

MEDIUM AND LONG TERM OUTCOME OF GROWTH HORMONE THERAPY IN GROWTH HORMONE DEFICIENT ADULTS

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Abstract We evaluated long-term replacement therapy outcomes in various subsets of patients with adult growth hormone (GH) deficiency (AGHD) as well as the patients' susceptibility to adverse events. Fifty-nine patients with AGHD were evaluated, 27 with childhood onset (CO) (18-44 years old, 12 females) and 32 with adult onset (AO) (27-70 years, 18 females). A significant improvement in HDL-cholesterol was observed in AGHD-AO males (basal: 41.3 ± 12.9 mg/dl, intratreatment: 47.5 ± 13.2 mg/dl, $p=0.009$). However, individual analyses showed that total cholesterol decreased below 240 mg/dl in 33% of AGHD-CO patients and in 50% of AGHD-AO patients, and below 200 mg/dl in 67% of AGHD-CO patients and in 29% of AGHD-AO patients; in the AGHD-AO group, normalization of LDL-cholesterol (≤ 160 mg/dl) and triglycerides (≤ 200 mg/dl) was found in 100% and 50% of patients, respectively; the total cholesterol/HDL ratio decreased below 4.5 in 20% of AGHD-CO patients and in 25% of AGHD-AO patients. The cardiometabolic evaluation showed a significant intra- and interindividual heterogeneity, but cardiac mass improved in patients with a baseline cardiac mass index below 60 g/m². Markers of bone apposition increased significantly, while bone resorption markers were found to remain unchanged during treatment. A correlation was found between increased bone mineral content and lean body mass ($p=0.0009$). Susceptibility to adverse events was not found to be dependent on gender or on the time of onset of the deficiency. Our findings would appear to confirm that a more severe metabolic impairment is correlated with a better therapeutic outcome.

Key words: growth hormone, adult growth hormone deficiency, metabolic alterations, growth hormone treatment

Resumen *Resultados en el mediano y largo plazo del tratamiento con hormona de crecimiento en adultos deficitarios de dicha hormona.* Evaluamos resultados terapéuticos a largo plazo en subgrupos de pacientes con deficiencia de hormona de crecimiento (GH) del adulto (AGHD) y la susceptibilidad para desarrollar eventos adversos. Estudiamos 59 pacientes con AGHD, 27 de inicio en la infancia (CO) (18-44 años, 12 mujeres) y 32 de inicio en la adultez (AO) (27-70 años, 18 mujeres). El HDL-colesterol mejoró significativamente en varones AGHD-AO (basal: 41.3 ± 12.9 mg/dl, intratratamiento: 47.5 ± 13.2 mg/dl, $p=0.009$). El análisis individual mostró que el colesterol total descendió por debajo de 240 mg/dl en el 33% de los AGHD-CO y en el 50% de los AGHD-AO, y por debajo de 200 mg/dl en el 67% de los pacientes AGHD-CO y en el 29% de los AGHD-AO; en el grupo AGHD-AO, se normalizó el LDL-colesterol (≤ 160 mg/dl) y los triglicéridos (≤ 200 mg/dl) en el 100% y 50% de los pacientes respectivamente; el índice colesterol total /HDL disminuyó por debajo de 4.5 en el 20% de los pacientes AGHD-CO y en el 25% de los AGHD-AO. La evaluación cardiológica mostró heterogeneidad intra e interindividual, con mejoría de la masa cardíaca en pacientes con valores menores a 60 g/m² pretratamiento. Se encontró incremento significativo en los parámetros de aposición ósea, sin modificaciones en los de resorción durante el tratamiento. Se evidenció correlación entre el incremento del contenido mineral óseo y la masa magra ($p=0.0009$). No se hallaron subgrupos más susceptibles para el desarrollo de eventos adversos. Nuestros hallazgos parecerían corroborar que la mayor gravedad de afectación metabólica se correlacionaría con una mejor respuesta terapéutica.

