

## ADULT GROWTH HORMONE DEFICIENCY

## METABOLIC ALTERATIONS AND EVALUATION OF DIFFERENT RISK GROUPS

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**Abstract** Adult growth hormone deficiency (AGHD) is an heterogeneous clinical entity characterized by increased cardiovascular morbidity and mortality, alterations in body composition, osteoporosis and impaired quality of life. In order to characterize higher risk subpopulations we studied 77 patients with AGHD, 35 with childhood onset (AGHD-CO): CA 18-44 yr.; 13 females and 22 males, and 42 with adult onset (AGHD-AO): CA 25-70 yr.; 22 females and 20 males. IGF-I, lipid profile, glycemia and glycosylated hemoglobin were measured. Cardiological evaluation: blood pressure, electrocardiogram, ergometry and 2D echocardiogram with mitral Doppler, evaluation of diastolic function (A/E waves ratio and deceleration time), systolic function (ejection and shortening fractions) and Cardiac Mass Index (CMI). The Body Mass Index and waist circumference were recorded. Total body composition and bone mineral density were evaluated by densitometry, and the following bone markers were measured: osteocalcin, bone-specific alkaline phosphatase, carboxyterminal propeptide of type I procollagen, Pyridinoline and Deoxypyridinoline. The subset of females with AGHD-AO had higher levels of total cholesterol: 240 mg/dl (156-351) ( $p < 0.005$ ), LDL: 140 mg/dl (62-262) ( $p < 0.04$ ) and of total cholesterol / HDL: 4.04 (3.12-12.7) ( $p < 0.04$ ); while females with AGHD-CO had a decreased CMI: 62 g/m<sup>2</sup> (53-107) ( $p < 0.01$ ), lower A/E waves ratio: 0.56 (0.39-0.72) ( $p < 0.01$ ) and lower deceleration time: 164 msec. (135-210) ( $p < 0.01$ ). The subset of males with AGHD-AO had a greater waist circumference: 98 cm (83-128) ( $p < 0.03$ ) and males with AGHD-CO had a lower shortening fraction: 41% (30-49) ( $p < 0.006$ ) and lower deceleration time: 153.5 msec. (127-230) ( $p < 0.03$ ). In both genders, the bone mineral content was lower in patients with AGHD-CO (females  $p < 0.02$ , males:  $p < 0.0008$ ). Our findings confirm the differences in impairment in AGHD patients, which are mainly dependent on gender and the time of onset of the deficiency, and thus demonstrate the heterogeneity of the syndrome.

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

**Resumen** *Deficiencia de hormona de crecimiento en el adulto. Alteraciones metabólicas y evaluación de diferentes grupos de riesgo.* El déficit de hormona de crecimiento (GH) del Adulto (AGHD) es una entidad clínica heterogénea caracterizada por incremento de la morbimortalidad cardiovascular, cambios en la composición corporal, osteoporosis y deterioro de la calidad de vida. Para caracterizar subpoblaciones con mayor riesgo de afectación, estudiamos 77 pacientes AGHD, 35 de inicio en la infancia (AGHD-CO): EC 18-44 a; 13 mujeres y 22 varones, y 42 de inicio en la adultez (AGHD-AO): EC 25-70 a; 22 mujeres y 20 varones. Se midió IGF-I, perfil lipídico, glucemia y hemoglobina glicosilada. Evaluación cardiológica: tensión arterial, electrocardiograma, ergometría y ecocardiograma bidimensional con Doppler mitral, evaluando función diastólica (relación ondas A/E y tiempo de desaceleración), función sistólica (fracciones de eyección y acortamiento) e índice de masa cardíaca (IMC). Se registró el índice de masa corporal y la circunferencia de cintura. Se evaluó, mediante densitometría, la composición corporal total y la densidad mineral ósea y se dosaron marcadores óseos: osteocalcina, fosfatasa alcalina fracción ósea, propéptido tipo I carboxiterminal del procolágeno, Pyridinolina y Deoxypyridinolina. El subgrupo de mujeres AGHD-AO presentó mayores niveles de colesterol total: 240 mg/dl (156-351) ( $p < 0.005$ ), LDL: 140 mg/dl (62-262) ( $p < 0.04$ ) y de colesterol total / HDL: 4.04 (3.12-12.7) ( $p < 0.04$ ); mientras que las mujeres AGHD-CO presentaron menor IMC: 62 g/m<sup>2</sup> (53-107) ( $p < 0.01$ ), menor relación A/E: 0.56 (0.39-0.72) ( $p < 0.01$ ) y menor tiempo de desaceleración: 164 msec (135-210) ( $p < 0.01$ ). El subgrupo de varones AGHD-AO presentó mayor circunferencia de cintura: 98 cm (83-128) ( $p < 0.03$ ) y los varones AGHD-CO, menor fracción de acortamiento: 41% (30-49) ( $p < 0.006$ ) y menor tiempo de desaceleración: 153.5 msec (127-230) ( $p < 0.03$ ). En ambos sexos, el contenido mineral óseo fue menor en los pacientes AGHD-CO (mujeres  $p < 0.02$ , varones:  $p < 0.0008$ ). Nuestros hallazgos confirman la diferente afectación de los pacientes AGHD, en particular en relación al sexo y al momento de inicio de la deficiencia, demostrando la heterogeneidad del síndrome.

