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Combined Therapy with Insulin and Growth Hormone in 17 Patients with Type-1 Diabetes and Growth Disorders

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Key Words
Growth hormone · Insulin therapy · GH deficiency · Type-1 diabetes · Turner syndrome

Abstract
Background/Aim: Combined growth hormone (GH) and insulin therapy is rarely prescribed by pediatric endocrinologists. We investigated the attitude of Italian physicians to prescribing that therapy in the case of short stature and type-1 diabetes (T1DM). ***Methods:*** A questionnaire was sent and if a patient was identified, data on growth and diabetes management were collected. ***Results:*** Data from 42 centers (84%) were obtained. Of these, 29 centers reported that the use of combined therapy was usually avoided. A total of 17 patients were treated in 13 centers (GH was started before T1DM onset in 9 patients and after the onset of T1DM in 8). Height SDS patterns during GH therapy in the 11 patients affected by GH deficiency ranged from –0.3 to +3.1 SDS. In the 8 diabetic patients in whom GH was added subsequently, mean insulin dose increased during the first 6 months of therapy from 0.7 ± 0.2 to 1.0 ± 0.2 U/kg ($p = 0.004$). HbA_{1c} was unchanged during the first 6 months of combined therapy. ***Conclusions:*** Most Italian physicians do not consider prescribing the combined GH-insulin therapy in diabetic children with growth problems. However, the results of the 17 patients identified would confirm that the combined therapy was feasible and only caused mild insulin resistance. GH therapy was effective in promoting growth in most patients and did not affect diabetes metabolic control.

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Introduction

Combined growth hormone (GH) and insulin therapy are rarely prescribed in pediatric patients. Apart from the recent multicenter German study describing 37 children treated with insulin and GH [1], so far only single case reports have been published dealing with both pediatric or adult patients [2–6]. The infrequency of this combined treatment is probably due to two main reasons. The first is purely statistical, since the possibility of the double association type-1 diabetes (T1DM) and GH deficiency (GHD) is extremely unlikely: the estimated prevalence, in fact, is between 1:2,000 and 1:5,000 for GHD, the most frequent disease where GH therapy is prescribed in children, and 1:800 for T1DM [7]. The second probably arises from the concerns in managing a multiple daily injection treatment involving two hormones having opposite effects on glucose metabolism. Finally, despite the reassuring published data that GH treatment is not associated with an increased incidence of T1DM [8, 9], the discordant results on the possible increased incidence of T2DM in GH-treated children have probably represented a further obstacle in prescribing the two hormones simultaneously [8–10].

To investigate the attitude of Italian Pediatric endocrinologists to treating patients simultaneously with GH and insulin, in the first part of 2012 a questionnaire was sent to all members of the Italian Society for Pediatric and Adolescent Endocrinology (ISPED). In cases where a patient was identified, specific details were requested for each case. The primary aim of the survey was, therefore, to test the general attitude of the participants towards the double therapy and, secondly, to collect data on the management of insulin therapy, growth outcome and possible side effects of the identified patients.

Materials and Methods

A questionnaire was sent by e-mail to all 480 members of the ISPED, belonging to 52 centers around the country. The first part of the questionnaire enquired about the general attitude of the pediatric endocrinologists to prescribing the combined therapy, and the second concerned the database of information on the patients, if any. Two possibilities were considered: (1) that an already diabetic child required GH for short stature and (2) that T1DM occurred in a child in the course of GH therapy. The only inclusion criterion to identify a patient was based on the combined therapy for at least 6 months with insulin (due to T1DM) and GH (due to any type of growth impairment). Exclusion criteria were hyperglycemia not due to T1DM and therapy with antidiabetic oral agents.

The questionnaire contained the following questions:

(1) In the last 20 years, have you ever treated a patient with GH and insulin who fulfilled the inclusion criteria?
(2) If no, is the reason because (a) you never had a similar patient, (b) you did not consider GH treatment in an already diabetic child or (c) you stopped GH therapy after the onset of T1DM?