Palabras clave: hormona de crecimiento, deficiencia de hormona de crecimiento del adulto, alteraciones metabólicas, tratamiento con hormona de crecimiento

Adult growth hormone (GH) deficiency (AGHD) has been recognized as a clinical entity since the 1980's, when it was described as a syndrome characterized by altera-

tions in body composition, bone mineral density, lipid profile, decreased muscle strength and exercise performance, impaired heart function and structure with increased

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cardiovascular risk factors and impaired quality of life^{1, 2}. In a previous study, we observed differences in impairment in AGHD patients, which are mainly dependent on gender and on the time of onset of the deficiency, and thus confirm the heterogeneity of this syndrome³.

Even if some of the beneficial effects of GH replacement therapy have been recognized, there are still some controversies over the medium- and long-term impact of GH therapy on the various areas involved^{2, 4-6}.

The use of individualized GH dosages, adjusted according to insulin-like growth factor type I (IGF-I) levels, in contrast with earlier studies where fixed higher dosage schedules were used, resulted at present in a decreased incidence of adverse effects with an improved tolerance to treatment^{7, 8}.

The aim of this study was to evaluate the potential differences in the outcomes of long-term GH replacement therapy in different subsets of patients and to verify potential differences in susceptibility to adverse effects.

Materials and Methods

Fifty-nine patients with AGHD were included: 27 with childhood onset (CO) with an age range between 18 and 44 years old (12 females and 15 males) and 32 with adult onset (AO) with an age range between 27 and 70 years old (18 females and 14 males). The etiologies of GHD for AGHD-CO were: idiopathic (17); craniopharyngioma (5); perinatal trauma or asphyxia, meningitis, oligodendroglioma, cholesteatoma, and pinealoma (1 each). GHD etiologies for AGHD-AO were: non-functioning pituitary tumor (8); prolactinoma (6); Sheehan's syndrome (5); craniopharyngioma (4); Cushing's disease (2); pituitary epidermoid cyst (2); pituitary granuloma, hypophysitis, empty sella, acromegalia and idiopathic (1 each).

The diagnosis of AGHD was made by the Insulin Tolerance Test (ITT)⁹. In patients in whom this test was contraindicated, an arginine test was performed¹⁰. In patients with isolated deficiency and in idiopathic patients, both tests were performed. Only patients with severe GH deficiency, defined by a peak GH response < 3 µg/l to any of the stimulation tests, were enrolled⁹.

In the AGHD-CO group, 19 patients had received GH therapy in childhood, but had discontinued such therapy at least 1 year before their enrollment in the study.

All patients received GH therapy at a starting dose of 0.1 mg/day, adjusted trying to maintain IGF-I levels between 0 and 2 SDS for gender and age. In the AGHD-CO group, the maintenance dose (mean and range) was 0.52 mg/day (0.17-1.07) in females and 0.33 mg/day (0.13-0.67) in males; in the AGHD-AO group, the maintenance dose was 0.38 mg/day (0.13-0.8) in females and 0.31 mg/day (0.13 -0.67) in males.

At baseline and during the fourth year of replacement therapy, the following evaluations were performed in 36 of the patients, 14 AGHD-CO (18-43 yr, mean 31.3 yr) and 22 AGHD-AO (31-66 yr, mean 48.2 yr): Anthropometric parameters: body mass index (BMI) and waist circumference; lipids: total cholesterol (TC), HDL-cholesterol, LDL-cholesterol, triglycerides (TG) and total cholesterol/ HDL-cholesterol ratio; cardiological evaluation: 2D echocardiogram with mitral Doppler (Esaote Model AU3). Diastolic function (A/E waves ratio), systolic function (ejection fraction) and cardiac mass index (CMI) were evaluated.

