RESEARCH

Mapping the journey of transition: a single-center study of 170 childhood-onset GH deficiency patients

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Abstract

Objective: To analyze metabolic parameters, body composition (BC), and bone mineral density (BMD) in childhood-onset GH deficiency (COGHD) patients during the transition period (TP).

Design: Single- center, retrospective study was performed on 170 consecutive COGHD patients (age 19.2 ± 2.0 years, range 16–25) transferred after growth completion from two pediatric clinics to the adult endocrine unit. Two separate analyses were performed: (i) cross-sectional analysis of hormonal status, metabolic parameters, BC, and BMD at first evaluation after transfer from pediatrics to the adult department; (ii) longitudinal analysis of BC and BMD dynamics after 3 years of GH replacement therapy (rhGH) in TP.

Results: COGHD was of a congenital cause (CONG) in 50.6% subjects, tumor-related (TUMC) in 23.5%, and idiopathic (IDOP) in 25.9%. TUMC patients had increased insulin and lipids levels ($P < 0.01$) and lower Z score at L-spine ($P < 0.05$) compared to CONG and IDOP groups. Patients treated with rhGH in childhood demonstrated lower fat mass and increased BMD compared to the rhGH-untreated group ($P < 0.01$). Three years of rhGH after growth completion resulted in a significant increase in lean body mass (12.1%) and BMD at L-spine (6.9%), parallel with a decrease in FM (5.2%).

Conclusion: The effect of rhGH in childhood is invaluable for metabolic status, BC, and BMD in transition to adulthood. Tumor-related COGHD subjects are at higher risk for metabolic abnormalities, alteration of body composition, and decreased BMD, compared to those with COGHD of other causes. Continuation of rhGH in transition is important for improving BC and BMD in patients with persistent COGHD.

Key Words
- COGHD
- transition period
- metabolism
- body composition
- bone mineral density

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Introduction

Patients with childhood-onset GH deficiency (COGHD) represent a heterogeneous group in terms of etiology of growth hormone deficiency (GHD), time of GHD onset and recombinant human GH (rhGH) replacement commencement, duration, length of the gap in rhGH between pediatric and adult endocrine care or in comorbidities. Reported studies are inconsistent regarding the anthropometric characteristics, metabolic profile alteration, body composition (BC) deterioration or bone mineral density (BMD) impairment in different COGHD subgroups (1). Observations are particularly contradictory concerning BC and BMD in respect of the role of rhGH continuation in the transition period (TP). Several studies have demonstrated improvement of these parameters, while some others have reported no change (2, 3, 4).

Almost all published studies related to COGHD in transition with a sizable number of patients are multicentric. Monocentric studies on this topic involved a smaller number of subjects (5, 6, 7, 8). We focused on investigating BC and BMD alterations in COGHD patients on rhGH during TP. Our framework consisted of assessment of hormonal and metabolic parameters, BC and BMD in different etiology-dependent subgroups of patients with COGHD, in relation to rhGH replacement in childhood and to the GHD persistence at retesting after growth completion. To our knowledge, this is the largest single-center study addressing different aspects of COGHD patients and the effects of rhGH treatment during TP.

Patients and methods

We conducted a single-center observational, retrospective study on 170 consecutive COGHD patients in TP transferred after growth completion from two pediatric clinics to adult endocrine care. The study was conducted at the Neuroendocrine Department at the Clinic for Endocrinology, Diabetes, and Metabolic Diseases, University Clinical Center of Serbia from December 2006 to March 2021. In this study, two separate analyses were performed: (i) cross-sectional analysis of auxological data, etiology of COGHD, start and duration of rhGH treatment in childhood, duration of rhGH pause after pediatric care termination, hormonal status, metabolic parameters, bone turnover markers, BC, BMD, and associated comorbidities at first evaluation after transfer from pediatrics to adult endocrine care; (ii) longitudinal analysis of BC and BMD alterations after 3 years of rhGH replacement in TP. Metabolic profile was assessed by analyzing fasting glycemia, fasting insulin, peak and AUC glycemia and peak and AUC insulin in OGTT, HOMA index, HbA1c, lipid profile – total cholesterol, HDL, LDL, and triglycerides. BMD at the lumbar spine (BMD LS) and femoral neck (BMD FN) presented as BMD – g/cm^2 and Z score, and BC (percentage of fat (Fat%), fat mass (FM), lean body mass (LBM), total bone mineral content (TBMC)) were examined by dual-energy x-ray absorptiometry (DXA; Discovery W-QDR, Software Apex 2.3.2; Hologic Inc., Waltham, MA, USA). Subjects were analyzed by comparison of following subgroups: (i) according to etiology (congenital vs tumor-related vs idiopathic COGHD); (ii) COGHD treated in childhood with rhGH vs COGHD untreated with rhGH before TP; (iii) persistent vs transient GHD group after retesting in TP.