**Palabras clave:** hormona de crecimiento, déficit de hormona de crecimiento del adulto, alteraciones metabólicas

Adult growth hormone (GH) Deficiency (AGHD) started to be recognized as a clinical entity in the late 80's<sup>1,2</sup>. When a syndrome was defined in hypopituitary patients characterized by increased cardiovascular morbidity and mortality, premature atherosclerosis with changes in lipid profile and in insulin sensitivity, alterations in body composition including increased fat mass, reduced lean body mass and redistribution of body water, reduced physical performance, osteoporosis and impaired quality of life<sup>3-7</sup>. Two groups of patients were identified: those with childhood onset GH deficiency (AGHD-CO) and those with adult onset GH deficiency (AGHD-AO). Later, the heterogeneity of the clinical presentation was confirmed in both groups of patients. Such heterogeneity is attributed not only to the onset but also to the etiology (functional or organic), the duration and severity of the deficiency, gender and impairment of other pituitary hormones<sup>8, 9</sup>.

Based on our recent experience in a multicenter study on the follow-up of AGHD patients, we attempted to make a critical analysis of the degree of clinical, metabolic, cardiovascular and bone impairment in the different subsets of patients evaluated, in order to characterize different higher risk subpopulations.

## Material and Methods

A total of 77 patients were studied: 35 AGHD-CO, with an age range between 18 and 44 years (13 females and 22 males), and 42 AGHD-AO, between 25 and 70 years (22 females and 20 males). The etiologies of the deficiency for AGHD-CO were: idiopathic (n = 22); craniopharyngioma (n = 6); perinatal trauma or asphyxia (n = 2); meningitis, oligodendroglioma, cholesteoma, empty sella and pinealoma (n = 1 each). The etiologies for AGHD-AO were: non-functioning pituitary tumor (n = 15); prolactinoma (n = 7); Sheehan's syndrome (n = 4); craniopharyngioma (n = 4); Cushing's disease (n = 3); pituitary epidermoid cyst (n = 2); pituitary granuloma, hypophysitis, empty sella, myoblastoma, dysgerminoma, acromegalia and idiopathic (n = 1 each).