In 38 patients, 14 AGHD-CO (19-44 yr, mean 34 yr) and 24 AGHD-AO (31-66 yr, mean 48.5 yr), bone formation and

resorption markers were measured at baseline and after 18 months of treatment: osteocalcin (RIA, Diagnostic Systems Laboratories, Inc., Webster, Texas, USA), bone-specific alkaline phosphatase (B-S ALP) and procollagen type I carboxyterminal propeptide (PICP), pyridinoline (Pyr) and deoxypyridinoline (DPyr) (Elisa, Metra Biosystems, Inc., Mountain View, CA, USA). In this group of patients, body composition was also evaluated at baseline and after 12-18 months of treatment by measuring the percentage of lean and fat mass with a Lunar DPX-L densitometer.

Two different assays were used to determine plasma levels of GH. First, an IRMA-Magnetic Solid Phase was used (Serono Maia Clone, Milan, Italy), calibrated against the 1st IRP 66/217. Then, a two-site chemiluminiscent enzyme immunometric assay (ICMA, Immulite, Diagnostic Products Corporation, Los Angeles, USA) was used, calibrated against the WHO IRP 80/505. The equation for the linear regression line comparing the two methods was $\log y = 0.9069 \log x + 0.3172$, where x was the IRMA and y was the ICMA (r: 0.9523). Serum IGF-I level was measured using IRMA after acid-ethanol extraction (Diagnostic Systems Laboratories, Inc., Webster, Texas, USA). Age -and sex-adjusted IGF-I values were obtained from a reference population obtained from blood donors: 384 serum samples from healthy adults (191 males and 193 females) with an age range between 18-70 years. The individual IGF-I standard deviation score (SDS) could then be calculated. SDS expresses the number of standard deviations away from the mean for the reference population.

Adverse events occurring during GH therapy were collected by means of a consistent questioning of subjects with regard to the occurrence of health-related events between visits, based on predesigned forms. Both GH-therapy possibly-related and possibly-unrelated events were recorded.

The statistical analysis was performed by the Wilcoxon test¹¹ to assess treatment response (baseline vs. intra-treatment), separately in AGHD-CO and AGHD-AO. HDL, body composition and waist circumference were separately analyzed for each gender in each group. The Chi-square test and Fisher's test were used to compare the prevalence of adverse events in each group¹¹. The correlation between bone mineral content and lean tissue percentage was analyzed by linear regression. These correlations were also compared to those from a control group (600 age-matched males and postmenopausal females) by means of an analysis of covariance (ANCOVA)¹². Results are expressed as median and range (between brackets) for IGF-I values, bone markers and bone mineral content since these variables follow a non-parametric distribution, and as mean ± standard deviation (SD), for anthropometric parameters, lipids, cardiological evaluation and body composition.

Written informed consent was obtained from all patients, and the Ethics and the Education and Research Committees approved the study.

Results

During GH therapy, serum IGF-I levels in the AGHD-CO group were 210 ng/ml (44-280) and 165 ng/ml (110-240) in females and males, respectively; in the AGHD-AO group, serum IGF-I levels were 170 ng/ml (18-340) and 240 ng/ml (40-440) in females and males, respectively. These levels, expressed as SDS, correspond to: 0.22 (-3.30 to 1.35) and 1.40 (-0.80 to 2.30) in the AGHD-CO group, in females and males, respectively, and to 0.61

(-5.80 to 2.80) and 0.95 (-3.60 to 5.90) in the AGHD-AO group, in females and males, respectively.

No difference was found in BMI between baseline and intra-treatment values (Table 1). In 20% of AGHD-CO patients and in 18% of AGHD-AO patients with elevated BMI at baseline (AGHD-CO: 26.1 ± 1.1 ; AGHD-AO: 26.9 ± 1.9), this index decreased to ≤ 25 kg/m² (AGHD-CO: 24.3 ± 0.9 ; AGHD-AO: 24.5 ± 0.7).

No differences were observed in waist circumference in any of the groups (Table 1). Normalization of waist circumference was observed (≤ 84 cm in females and ≤ 92 cm in males) in 33% and 25% of AGHD-CO patients, females and males respectively (baseline females: 87 ± 2.5 and males: 96.2 ± 1.9 ; intra-treatment females: 79.1 ± 2.9 and males: 89.7 ± 2.1). In 30% of AGHD-AO females a similar normalization was observed (baseline: 85.3 ± 2.1 ; intra-treatment: 81.5 ± 2.4).