Only if a patient was identified were specific data asked. The patients were subdivided into 2 groups: (1) patients with onset of T1DM first and subsequent start of GH therapy and (2) patients already treated with GH and subsequent onset of T1DM. In both cases the file included information on the growth of the subject before treatment, at the end of GH treatment or (if therapy was still ongoing) at the last visit and, finally, on final height if reached. Furthermore, the reasons for treating the patient with GH, the duration of the combined treatment and the type of insulin therapy were also included. In the patients with onset of T1DM first, specific data on variations in insulin doses and degree of metabolic control after GH was started were collected. In the patients with GH as first treatment, further data were asked on the interval before diabetes onset, possible transient withdrawal from GH therapy and the type of insulin therapy chosen.

T1DM was diagnosed according to the International Society for Pediatric and Adolescent Diabetes (ISPAD) criteria [11]. The diagnosis of GHD was performed following the Italian NHS, combining auxological criteria and a GH peak <10 ng/ml after 2 pharmacological stimuli. Other diseases in which GH is permitted as a promoting agent are Turner syndrome and small-for-gestational-age children. In selected cases, after obtaining permission from the local ethical committees, GH therapy was prescribed for other conditions associated with short stature not due to the aforementioned reasons.

GH and HbA_{1c} were determined locally using various commercial kits and results of HbA_{1c} of the patients described were performed with DCCT-centerd methods. The Italian standards by Cacciari et al. [12] were used to determine height SDS.

Results

Data were obtained from 42 centers (84%), 13 of which identified 17 patients fulfilling the inclusion criteria; 1 center treated 3 patients and 2 centers treated 2 patients each.

More than two-thirds of the centers (29/42; 69%) stated that the use of combined therapy was considered uncomfortable and therefore to be avoided. They reported either to never have had a patient with a simultaneous diagnosis of GHD and T1DM (26 centers) or to not consider GH therapy for any problem affecting growth in an already diabetic patient. Three centers reported on 3 patients treated for GHD withdrawal from GH therapy after the diagnosis of T1DM. In contrast, 13 centers reported the treatment of 17 patients (9 males, 8 females). In the whole group of patients, mean height at GH therapy start was −2.9 ± 0.7 SDS, mean age at T1DM onset was 7.6 ± 4.3 years and mean age at GH therapy start 8.0 ± 3.3 years.

Table 1. Characteristics of the 9 patients in whom GH therapy was started before T1DM onset

No.	Sex	Reason for GH therapy	Age at GH therapy start, years	Age at T1DM onset, years	GH peak, ng/ml	Height SDS at GH start	Height SDS at GH stop	Final height SDS	GH dose, mg/kg/week	Duration of GH therapy, months
1	M	GHD	12	13	7.7	–2.6	–2.9	not reached	0.21	24
2	F	GHD	3.6	8.8	3	–2.3	–1.3	–1.9	0.2	112
3	M	GHD	2.5	2.6	5.9	–3.1	–0.8	pending	0.2	84 ongoing
4	M	GHD	6.1	6.6	9	–3.5	–2.6	pending	0.2	33 ongoing
5	F	organic GHD	9.3	13.1	3	–3.1	–1.1	+0.8	0.2	27
6	F	Turner syndrome	6	7	not done	–2.8	–1.30	not reached	0.4	63
7	F	GHD	6	13	6.3	–3.7	–2.6	–2.6	0.25	24
8	M	GHD	8	9	4	–2.6	–1.1	–1.4	0.2	30
9	M	MPHD	3	13	2.1	–3.3	–3.2	–2.7	0.3	180

GH therapy is still ongoing in cases No. 3 and 4. MPHD = Multiple pituitary hormone deficiency.

