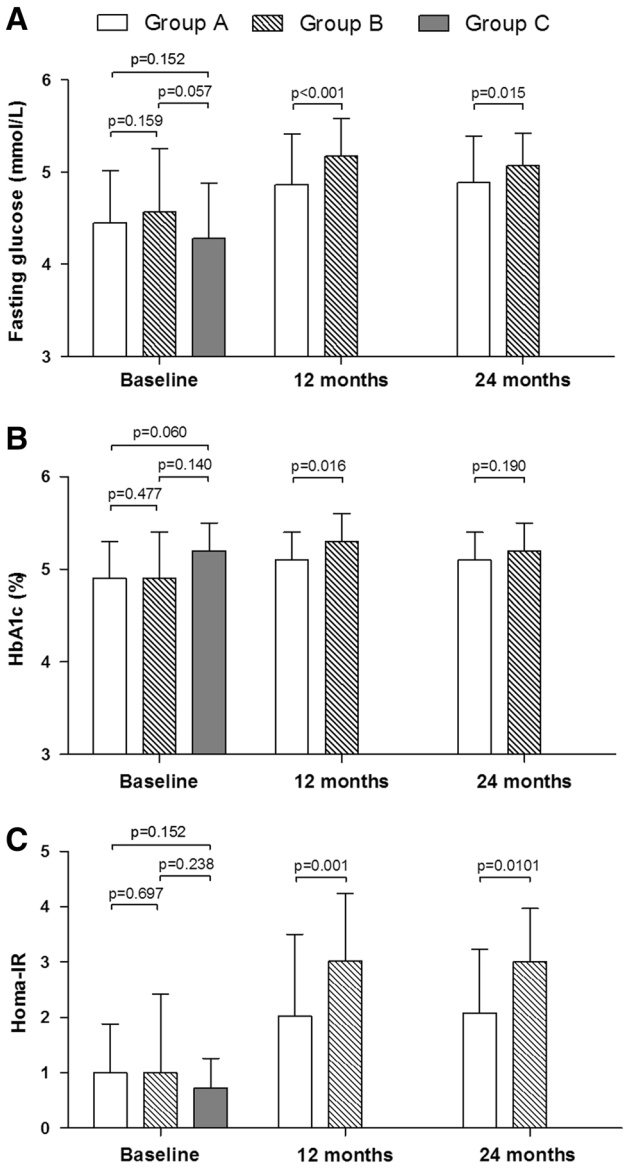

Fig. 1 Fasting glucose (mmol/L), HbA1c (%) and Homa-IR in children grouped according to GH peak after stimulation test into Group A (No. 181 with a peak of GH <8 µg/l), Group B (No. 103 with a peak of GH ≥8 and <10 µg/l) and Group C (No. 26 with a peak of GH >10 µg/l) at baseline and after 12 and 24 months of GH treatment (in Group A and B)

different dose used [31] and a larger prospective study where patients of both groups are randomized to different GH doses can give more complete information. Furthermore, the short-term clinical and metabolic evaluation performed in this study does not allow to affirm with certainty that children with a GH peak between 8 and 10 µg/l cannot fully benefit from GH therapy and a longer follow-up would be required.

In conclusion, this study demonstrates that the reduction of the GH cut-off can probably be supported by auxological and metabolic data, since children with lower levels of stimulated GH show a better response to treatment, although a degree of growth improvement in Group B is also to be considered. The real clinical and metabolic benefits from GH therapy in this group of children with higher stimulated GH levels at diagnosis, as well as in other non-GHD groups of patients currently treated (i.e. children with Turner syndrome, born small for gestational age, ISS), remains to be better understood. We need more well-designed long-term studies with large number of patients looking at different subgroups of children, also according to GH cut-off, to better assess their different auxological and metabolic response to treatment.

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards

Informed consent Informed consent for the scientific use of the data was obtained from all individual participants included in the study and from their parents.

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