Results of total cholesterol, HDL-cholesterol, triglycerides, LDL-cholesterol, and the total cholesterol/HDL-cholesterol ratio are shown in Table 1. A statistically significant intra-treatment improvement was found in HDL-cholesterol in males of the AGHD-AO group ($p = 0.009$).

The individual analysis showed that, in patients with elevated basal levels, total cholesterol decreased below 240 mg/dl but above 200 mg/dl in 33% of AGHD-CO patients and in 50% of AGHD-AO patients, and, in those with basal levels above 200 mg/dl, it decreases below this value in 67% of AGHD-CO patients and in 29% of AGHD-AO patients. In the AGHD-AO group, normalization of LDL-cholesterol (≤ 160 mg/dl) and triglycerides (≤ 200 mg/dl) was found in 100% and 50% of patients with elevated levels at baseline, respectively. Thirty-three percent of AGHD-AO patients with normal cholesterol

levels at baseline had increases above 160 mg/dl during treatment. The total cholesterol/HDL ratio decreased below 4.5 in 20% of AGHD-CO patients and in 25% of AGHD-AO patients.

None of the cardiological variables assessed showed significant changes after treatment (Table 2). The only finding was a consistent improvement in the CMI in patients (7) with lower baseline values (< 60 g/m²): 57 and 85 g/m², 51 and 59 g/m², 46 and 70 g/m², 53 and 89 g/m², 50 and 72 g/m², 57 and 85 g/m² and 57 and 72 g/m² (basal and intra-treatment respectively).

The individual analysis showed heterogeneity in the echocardiographic response. Nevertheless, an improvement in diastolic function was observed in 50% of AGHD-CO patients and in 86% of AGHD-AO patients.

No differences were found between baseline and intra-treatment values in percentages of fat and lean tissues (Table 3).

Results of osteocalcin, bone-specific alkaline phosphatase, procollagen type I carboxyterminal propeptide, pyridinoline, deoxypyridinoline and bone mineral content are shown in Table 3. A statistically significant intra-treatment increase was found in osteocalcin ($p = 0.037$) and procollagen type I carboxyterminal propeptide ($p = 0.026$) in the AGHD-CO group. In the AGHD-AO group, osteocalcin, bone alkaline phosphatase and procollagen type I carboxyterminal propeptide showed a statistically significant intra-treatment increase ($p = 0.008$). Correlations between bone mineral content and lean tissue percentage, both at baseline and during treatment, were significant ($p = 0.0009$) and did not differ significantly from the control group. Treatment resulted in a proportional increase in bone mineral content and lean mass in both

TABLE 1.— Antropometric parameters and lipid profile in AGHD patients (childhood onset: CO, adult onset: AO): baseline and intra-treatment (fourth year of GH replacement therapy) data.

	CO (n= 14)		AO (n= 22)	
	Basal	Intratreatment	Basal	Intratreatment
BMI	24.9 ± 3.7	25.9 ± 4.2	27.9 ± 5.3	28.0 ± 5.5
Females-waist circumference (cm)	75.8 ± 10.0	74.0 ± 10.0	86.1 ± 10.1	84.5 ± 11.5
Males-waist circumference (cm)	91.3 ± 7.3	91.7 ± 7.3	99.1 ± 10.3	98.1 ± 7.4
TC(mg/dl)	209.7 ± 43.8	203.8 ± 55.8	221.7 ± 51.1	216.6 ± 43.0
Females-HDL (mg/dl)	49.0 ± 25.6	46.9 ± 17.1	51.8 ± 14.5	52.2 ± 16.3
Males-HDL (mg/dl)	47.5 ± 14.9	44.1 ± 6.8	41.3 ± 12.9	47.5 ± 13.2*
TC / HDL ratio	5.0 ± 2.3	5.1 ± 1.7	5.0 ± 1.6	4.9 ± 2.5
TG (mg/dl)	142.7 ± 97.0	164.5 ± 76.1	170.5 ± 123.1	167.6 ± 117.6
LDL (mg/dl)	126.3 ± 37.9	134.3 ± 46.2	141.4 ± 46.1	137.4 ± 50.7

* $p = 0.009$

Results expressed as mean ± 1 SD.