Table 2. Characteristics of the 8 patients in whom GH therapy was started after T1DM onset

No.	Sex	Reason for GH therapy	Age at T1DM onset, years	Age at GH therapy start, years	GH peak, ng/ml	Height SDS at GH start	Height SDS at GH stop	Final Height SDS	GH dose, mg/kg/week	HbA_{1c} at GH start, %	HbA_{1c} after 6 months of combined therapy, %	Duration of GH therapy, months
10	M	GHD	8	11	6.4	–3.2	–1.9	–2.3	0.20	7.4	7.3	60
11	F	ISS	12.1	13.7	20	–2.5	–1.3	–1.3	0.26	7.2	7.6	18
12	M	Bone dysplasia	1.0	10.5	7.7	–2.9	–2.6	pending	0.26	9.4	8.5	18 ongoing
13	F	Léri-Weill syndrome	9.6	10.1	12	–2.5	–3.5	pending	0.28	8.1	8.1	12 ongoing
14	F	GHD	2.5	9.5	6.4	–3.2	–0.1	pending	0.21	8.3	8	46 ongoing
15	M	GHD	3.3	5	3.7	–3.0	–2.7	pending	0.22	7	7.1	13 ongoing
16	F	Turner syndrome	1.7	11.5	not done	–3.9	–3.9	–3.9	0.30	7.1	6.8	84
17	F	Turner syndrome	5.6	8.7	not done	–0.9	–0.9	pending	0.27	8.5	7.9	6 ongoing

GH therapy is still ongoing in cases No. 12–15 and 17. ISS = Isolated short stature.

Table 1 shows the clinical characteristics of the patients in whom GH therapy was started before the diagnosis of T1DM. As shown, most patients were treated for isolated GHD, whereas 1 patient had multiple pituitary hormone deficiency (GH, TSH, ACTH, gonadotrophins), 1 patient had secondary GHD due to cranial irradiation for non-Hodgkin lymphoma and 1 girl had Turner syndrome. The patient with multiple pituitary deficiencies showed a poorly visible pituitary stalk and hypoplastic anterior lobe at the MRI. In 2 patients of this group GH therapy was transiently withdrawn (1 month in patient No. 1 and 6 months in patient No. 8) after the diagnosis of T1DM and then restarted. In all patients but 1 the diagnosis and GH treatment was started before the age of 10 years. As shown, the time period between the start of GH therapy and the onset of T1DM ranged from 1 month to 7 years. The duration of GH therapy was highly variable, ranging from 24 to 180 months (still ongoing in 2 cases), and height SDS patterns from the start to the end of therapy ranged from –0.3 to +2.3 SDS in the patients with GHD. In the 5 patients who already reached final height, height gain from GH therapy start ranged from +0.4 SDS (patient No. 2 with isolated GHD) to +3.9 SDS (patient No. 5 with organic GHD). GH dosages were not modified after the diagnosis of T1DM.

Table 2 describes the patients with an initial diagnosis of T1DM and a subsequent start of GH therapy. As shown, GH therapy was started for GHD in only 3 patients, whereas in the remaining patients it was chosen to correct short stature associated with Turner syndrome, for bone dys-