At first evaluation upon transfer to adult care, all enrolled patients were reassessed regarding GHD etiology and retested for GHD persistence. One or two tests were performed (insulin tolerance test – ITT and glucagon test) depending on the presence of isolated GHD or multiple pituitary hormone deficiency (MPHD) during childhood. Stimulated peak GH of less than 15 mU/L was considered confirmatory for GHD in both tests (9, 10, 11). Prior to retesting, rhGH therapy was discontinued for at least 1 month. Subjects with three or more pituitary hormones deficiencies were exempt from further testing of GH secretion. All patients who continued rhGH in transition were on an adequate replacement for other hormonal deficiencies.

The study was approved by the Ethical Committee of the University Clinical Center of Serbia. Written consent has been obtained from each subject after a full explanation of the purpose and nature of all procedures used.

Statistics

Results were presented as count (%), means ± S.D. (range), or median (25th–75th percentile) depending on data type and distribution. Groups were compared using parametric tests (*t*-test, ANOVA). To assess correlation between variables, Pearson and Spearman's correlation were used. All *P* values less than 0.05 were considered significant. Integrated areas of serum glucose and insulin levels during OGTT ($AUC_{0-120\ min}$) were calculated using the trapezoidal method. All data were analyzed using SPSS 20.0 (IBM Corp.).

Results

We enrolled 170 COGHD patients (mean age 19.2 ± 2.0 years, range 16–25), 123 males (72.4%) and

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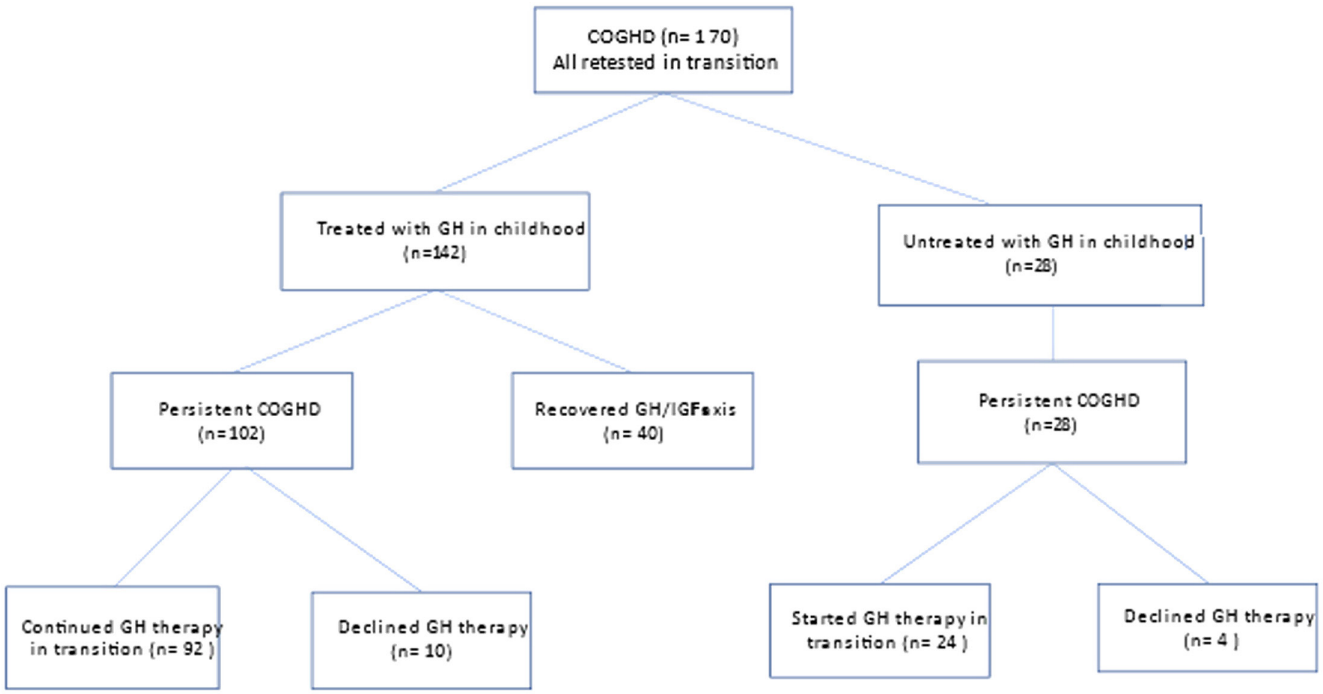