TC: total cholesterol; HDL: HDL cholesterol; TC/HDL: total cholesterol / HDL cholesterol ratio; TG: triglycerides; LDL: LDL cholesterol.

TABLE 2.— *Cardiological evaluation in AGHD patients (childhood onset: CO, adult onset: AO): baseline and intra-treatment (fourth year of GH replacement therapy) data.*

	CO (n= 14)		AO (n= 22)	
	Basal	Intratreatment	Basal	Intratreatment
A/E waves ratio	0.63 ± 0.17	0.67 ± 0.19	0.87 ± 0.36	0.87 ± 0.36
Ejection fraction (%)	69.6 ± 7.0	70.0 ± 7.58	74.0 ± 5.4	74.0 ± 5.7
CMI (g/m ²)	75.3 ± 25.5	71.4 ± 11.9	77.3± 12.9	68.7 ± 10.0

Results expressed as mean ± 1 SD.

TABLE 3.— *Bone markers and body composition in AGHD patients (childhood onset: CO, adult onset: AO): baseline and intra-treatment (fourth year of GH replacement therapy) data.*

	CO (n= 14)		AO (n= 24)	
	Basal	Intratreatment	Basal	Intratreatment
Osteocalcin (ng/ml)	3.7 (1.0-12.0)	3.5* (2.0-16.0)	3.4 (1.0-7.4)	4.6# (2.9-21.0)
Bone alkaline phosphatase (U/l)	18.0 (6.0-32.0)	16.0 (12.0 - 92.0)	14.5 (7.0-47.0)	24.0# (13.0-70.0)
Procollagen type I carboxyterminal propeptide (ng/ml)	94.0 (50.0-216)	95.0** (67.0 - 648)	82.0 (47.0-198)	120# (72.0-276)
Pyridinoline (nM/mM creatinine)	23.5 (5.0-53.0)	22.0 (2.6-54.0)	30.0 (6.5-132)	31.0 (10.0-82.0)
Deoxypyridinoline (nM/mM creatinine)	6.0 (2.4-13.3)	5.5 (1.3-14.4)	6.0 (3.7-35.5)	6.5 (2.3-11.1)
Bone mineral content (g)	1950 (800-3000)	2090 (1700-2200)	2350 (1200-3800)	2680 (1300-3510)
% Lean mass females	58.30 ± 6.21	61.73 ± 4.65	56.93 ± 5.97	58.88 ± 6.36
% Lean mass males	63.27 ± 5.74	66.06 ± 7.10	67.32 ± 3.77	66.33 ± 3.87
% Fat mass females	38.3 ± 6.11	34.63 ± 4.82	39.86 ± 6.27	37.77 ± 6.66
% Fat mass males	33.33 ± 5.82	30.30 ± 7.53	29.08 ± 4.02	30.08 ± 3.99

* $p = 0.037$ vs. basal ; ** $p = 0.026$ vs. basal ; # $p = 0.008$ vs. basal

Results expressed as median and range (between brackets) for bone markers and bone mineral content, and as mean ± 1 SD for fat mass and lean mass.

genders; the curves intercepts remained unchanged. This effect was even more evident when only lower limbs measurements were considered (baseline $r = 0.938$, $p = 0.0009$; intra-treatment $r = 0.949$, $p = 0.0008$).

In the AGHD-CO group, 58% of females and 67% of males experienced adverse events during treatment. In the AGHD-AO group, adverse events were observed in 67% of females and in 50% of males.