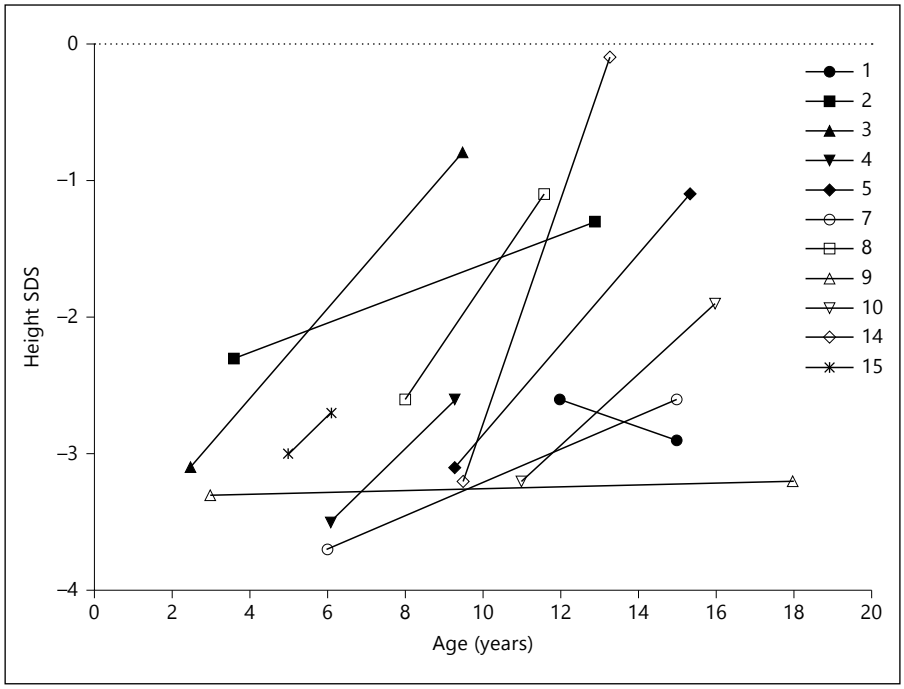

Fig. 1. Height SDS patterns during GH therapy of the 9 patients with isolated GHD, the patient with multiple hormone pituitary deficiency and the patient with organic GHD (therapy was ongoing in 4 cases).

plasias and in 1 case for isolated short stature. In only 2 patients was GH therapy started before the age of 10 years. The time period between the onset of T1DM and start of GH therapy ranged from 6 months to almost 10 years. The duration of GH therapy ranged from 6 to 84 months (still ongoing in 5 cases) and height gain SDS from the start to the end of therapy ranged from +0.3 to +3.1 SDS in the patients with GHD. Height gain from GH therapy start in the 3 patients who already reached final height ranged from 0 SDS in the patient with Turner syndrome to +1.2 SDS in the patient with isolated short stature.

Figure 1 shows height SDS patterns during GH therapy of the 9 patients with isolated GHD, the patient with multiple hormone pituitary deficiency and the patient with organic GHD (therapy was ongoing in 4 cases).

As for diabetes management, insulin therapy was performed with MDI in 11 patients and with CSII in the remaining 6. In the latter patients the pediatric diabetologist reported that the choice was based on the better management of nocturnal hyperglycemia following GH administration due to the possibility of increasing the nocturnal basal rate. In the patients already affected by T1DM at GH therapy start, the mean insulin dose increased during the first 6 months after GH start from 0.7 ± 0.2 to 1.0 ± 0.2 U/kg ($p = 0.004$) and in 1 patient (No. 8; table 1) the insulin requirement increased from 0.3 to 0.8 U/kg soon after GH therapy was started after the transient withdrawal. HbA_{1c} was unchanged in these patients during the first 6 months of combined therapy (pre-GH values: 7.9 ± 0.8 vs 7.7 ± 0.6%, $p = 0.91$). No significant side effects related to GH therapy were reported and compliance to GH therapy was recorded as good in all cases.

Discussion

Although combined therapy with insulin and GH was rarely performed by Italian pediatric endocrinologists, we were able to collect data of 17 children treated in the last 20 years, in whom GH was not only used as a replacement therapy but also as a growth-promoting agent despite the simultaneous presence of T1DM. We could identify opposite attitudes among Italian pediatric endocrinologists towards the combined therapy: in fact, about two-thirds of the physicians declared avoiding the double treatment and three of them specifically reported to have withdrawn GH therapy after the diagnosis of diabetes. Other centers, on the other hand, used the combined therapy also outside the field of strict replacement therapy, by starting it even after the diagnosis of T1DM. To justify the attitude of many Italian colleagues to avoiding the combined therapy, one must consider the fact that insulin is a life-saving therapy, whereas GH is not. It is likely, therefore, that in the case of T1DM onset after the start of GH therapy, par-

ents and caregivers had to cope with the difficult task of adapting to the new lifestyle (requiring a multiple daily injection treatment after the new diagnosis), with the problem of short stature becoming less important.