Figure 1
Study cohort flow chart.

47 females (27.6%) referred by two pediatric centers to our adult neuroendocrine unit. Patients with pituitary and midline axial structural abnormalities or genetic syndromes were classified as congenital (CONG) COGHD accounting for more than half of all included patients (86/170; 50.6%) (Fig. 1). Patients with a history of cranial tumor, hematological malignancies, or pituitary TSH hyperplasia (non-tumoral TSH cell hyperplasia occurring in primary hypothyroidism) were marked as a tumoral cause (TUMC) of COGHD; TUMC included 40/170 patients, (23.5%). Patients with normal cranial/pituitary MRI and unknown cause were assigned to a group of idiopathic (IDOP) COGHD which included 44/170 patients (25.9%). Detailed distribution according to the etiology of all 170 patients is presented in Table 1. In the TUMC group, cranial surgery was performed in 87.5% of patients (35/40), while 40.0% (16/40) of TUMC subjects were treated with chemotherapy, and 61.0% (25/40) received cranial radiotherapy. Concomitant comorbidities observed in the investigated COGHD cohort in TP are presented in Table 2.

Upon first assessment after transfer from pediatric care, isolated GHD was detected in 40/170 (23.5%) of patients. MPHD was detected in 88/170 (51.8%) (Table 3). Diabetes insipidus was observed in 21 patients (12.3%) – out of which 3 from the CONG group and the remaining 18 from the TUMC group. MPHD was confirmed in 80% (20/25) subjects treated with cranial irradiation and 62.5% (10/16) treated with chemotherapy. After the first evaluation of our patients, thyroxine replacement was continued in 46.4%, hydrocortisone in 35.8%, testosterone in 36.5% of males, and estradiol in 55.3% of females.

Growth hormone replacement

One hundred and forty-two patients (142/170; 83.5%) received rhGH during childhood for an average duration of 6.7 ± 3.7 years (range 2.5–17 years). The mean age at the start of childhood rhGH was 10.7 ± 3.5 years (range 2–16). rhGH replacement was discontinued prior to transfer to adult care at an average age of 17.4 ± 1.8 (11–25) years. Duration of rhGH gap between pediatric and adult care evaluation was 1.7 ± 2.4 years (range 0.1–14 years) (Table 4). Majority of subjects had an interval without rhGH of 1 to 3 months before retesting in TP (88/142; 62.0%). Recovery of GH/IGF-I axis was confirmed in 28.2% of all patients in this cohort (40/142). The prevalence of GH/IGF-I axis recovery was greatest in the IDOP subgroup (31/43; 72%). TUMC and CONG groups demonstrated a significantly lower prevalence of transient GHD (3/28; 10.7% and 6/71; 8.4%, respectively). Patients with persistent COGHD had lower IGF-I than the transient GHD group after cessation of rhGH at retesting in the adult care unit