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

The diagnosis of AGHD was made by the Insulin Tolerance Test (ITT)<sup>10</sup>, and in patients in whom this test is contraindicated, an arginine test was performed<sup>11</sup>. In patients with isolated or idiopathic deficiency, 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 enrolled<sup>10</sup>. The following parameters were evaluated in all patients: total cholesterol, HDL, LDL, triglycerides, total cholesterol/HDL ratio, glycemia and glycosylated hemoglobin A1 or A1C. 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 1<sup>st</sup> 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  $\log Y = 1.03 \cdot \log X - 0.09$ , where X was the IRMA and Y was the ICMA (r = 0.97; standard error of estimate = 0.11). 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 of 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 SD scores could then be calculated. Cardiological evaluation included systolic and diastolic blood pressure, electrocardiogram, ergometry and 2D echocardiogram with mitral Doppler (*Esaote Model AU3*). Diastolic function (A/E waves ratio and deceleration time), systolic function (ejection fraction and shortening fraction) and cardiac mass index (CMI) were evaluated. The body mass index (BMI) and waist circumference were recorded. Total body composition: lean body mass (LBM), fat mass and bone mineral content (BMC) were evaluated, and bone mineral density (BMD) was measured at the lumbar spine, femoral neck and for total body with a Lunar DPX-L densitometer. As the population studied included patients under 20 and older than 65, in all cases the BMD was expressed as Z-score to make the sample homogeneous. In 10 AGHD-CO and 21 AGHD-AO patients, bone formation markers were measured: Osteocalcin (RIA, *Diagnostic Systems Laboratories, Inc., Webster, Texas, USA*), bone-specific alkaline phosphatase (BS AP) and carboxyterminal propeptide of type I procollagen (PICP) (*Elisa, Metra Biosystems, Inc., Mountain View, CA, USA*). Bone resorption markers: Pyridinoline (Pyr) and Deoxypyridinoline (DPyr) (*Elisa, Metra Biosystems, Inc., Mountain View, CA, USA*) were measured in 8 AGHD-CO and 19 AGHD-AO patients.

The statistical analysis was performed by the Mann-Whitney test<sup>12</sup> to compare the various variables between AGHD-CO vs. AGHD-AO separated by gender, except for bone markers, where data were analyzed by comparing AGHD-CO vs. AGHD-AO with no separation by gender. BMC was correlated vs. LBM by the Spearman rank order correlation test<sup>13</sup>.

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

## Results

### Clinical Characteristics

Results of BMI, waist circumference, systolic and diastolic blood pressure are shown in Table 1. Out of 13 females, 7 (54%) in the AGHD-CO group had a BMI > 25 kg/m<sup>2</sup>, 5 of them (39%) had a BMI consistent with increased cardiovascular risk (BMI > 27 kg/m<sup>2</sup>) and 3 of these 5 females (23%) had obesity (BMI > 30 kg/m<sup>2</sup>). Out of 22 females, 15 (68%) in the AGHD-AO group had a BMI > 25 kg/m<sup>2</sup>, 10 of them (46%) had a BMI > 27 kg/m<sup>2</sup> and 6 of these 27 females (27%), had a BMI > 30 kg/m<sup>2</sup>. Out of 22 males, 13 (59%) in the AGHD-CO group had a BMI > 25 kg/m<sup>2</sup>, 9 of them (4%) had a BMI > 27 kg/m<sup>2</sup> and 4 of these 9 males (18%), had a BMI > 30 kg/m<sup>2</sup>. Out of 20 males, 15 (75%) in the AGHD-AO group had a BMI > 25 kg/m<sup>2</sup>, 12 of them (60%) had a BMI > 27 kg/m<sup>2</sup> and 7 of these 12 males (35%), had a BMI > 30 kg/m<sup>2</sup>.

Waist circumference consistent with central obesity (> 84 cm in females and > 92 cm in males) was found in 7/13 (54%) AGHD-CO females, 10/22 (46%) AGHD-AO

females, 8/22 (36%) AGHD-CO males and 16/20 (80%) AGHD-AO males.

Increased systolic blood pressure ( $\geq 140$  mmHg) was observed in 3/13 (23%) AGHD-CO females and in 4/22 (18%) AGHD-AO females. Increased systolic and diastolic blood pressure ( $\geq 95$  mmHg) was observed in 1/22 AGHD-CO males, while in AGHD-AO males, systolic blood pressure was elevated in 5/20 (25%) and diastolic blood pressure was elevated in 3/20 (15%).

#### IGF-I measurement (Table 1)

IGF-I SDS was below the reference values for the normal population (below - 2 SDS) in 12/13 AGHD-CO females (92%), in 20/22 AGHD-AO females (91%), in 19/22 AGHD-CO males (86%) and in 14/20 AGHD-AO males (70%).

#### Lipid Profile and Carbohydrate Metabolism

Results of total cholesterol, LDL, HDL, total cholesterol/HDL ratio, triglycerides, glycemia and glycosilated hemoglobin are shown in Table 1.

Total cholesterol levels above 200 mg/dl were observed in 2/13 AGHD-CO females (18%), in 14/22 AGHD-AO females (65%), in 16/22 AGHD-CO males (71%) and in 13/20 AGHD-AO males (64%), and levels above 240 mg/dl were observed in 10/22 AGHD-AO females (47%), in 5/22 AGHD-CO males (24%) and in 9/20 AGHD-AO males (45%).