Clinical adverse events reported in AGHD-CO females were: edema (4), myalgia, hypotension, depression, headache, arthralgia, abdominal pain (1 each); AGHD-CO males: myalgia (6), arthralgia (3), hypotension, edema, gastroenteritis, headache, trauma fracture, asthenia (2 each), diabetes (1); AGHD-AO females: arthralgia (9),

edema (8), headache (4), gastroenteritis (3), tiredness, depression, trauma fracture, hepatitis, toothache (2 each), hypotension, breast adenoma, acute myocardial infarction, urinary infection, hypercalciuria, Sjogren's syndrome, epigastric distress, fever, weakness, myalgia, bronchitis, metrorrhagia, anemia, diabetes, death due to stroke (1 each); and AGHD-AO males: myalgia, bronchitis, hepatitis, facial palsy, anemia, intermittent claudication, enlargement of residual pituitary tumor, sleep apnea, multiple atheromatosis, edema, gynecomastia, blood hypertension (1 each). Biochemical adverse events observed in AGHD-CO females were: elevated liver transaminases (1); AGHD-CO males: increased levels of total cholesterol, increased levels of LDL cholesterol, increased

triglycerides levels (4 each), elevated liver transaminases (2), increased glycosylated hemoglobin, increased total alkaline phosphatase (1 each); AGHD-AO females: increased levels of total cholesterol (5), increased triglycerides levels (4).

No differences were found in the frequency of occurrence of adverse events between any of the subsets evaluated.

Discussion

Since the GH deficiency syndrome was first described in adults over 15 years ago, various studies have shown that patients suffering from this condition have experienced a number of alterations, as compared to age- and sex-matched healthy subjects. In patients with panhypopituitarism under standard hormone replacement other than GH, some authors reported an increased mortality rate related to an increased incidence of atherosclerosis^{13, 14}. GH deficiency might play a role in this increase, possibly due to an increased abdominal adiposity and associated dyslipidemia. Various studies in which GH replacement therapy has been evaluated in GH deficient subjects have reported a marked improvement in the short-term in body composition^{4, 5, 15}, lipid profile^{16, 17} and quality of life^{18, 19}. However, data in the literature, as well as our data, show, in some aspects, controversial medium- and long-term outcomes. These discrepancies were first attributed to the use of inadequate replacement doses. On the one hand, excessively high doses were used (even with weight- and body surface area-adjusted dosages), which might account for many of the adverse effects observed. On the other hand, suboptimal doses have been associated with inadequate treatment responses²⁰. Therefore, it has been suggested that the GH dosage should be adjusted to IGF-I concentrations. But IGF-I measurements expressed in absolute values showed some limitations. These limitations appear to be related to the wide range of IGF-I values in normal populations, with a resulting overlapping between healthy subjects and GH-deficient subjects, to circadian variations in plasma levels, and to the variability and reproducibility depending on the various measurement methods employed. For this reason, and to overcome some of these limitations, it has been suggested that values of IGF-I should be expressed in terms of SDS²¹ and should be maintained at approximately the 50th percentile, within 2 SD of the mean, in patients on GH therapy²². However, even the normalization of these parameters in the follow-up of patients has not been enough to solve all the controversies, and there is still a considerable heterogeneity in therapeutic outcomes. In our study, we succeeded in maintaining satisfactory IGF-I levels in most patients, but despite this, and in agreement with other authors' reports, outcomes have been

clearly variable²³. Some patients had IGF-I levels outside target values at some moment during follow-up. A clear example is the variability in the results reported in the literature with regard to the lipid profile^{24, 25}. We have found a significant improvement in HDL-cholesterol levels only in the group of AGHD-AO males. However, the individual analysis showed that in a considerable number of patients, lipid parameters were clearly improved and even normalized in many of them. This could be partly attributed to a different response to treatment due to a different individual sensitivity, based on the degree of metabolic impairment, the severity of somatotropin deficiency, etc. This could be also explained by the fact that patients may often change their eating habits and physical activity lifestyle during follow-up, particularly in medium- and long-term studies such as this one. Some of these considerations might also account for the variability in the results obtained in body composition. Finally, we should highlight the limitations in the comparison between different studies, given the high percentage of biological and analytical variability observed in plasma lipid measurements. In this respect, coefficients of variation of up to 37% have been reported for triglycerides, 18.6% for LDL-cholesterol, 23.6% for HDL-cholesterol and 12.4% for total-cholesterol²⁶.