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Table 1 Distribution of patients according to the etiology of COGHD in all included patients (n = 170).

	n	%
Congenital COGHD	86	50.6
Pituitary/midline structural abnormalities		
Anterior pituitary hypoplasia	25	14.7
PSIS	6	3.5
Anterior pituitary hypoplasia + EP	5	2.9
Anterior pituitary hypoplasia +PSIS	8	4.7
Anterior pituitary hypoplasia + EP + PSIS	13	7.6
Empty sella	5	2.9
Rathke cleft cyst	6	3.5
Arachnoid cyst	2	1.1
SOD	12	7.0
Genetic syndromes		
Charge	1	0.5
Prader–Willi	1	0.5
Noonan	1	0.5
Tuberous sclerosis	1	0.5
Tumor-related COGHD	40	23.5
Cranial tumor		
Craniopharyngioma	15	8.8
Germinoma	4	2.3
Histiocytosis X	6	3.5
Meduloblastoma	5	2.9
PNET	1	0.5
Hamartoma	1	0.5
Ganglioglioma	1	0.5
Astrocytoma	2	1.1
Pituitary pseudotumor (TSH hyperplasia)	2	1.1
Hematological malignancies		
ALL	2	1.1
Other malignancies		
Malignant triton tumor	1	0.5
Idiopathic COGHD	44	25.9

ALL, acute lymphoblastic leukemia; COGHD, childhood-onset growth hormone deficiency; EP, ectopic posterior pituitary; PNET, primitive neuroectodermal tumor; PSIS, pituitary stalk interruption syndrome; SOD, septo-optic dysplasia.

(77.5 vs 373.5 ng/mL, P < 0.01). Besides etiology, the number of missing pituitary hormones was associated with the persistency of GHD in transition (P < 0.01). Of the 102 patients with persistent COGHD treated during childhood, 10 have declined the advice to continue rhGH and were subsequently lost to follow-up (Fig. 1). In the remaining 92 patients, rhGH was reintroduced at age 19.3 ± 2.0 years (15–25).

Twenty-eight patients (28/170;16.5%) were not treated with rhGH during childhood and 24 of them started with rhGH in TP at the average age of 18.8 ± 1.7 years (16–22 years). Thus, a total of 116 patients have been on rhGH in TP, receiving the average daily rhGH dose of 0.5 ± 0.3 mg (Fig. 1).

Glucose and lipids metabolism

Metabolic profiles of 142 patients rhGH-replaced in childhood were analyzed according to their COGHD etiology (Table 5). TUMC subjects had increased peak insulin and insulin-AUC in OGTT, total cholesterol, LDL cholesterol and triglycerides, compared to CONG and IDOP groups (significant at 0.001 level) (Table 5).

Comparison of metabolic parameters in childhood GH-treated and untreated patients revealed significantly higher fasting insulin, insulin peak, insulin AUC, and glucose AUC in OGTT, HOMA index, and triglycerides (Table 4).

Subjects who recovered GH/IGF-I axis in transition (majority belonging to the IDOP group) demonstrated significantly higher fasting glucose (P=0.05), glucose peak and glucose AUC in OGTT (P < 0.001), but lower total cholesterol and LDL cholesterol (P < 0.001) compared to those with persistent GHD after growth completion (P <0.001) (Table 4). Insulin levels and HOMA index did not differ between persistent and transient GHD groups.

We found that the length of the rhGH-treatment gap between pediatric and adult care (rho = –0.23; P=0.013) correlated negatively with HDL levels after transfer to adult care (Fig. 2).