LDL values were increased ( $> 160$  mg/dl) in 9/22 AGHD-AO females (39%), in 9/22 AGHD-CO males (42%) and in 10/20 AGHD-AO males (50%) and HDL levels were decreased ( $< 45$  mg/dl in females and  $< 35$  mg/dl in males) in 3/13 AGHD-CO females (20%), in 5/22 AGHD-AO females (24%), in 8/22 AGHD-CO males (36 %) and in 6/20 AGHD-AO males (30%).

Total cholesterol/HDL ratio  $> 4.5$  (consistent with increased cardiovascular risk) was observed in 3/13 AGHD-CO females (20%), in 8/22 AGHD-AO females (35%), in 14/22 AGHD-CO males (65%) and in 14/20 AGHD-AO males (70%).

Triglycerides levels above 200 mg/dl were observed in none of the AGHD-CO females, in 3/22 AGHD-AO females (14%), in 9/22 AGHD-CO males (42%) and in 4/20 AGHD-AO males (18%).

TABLE 1.- Adult Growth Hormone Deficiency (AGHD): anthropometric, biochemical and cardiological parameters (values expressed as median and range)

	Females		Males	
	AGHD-CO (n: 13)	AGHD-AO (n:22)	AGHD-CO (n:22)	AGHD-AO (n:20)
Talla (cm)	148 (130-159)	156 (145-174) *	155 (138-181)	170 (153-196) ##
BMI (kg / m <sup>2</sup> )	25.3 (16-41)	26.8 (19-43)	26 (17.1-42.2)	28.7 (22.6-36.3)
Waist circumference (cm)	85 (57-105)	85 (68-134)	92 (71-123)	98 (83-128) **
Diastolic blood pressure (mmHg)	80 (60 - 90)	80 ( 65 - 90)	70 (50-100)	80 (58-100)
Systolic blood pressure (mmHg)	115 (100-150)	120 (105-140)	120 (90-150)	120 (88-150)
IGF-I (SDS)	-7.47 (-10 a -1.7)	-2.91 * (-5.59 a 0.23)	-5.00 (-10.5 a -0.54)	-2.95 ** (-6.7 a 0.93)
Total cholesterol (mg/dl)	187 (141-220)	240 (156-351) *	224 (151-350)	232 (131-280)
LDL cholesterol (mg/dl)	106.5 (66-132)	140 (62-262) ***	155 (77-189)	148.5 (61-204)
HDL cholesterol (mg/dl)	61.5 (34-78)	50 (20-79)	39 (22-69)	42 (17-76)
Total cholesterol / HDL ratio	3.02 (2.5-4.79)	4.04 *** (3.12-12.7)	4.82 (2.19-10)	6.18 (3.45-9.71)
Triglyceride (mg/dl)	71 (40-130)	117 (59-902)	144 (48-1146)	166 (95-564)
Fasting glycemia (mg/dl)	86 (69-102)	77 (56-106)	85 (59-105)	79 (60-105)
Glycosilated hemoglobin (%)	5.2 (4.5-5.8)	5.15 (4.4-7.8)	5.3 (4.5-7)	5.5 (4.5-8)
Cardiac Mass Index (g/m <sup>2</sup> )	62 (53-107)	89 (57-120) #	76 (41-118)	84 (52-177)
Ejection fraction (%)	59.5 (56-77)	59 (51-69)	63 (45-75)	60 (48-71)
Fractional Shortening (%)	43 (29-48)	46 (36-52)	41 (30-49)	43 (25-51) ##
A/E waves ratio	0.56 (0.39-0.72)	0.79 # (0.41-1.94)	0.59 (0.46-1.95)	0.85 (0.41-1.39)
Deceleration time (msec.)	164 (135-210)	203.5 # (142-249)	153.5 (127-230)	188.5 ** (156-277)

\*  $p < 0.005$  vs. CO females

\*\*\*  $p < 0.04$  vs. CO females

#  $p < 0.01$  vs. CO females

\*\*  $p < 0.03$  vs. CO males ##  $p < 0.006$  vs. CO males

No AGHD-CO female patient had total cholesterol levels above 240 mg/dl, LDL levels above 160 mg/dl or triglycerides above 200 mg/dl.