Many physicians were probably also influenced by the notorious antagonist effect of GH on insulin action [12–14], which is probably thought to make the management of T1DM insulin therapy difficult, especially during the pubertal years. Interestingly enough, in 3 centers GH therapy was withdrawn in 3 patients affected by isolated GHD after the diagnosis of diabetes, while this was not the case for the 9 patients described in table 1. Despite the recent and reassuring data on the lack of increase of T1DM incidence in children treated for GH, the fact that GH therapy increases insulin resistance and T2DM incidence in predisposed individuals [8–10] may have acted as a subtle psychological deterrent for any physician. The final judgment on this matter largely depends not only on the attitude of the physician, but also on the height of the child at the time of T1DM diagnosis and on the family reaction in the face of the second diagnosis. Our survey is in partial agreement with the recent German-Austrian collaborative study that identified 50 patients from a large national database treated with both insulin and GH therapy [1]. The collaborative study was specifically designed to evaluate insulin requirement and metabolic control in 37 children with T1DM in whom GH therapy was added to insulin subsequently, but indirectly provided evidence that our colleagues are even less reluctant to prescribe GH therapy in an already diabetic child: although the 37 patients described in that study were derived from a large national database, our survey of only 7 patients with GH started after the diagnosis of T1DM (table 2) included 42 Italian centers (84%) that are likely to follow most of the patients affected by growth problems or T1DM.

In our study and in the German-Austrian study, it is demonstrated that insulin therapy during GH therapy can be managed with adequate titration of insulin dosage. In both case series HbA_{1c} remained unchanged after GH therapy start (table 2) and the insulin requirement was quite surprisingly similar (1 U/kg) in the 2 investigations, where both multiple daily injections and pumps were used. In our study, the pump was preferred to the injection regimen in about a third of cases to better manage the nocturnal insulin resistance consequent to the GH administration. Insulin regimens for all children with T1DM have improved consistently in the last years and, thanks to the availability of different insulin analogs and also of pumps, it is possible to tailor the insulin schedule for almost every child and clinical condition.

The growth response to GH therapy obtained in our relatively small group of patients affected by different diagnosis, treated for different periods of times with standard GH doses in most cases, was roughly comparable to that described in the literature for the various types of growth disturbances [15]. Despite being highly variable in the different diagnostic groups and despite the different therapy durations (still ongoing in 7 patients), height patterns ranged from –0.3 to 3.1 SDS in the patients with GHD; the more homogeneous group of patients with GHD is depicted in figure 1. This result shows that GH therapy was more effective than that reported by the German-Austrian study (mean value +0.3 SDS after 2 years of GH therapy), indicating that perhaps diabetes itself is not the cause of a poor response to GH therapy and that the growth response is more dependent on the type of disease that affects the patient. In fact, compared to the German patients, who were all affected by isolated GHD, our patients were on average significantly younger and consistently shorter – parameters with a known positive influence on growth response to GH. Also, poor compliance to GH therapy, a known parameter with a negative influence on growth response, should also be considered as a possible determinant of insufficient growth.

A similar good response was reported in the pediatric case described by Quintos et al. [5] where, in terms of statistical exceptionality, the patient resembles our case affected by T1DM and multiple pituitary hormone deficiency. To our knowledge, no patients affected by multiple hormone deficiencies developing T1DM during replacement therapy have been described.

In conclusion, our survey demonstrated that many physicians from Italian centers of pediatric endocrinology do not consider combined therapy with GH and insulin in a diabetic child with growth problems. At the same time, the results obtained from the 17 patients described would confirm that GH therapy is feasible in diabetic children and caused only mild insulin resistance. In our case series GH was effective in promoting growth in most patients and did not affect diabetes metabolic control.