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Table 2 Comorbidities in enrolled patients (n = 170).

	n	%
No comorbidities	89	54.0
Visual filed defect	15	8.8
Mental retardation	10	5.8
Epilepsy	10	5.8
Primary hypothyroidism	9	5.2
Undescended testis	8	4.7
Inguinal hernia	6	3.5
Heart defects	6	3.5
Benign tumors/cyst (kidney 2, adrenal 1, mediastinum 1, skin 2)	6	3.5
Skeletal deformities	5	2.9
Thyroid nodule	3	1.7
Schizophrenia	2	1.1
Gallbladder calculosis	2	1.1
Bronchial asthma	2	1.1
Atopic dermatitis	2	1.1
Eyelid defect	2	1.1
Hepatic steatosis	2	1.1
Hyperthyroidism	1	0.5
Pyloric stenosis	1	0.5
Celiac disease	1	0.5
Renal calculosis	1	0.5
Acute pancreatitis	1	0.5
Bacterial meningitis	1	0.5
Sleep apnea	1	0.5

Body composition

BC analysis in 142 patients on rhGH in childhood revealed that body weight, BMI, and waist circumference were significantly increased in TUMC compared to CONG and IDOP groups (P < 0.05). IDOP subjects had significantly higher LBM compared to the CONG group (P < 0.05) and lower Fat% and FM compared to TUMC and CONG group (P < 0.01) (Table 5).

Increased TBMC (P=0.05), lower Fat% (P=0.03), and tendency to LBM increase (P=0.08) were demonstrated in childhood GH-treated compared to GH-untreated group (n=28) (Table 4).

Table 3 Pituitary function in different etiologies of COGHD (n = 170).

	Isolated GHD	Multiple GHD	Normal pituitary function
Congenital COGHD (n = 86)	24	56	5
Tumor-related COGHD (n = 40)	6	31	2
Idiopathic COGHD (n = 44)	10	1	31
Total	40 (23.5%)	88 (51.8%)	38 (22.3%)[a]

[a]Four patients (4/170; 2.3%) had deficiency of one anterior pituitary hormone other than GH.

Patients who recovered GH/IGF-I axis were taller (P=0.01), with lower Fat% and FM compared to persistent GHD subjects (P < 0.001) (Table 4).

In search for predictors of BC outcomes, we observed that final body height correlated significantly negatively with Fat% and positively with LBM and TBMC (data not shown). BMI was predictive of higher Fat%, FM, LBM, and TBMC at first evaluation in the adult endocrine unit (data not shown). Number of missing pituitary hormones was associated with Fat% increase (rho=0.49, P < 0.001) and FM (rho=0.41, P < 0.001) of investigated COGHD patients. Duration of rhGH was positive predictor of Fat% (rho=0.23; P=0.019) and FM (rho=0.26; P=0.01).

Bone mass

Densitometric (DXA) analysis at first evaluation after transfer from pediatric care, on 142 COGHD patients treated with rhGH during childhood revealed BMD Z-scores (Z-sc) of < –2 in 31.4% at the lumbar spine (LS) and 8% at the femoral neck level (FN). TUMC subjects had significantly lower Z-sc LS (P < 0.05) and bone turnover markers compared to CONG and IDOP groups (Table 5).

By comparing patients receiving rhGH in childhood and those deprived of rhGH before TP (n= 28) lower BMD LS, Z-sc LS and Z-sc FN were demonstrated in the untreated group (P < 0.01) (Table 4). Subjects from the untreated

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Table 4 Comparison of COGHD patients according to rhGH replacement during childhood and persistency of GHD at first evaluation after transfer from pediatric care. Data shown as mean ± S.D.