In all cases glycemia and glycosilated hemoglobin levels were within normal reference values for each method used.

### Cardiological evaluation

Results of CMI, ejection fraction, fractional shortening, A/E waves ratio and deceleration time are shown in Table 1.

A trend towards a restrictive echocardiographic pattern of diastolic function (A/E waves ratio < 0.84) was observed in 12/13 AGHD-CO females (92%), in 11/22 AGHD-AO females (50%), in 18/22 AGHD-CO males (82%) and in 8/20 AGHD-AO males (40%). A prolonged diastolic function pattern (A/E waves ratio > 1.00) was observed in none of the AGHD-CO females, 7/22 AGHD-AO females (32%), in 2/22 AGHD-CO males (9%) and in 4/20 AGHD-AO males (20%).

A mild decreased in ejection fraction (< 50%) was observed in 1 AGHD-CO male and in 2 AGHD-AO males.

Decreased CMI (< 90 g/m<sup>2</sup>) was observed in 11/13 AGHD-CO females (85%), in 11/22 AGHD-AO females (50%), in 12/22 AGHD-CO males (55%) and in 11/20 AGHD-AO males (55%). CMI consistent with cardiac hypertrophy was observed only in 1 AGHD-AO male patient (> 130 g/m<sup>2</sup>).

### Body composition, BMD and Bone Markers

Results of body composition and BMD are shown in Table 2.

A positive correlation was found between bone mineral content (BMC) and lean body mass ( $r = 0.84$ ,  $p = 0.001$ ).

Serum and Urinary bone turnover markers could be measured in 10 AGHD-CO patients and in 21 AGHD-AO patients; therefore results (median and range) are described for both genders as a whole. Serum osteocalcin levels ( $\mu\text{g/L}$ ) were: 3.65 (1.10-12.00) for AGHD-CO and 3.50 (1.00-7.40) for AGHD-AO; BS AP levels (U/L) were 19 (6-32) for AGHD-CO and 14 (7-47) for AGHD-AO, while PICP levels ( $\mu\text{g/L}$ ) were 96 (50-216) for AGHD-CO and 82 (47-198) for AGHD-AO. Urinary Pyr levels (nM/nM of creatinine) were 23.5 (5.0-53.0) for AGHD-CO and 30 (6.5-132) for AGHD-AO and Dpyr levels (nM/nM of creatinine) were 6 (2.4-13.3) for AGHD-CO and 6 (3.7-35.5) for AGHD-AO. Osteocalcin levels were below reference values in AGHD-CO: 3/10 (30%) and in AGHD-AO: 13/21 (62%). PICP levels were decreased in 3/10 (30%) AGHD-CO patients and in 6/21 (29%) AGHD-AO patients, and increased in 1/10 AGHD-CO patients and in 1/21 AGHD-AO patients. BS AP was decreased in 1/10 AGHD-CO patients and in 7/21 (33%) AGHD-AO patients, and increased in 1 AGHD-AO patient. Pyr levels were decreased in 3/10 (30%) AGHD-CO patients and in 4/21 (19%) AGHD-AO patients, and increased in 4/10 (40%) AGHD-CO patients and in 8/21 (38%) AGHD-AO patients. Dpyr was elevated in 5/10 (50%) AGHD-CO patients and in 7/21 (33%) AGHD-AO patients. No significant differences were found in any of these parameters between AGHD-CO and AGHD-AO.

### Discussion

Since the publication of the first papers reporting increased cardiovascular morbidity and mortality in hypopituitary patients receiving replacement therapy for all hormone deficiencies except for somatotropin deficiency, many authors have reported alterations in the lipid, carbohydrate and phosphocalcium metabolism and

TABLE 2.- Adult Growth Hormone Deficiency (AGHD): Body composition and densitometry (values expressed as median and range)