References

1 Bonfig W, Molz K, Woelfle J, Hofer SE, Hauffa BP, Schoenau E, Golembowski S, Wudy SA, Holl RW; Diabetes Patienten Verlaufsdocumentationsystem Initiative of the German Working Group for Pediatric Diabetology; German Bundesministerium für Bildung und Forschung Competence Net for Diabetes Mellitus: Metabolic safety of growth hormone in type 1 diabetes and idiopathic growth hormone deficiency. J Pediatr 2013;163:1095–1098.

2 Pankowska E, Szalecki M, Romer TE: Metabolic control and insulin administration in a girl with Turner syndrome and type 1 diabetes during long-term growth hormone therapy. Pediatr Endocrinol Diabetes Metab 2007; 13:213–215.
3 Fuglsang J, Lauszus F, Ørskov H, Ovesen P: Placental growth hormone during pregnancy in a growth hormone deficient woman with type 1 diabetes compared to a matching diabetic control group. Growth Horm IGF Res 2004;14:66–70.
4 Christ ER, Simpson HL, Breen L, Sönksen PH, Russell-Jones DL, Kohner EM: The effect of growth hormone (GH) replacement therapy in adult patients with type 1 diabetes mellitus and GH deficiency. Clin Endocrinol (Oxf) 2003;58:309–315.
5 Quintos JB, Grover M, Boney CM, Salas M: Autoimmune polyglandular syndrome Type 3 and growth hormone deficiency. Pediatr Diabetes 2010;11:438–442.
6 Pun T, Chandurkar V: Growth hormone deficiency, short stature, and juvenile rheumatoid arthritis in a patient with autoimmune polyglandular syndrome type 1: case report and brief review of the literature. ISRN Endocrinol 2011;2011:462759.
7 Bruno G, Maule M, Merletti F, Novelli G, Falorni A, Iannilli A, Iughetti L, Altobelli E, d'Annunzio G, Piffer S, Pozzilli P, Iafusco D, Songini M, Roncarolo F, Toni S, Carle F, Cherubini V; RIDI Study Group: Age-period-cohort analysis of 1990–2003 incidence time trends of childhood diabetes in Italy: the RIDI study. Diabetes 2010;59:2281–2287.
8 Cutfield WS, Wilton P, Bennmarker H, Albertsson-Wikland K, Chatelain P, Ranke MB, Price DA: Incidence of diabetes mellitus and impaired glucose tolerance in children and adolescents receiving growth-hormone treatment. Lancet 2000;355:610–613.
9 Child CJ, Zimmermann AG, Scott RS, Cutler GB Jr, Battelino T, Blum WF; GeNeSIS International Advisory Board: Prevalence and incidence of diabetes mellitus in GH-treated children and adolescents: analysis from the GeNeSIS observational research program. J Clin Endocrinol Metab 2011;96:1025–1034.
10 Bell J, Parker KL, Swinford RD, Hoffman AR, Maneatis T, Lippe B: Long-term safety of recombinant human growth hormone in children. J Clin Endocrinol Metab 2010;95:167–177.
11 Hanas R, Donaghue KC, Klingensmith G, Swift PG: ISPAD clinical practice consensus guidelines 2009 compendium. Introduction. Pediatr Diabetes 2009;10(suppl 12):1–2.
12 Cacciari E, Milani S, Balsamo A, Spada E, Bona G, Cavallo L, Cerutti F, Gargantini L, Greggio N, Tonini G, Cicognani A: Italian cross-sectional growth charts for height, weight and BMI (2 to 20 years). J Endocrinol Invest 2006;29:581–593.
13 Bratusch-Marrain PR, Smith D, DeFronzo RA: The effect of growth hormone on glucose metabolism and insulin secretion in man. J Clin Endocrinol Metab 1982;55:973–982.
14 Møller N, Butler PC, Antsiferov MA, Alberti KG: Effects of growth hormone on insulin sensitivity and forearm metabolism in normal man. Diabetologia 1989;32:105–110.
15 Ranke MB, Price DA, Reiter EO: Growth Hormone Therapy in Pediatrics: 20 Years of KIGS. Basel, Karger, 2007.