The cardiological evaluation showed inter- and intra-individual heterogeneity, a finding that appears to be consistent in the interpretation of results²⁷. In practice, this means that not all patients from a same group have a homogeneous behavior, but we have also observed that many patients did not show an identical response pattern in the medium and long term. Even if there is no clear explanation for this variability, it may be speculated that the difference in response is possibly related to variations in the concentration of GH receptors in the myocardium. It has been shown that by interacting with circulating GH, such receptors stimulate local biosynthesis of IGF-I, which acts in an autocrine or paracrine manner by binding to high-affinity sarcolemmatic receptors²⁸. An exception to the heterogeneity reported above was the pretty consistent improvement in cardiac mass in patients with cardiac mass index values below 60 g/m².

As regards bone mineral metabolism, we found a significant increase in apposition parameters, with no changes in resorption parameters during GH treatment. At least part of the bone anabolic effect of GH therapy is likely to be due to the increased muscle mass. In agreement with other authors, we were able to show a very good correlation between increased bone mineral content and increased lean mass²⁹.

The high rate of adverse events is common to all pharmacovigilance studies, where both possibly-related and possibly-unrelated events are collected. Forty-five percent of adverse events could be considered to be possibly related to therapy. Most of them (94%) were mild

and transient in nature, and generally dependent on fluid retention. The moderate prevalence of these events might be dependent on the initiation of treatment at low doses and on the dose adjustment according to IGF-I levels. Unlike other reports in the literature, we have not found susceptibility to adverse events to be dependent either on gender or on the time of onset of the deficiency³⁰. However, because of the three possibly-related serious adverse events observed (two cases of diabetes and one of enlargement of residual pituitary tumor), high risk patients should be carefully monitored. As regards the patient who died due to a stroke, it is doubtful whether this should be considered as an adverse event since the patient had a history of vascular disease.

To sum up, from our findings and reports in the literature it can be inferred that the beneficial effects of GH replacement therapy in GH-deficient adults are mainly evidenced in subjects with a greater degree of impairment in each area (in our experience: cardiovascular parameters and lipid abnormalities). In the same way as in GH-deficient children a lower growth rate is one of the variables related to a better response to treatment, it is possible that in adults a more severe metabolic impairment may be correlated with a better outcome. This has already been shown in some areas such as quality of life (not assessed in this work)^{31, 32}.

In conclusion, GH therapy is beneficial in deficient adults as replacement therapy, regardless of the time of onset of the deficiency (prepubertal period or adulthood). Other indications for GH therapy are being investigated and probably some of the ongoing studies may demonstrate further beneficial effects. Although replacement therapy started to be used in deficient adults over fifteen years ago, there are still unsettled issues regarding its long-term benefits and its influence on morbidity and mortality.

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Nunca nos cansaremos de criticar a quienes deforman el pasado, lo reescriben, lo falsifican, exageran la importancia de un acontecimiento o callan otro; estas críticas están justificadas (no pueden no estarlo), pero carecen de importancia si no van precedidas de una crítica más elemental: la crítica de la memoria humana como tal. Porque, la pobre, ¿qué puede hacer ella realmente? Del pasado, sólo es capaz de retener una miserable pequeña parcela, sin que nadie sepa por qué exactamente ésta y no otra, pues esa elección se formula misteriosamente en cada uno de nosotros ajena a nuestra voluntad y nuestros intereses. No comprenderemos nada de la vida humana si persistimos en escamotear la primera de todas las evidencias: una realidad, tal cual era, ya no es; su restitución es imposible.

Milan Kundera

La ignorancia (2000), Buenos Aires: Fábula Tusquets, 2004, p 128