	Females		Males	
	AGHD-CO (n: 13)	AGHD-AO (n: 22)	AGHD-CO (n: 22)	AGHD-AO (n: 20)
Lean body mass (%)	51.9 (40.9-65.1)	54.3 (39.8-67.5)	66.4 (52.5-77.5)	67.4 (59.2-73.6)
Fat mass (%)	44.2 (30.6-55.8)	43.1 (29-58.4)	29.8 (18.6-44.8)	29.4 (22.4-37.6)
BMD at L2 - L4	-1.99	-1.56	-1.38	-0.23
(Z-score)	(-3.45 to -0.20)	(-3.17 to 1.23)	(-3.63 to 1.39)	(-3.65 to 2.83)
BMD at femoral neck	-1.22	-0.88	-0.81	-0.83
(Z-score)	(-2.70 to 0.20)	(-3.60 to 1.19)	(-3.29 to 1.30)	(-2.92 to 0.81)
BMD for total body	-0.86	-0.52	-1.10	-1.04
(Z-score)	(-2.70 to 0.80)	(-3.04 to 1.57)	(-3.67 to 1.00)	(-1.65 to 1.35)
BMC (kg)	1.7 (1.4-2.6)	2.1 (1.2-2.8) *	2.2 (1.6-3.0)	2.85 (1.8-3.8) #

\*  $p < 0.02$  vs. CO females, #  $p < 0.0008$  vs. CO males

in the quality of life<sup>1-7</sup>. Different subsets of patients who are at different risk levels of impairment in each of the aforementioned areas have been identified. The two clearly defined groups include patients with childhood onset GH deficiency and patients with adult onset GH deficiency<sup>8, 9, 14</sup>. Possible gender-dependent differences in impairment have also been reported<sup>14, 15</sup>. Despite the long time elapsed and the large number of publications, many doubts still persist. For this reason, a critical re-evaluation of the degree of impairment of the various parameters has been proposed.

As alterations secondary to GHD have been well characterized in severe deficiencies but not in partial GH deficiencies, we have only included those patients with a GH response below 3 µg/L, as recommended by various international consensus<sup>10, 16</sup>. Severe GH deficiency in our patients would be confirmed by the high percentage of patients with IGF-I levels below -2 SDS, which correlates with low GH secretion. Our AGHD-CO patients had IGF-I levels significantly lower than AGHD-AO patients, as reported by many authors<sup>8, 17, 18</sup>. This could be attributed to the fact that many AGHD-CO patients might have a more severe and/or more prolonged somatotropin deficiency.

It is interesting to highlight the significant tendency towards overweight and obesity in our patients, since only 25% to 46% of patients, depending on the subset evaluated, had a BMI consistent with normal weight, a finding supported by many authors<sup>19, 20</sup>. In agreement with this finding, our patients showed a high percentage of fat mass with a concomitant decrease in lean body mass, which was equally observed in AGHD-CO and AGHD-AO patients of both genders. However, Korangy et al.<sup>21</sup> reported an increase in body fat percentage greater than predicted in AGHD-CO patients, in spite of not having found any differences in absolute values of body fat between AGHD-CO and AGHD-AO patients. This is aggravated by the important prevalence of central obesity, found in up to 80% of our AGHD-AO male patients and evaluated by increased waist circumference. It is well known that this fact is associated to increased cardiovascular morbidity and mortality, as shown in epidemiological studies<sup>22-24</sup>. Therefore, some authors<sup>3, 25</sup> have established an analogy between AGHD and the endocrine-metabolic syndrome reported by Reaven<sup>26</sup> in 1988. As regards carbohydrate metabolism, none of our patients showed alterations in fasting glycemia or glycosylated hemoglobin.

GH influences both production and secretion of lipoproteins by the liver and their plasma clearance<sup>25</sup>. This would partly account for the high percentage of patients (over 50%) with total cholesterol levels above 200 mg/dl and total cholesterol / HDL ratio above 4.5. This would be worsened by the fact that approximately one-third of our patients had elevated LDL levels. The lower percentage

of alterations in lipid and lipoprotein levels found in AGHD-CO females is worth noting. This could possibly be attributed to the higher prevalence of isolated and idiopathic GHD in this subgroup, with other axes, specially the gonadotropic axis, being unimpaired. The significance difference in chronological ages between groups should also be noted.

In our experience, a variable percentage of patients of both genders showed a mild increase in systolic blood pressure. However, elevated diastolic blood pressure was detected only in some males. Multicenter studies have reported hypertension in 26% of AGHD patients<sup>20</sup>, which is similar to the prevalence of hypertension in the general population<sup>27</sup>. Hypertension in some of these patients could be attributed to the impaired vascular reactivity related to a defect in the generation and/or metabolism of nitride oxide in the vascular wall<sup>28, 29</sup>.

The high prevalence of impaired diastolic function was noticeable, with a predominance of restrictive patterns in AGHD-CO patients and a larger number of cases with prolonged pattern in AGHD-AO patients. The predominance of restrictive pattern in AGHD-CO patients (physiological during childhood) could be assumed to be related to certain difficulty in diastolic function maturation due to somatotropin deficiency<sup>30</sup>. As the prolonged diastolic pattern is frequently observed during aging, a relatively early diastolic function impairment could possibly be assumed in our AGHD-AO patients. Some papers report variable percentages of patients with impaired systolic function<sup>31, 32</sup>, while others do not find such impairment<sup>33</sup>. In our experience, we found only a small number of male patients with a minimal decrease in the ejection fraction both in the AGHD-CO and AGHD-AO group. It is interesting to point out that in our series the percentage of patients with reduced cardiac mass exceeded 50%, reaching 85% in females of the AGHD-CO group. The GH / IGF-I system targets and activates specific high affinity sarcolematic receptors and induces multiple signal transduction pathway which results in an increased protein synthesis and promotes myocyte cell mass growth<sup>34</sup>. This would partly account for the reduced cardiac mass found in our AGHD patients.

Our patients showed a clear tendency towards abnormally low values of bone mineral density both at the lumbar spine and femoral neck. Bone mineral content values were lower in the AGHD-CO group than in the AGHD-AO group, for both genders; this could be partly due to the smaller size of bones in these patients due to their shorter stature. It is accepted that GH plays an important role in the acquisition of an adequate peak bone mass, even after completing lineal growth, and in maintaining such bone mass during adulthood<sup>35</sup>. Hypopituitary AGHD-AO patients receiving standard endocrine replacement therapy have been reported to have osteopenia, as compared to age-matched healthy

controls<sup>36, 37</sup>. An increased incidence of osteoporotic fractures has also been observed in this group of patients<sup>38</sup>; furthermore, some data indicate that the severity of bone loss would be proportional to the degree of GH deficiency<sup>35</sup>. On the other hand, bone remodeling activity can be evaluated by measuring bone formation and resorption markers. Many studies resulted in controversial data when measuring these markers<sup>8, 39, 40</sup>. In our experience, 30% of patients showed a clear decrease in bone formation markers, and an increase in bone resorption markers, which accounts for the decrease observed in bone mineral content. However, this finding has not been consistent, since some cases had increased markers of bone apposition and decreased markers of bone resorption. The correlation observed between bone mineral content and lean body mass (primarily an expression of muscular tissue) could be supported by the "mechanostat theory", which proposes that because of a biomechanical effect, the greater the muscular mass, the higher the bone mineral content<sup>41</sup>.

The importance of maintaining normal GH concentrations throughout life has been well established. Many papers have been published and much information is available on severe GH deficiency in adults. Data on morbidity and mortality, impaired bone metabolism, prevalence of metabolic and cardiovascular risk factors and quality of life have accumulated in recent years. Our findings confirm the differences in impairment in AGHD patients, which are mainly dependent on gender and the time of onset of the deficiency, and thus demonstrate the heterogeneity of the syndrome.

At present, GH replacement therapy can be considered to be safe, given the scarce adverse effects. It is also considered as a supplement to other replacement therapies for other impaired axes in pituitary patients<sup>40</sup>. However, the evaluation of the effects of medium and long-term treatment on the various areas involved will make it possible to clarify the benefits and risks of extending therapy to all patients with AGHD.

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#### FE DE ERRATA

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ANALISIS DEL SIGNO DE HOOVER EN RELACION CON PARAMETROS FUNCIONALES, RADIOGRAFICOS Y DE RADIO DE CURVATURA EN PACIENTES CON ENFERMEDAD PULMONAR OBSTRUCTIVA CRÓNICA

aparece un error en el apellido de uno de los autores:

en lugar de MARIA E. CAPRIA, CARLOS DE NEGRI, EDUARDO L. DE VITO

debe decir MARIA E. CAPRIA, CARLOS D'NEGRI, EDUARDO L. DE VITO