Variable	**Treated with GH in childhood** (*n* = 142)	*n*	**Untreated with GH in childhood** (*n* = 28)	*n*	**Persistent GHD** (*n* = 102) **treated with GH in childhood**	*n*	**Transient GHD** (*n* = 40) **treated with GH in childhood**	*n*
Body weight (kg)	66.7 ± 16.8	142	63.5 ± 24.8	28	67.3 ± 17.7	102	65.3 ± 14.8	40
Body height (cm)	171.0 ± 9.9	142	160.0 ± 11.8[b]	28	169.2 ± 10.8	102	173.8 ± 6.6[d]	40
BMI (kg/m^2)	22.6 ± 4.8	142	24.4 ± 7.6	28	23.1 ± 5.0	102	21.4 ± 4.0	40
Waist circumference (cm)	82.0 ± 11.9	64	85.8 ± 13.9	15	85.0 ± 12.8	43	76.1 ± 6.8[c]	21
Age at start of rhGH	10.7 ± 3.5	142	–		9.8 ± 3.6	102	13.0 ± 2.1[d]	40
Duration of rhGH	6.7 ± 3.7	142	–		7.6 ± 3.8	102	4.4 ± 1.9[c]	40
Duration of rhGH treatment gap between pediatric and adult care	1.7 ± 2.4	142	–		2.1 ± 2.7	102	0.8 ± 0.9	40
Fasting glucose (mmol/L)	4.5 ± 0.6	119	4.7 ± 0.5	24	4.4 ± 0.6	82	4.7 ± 0.5[c]	37
Fasting insulin (mU/L)	16.6 ± 13.3	99	20.3 ± 10.3[a]	18	17.3 ± 15.4	64	15.4 ± 10.4	35
Peak glucose in OGTT (mmol/L)	7.5 ± 1.8	95	8.0 ± 1.6	14	7.0 ± 1.5	63	8.4 ± 1.9[d]	32
Peak insulin in OGTT (mU/L)	91.8 ± 57.3	95	116.3 ± 56.9[a]	18	89.9 ± 58.8	62	95.5 ± 55.1	33
AUC glucose in OGTT (mmol/L/120 min)	24.3 ± 5.0	95	27.3 ± 5.1[a]	15	23.3 ± 4.6	63	26.7 ± 5.1[d]	32
AUC insulin in OGTT (mU/L/120 min)	253.3 ± 176.2	92	329.0 ± 171.2[a]	17	250.4 ± 171.5	59	258.6 ± 186.9	33
HbA1c (%)	5.1 ± 0.3	80	5.2 ± 0.3	15	5.0 ± 0.4	54	5.1 ± 0.3	26
HOMA index	3.2 ± 2.6	96	4.3 ± 2.2[b]	18	3.3 ± 2.8	62	3.1 ± 2.4	34
Total cholesterol (mmol/L)	4.6 ± 1.2	122	4.7 ± 1.2	25	4.8 ± 1.3	85	3.9 ± 0.6[d]	37
HDL cholesterol (mmol/L)	1.3 ± 0.3	112	1.1 ± 0.3[a]	21	1.3 ± 0.3	77	1.4 ± 0.4	35
LDL cholesterol (mmol/L)	2.6 ± 1.0	108	2.7 ± 0.9	21	2.9 ± 1.1	75	2.0 ± 0.6[d]	33
Triglycerides (mmol/L)	1.3 ± 1.0	119	1.7 ± 0.9[a]	24	1.3 ± 1.1	83	1.1± 0.9	36
OCL (ng/mL)	54.8 ± 38.4	52	48.4 ± 31.1	12	41.2 ± 24.0	34	80.3 ± 47.4[d]	18
BCL (pg/mL)	1197.2 ± 871.1	50	1112.8 ± 687.5	10	1011.8 ± 634.1	33	1558.4 ± 1145.2[c]	17
Fat%	27.5 ± 9.4	97	32.4 ± 9.4 [a]	20	30.7 ± 8.3	71	18.9 ± 6.7[d]	26
FM (kg)	19.4 ± 9.8	97	23.7 ± 12.5	18	21.6 ± 9.3	71	13.2 ± 8.8[d]	26
LBM (kg)	45.1 ± 10.4	95	40.2 ± 13.7	18	44.3 ± 11.2	70	47.0 ± 7.8	25
TBMC (kg)	2.2 ± 0.5	96	2.0 ± 0.7[a]	17	2.2 ± 0.4	70	2.3 ± 0.4	26
BMD lumbar spine (g/cm^2)	0.90 ± 0.1	103	0.80 ± 0.1[b]	21	0.89 ± 0.1	75	0.90 ± 0.1	28
Z-sc lumbar spine	−1.3 ± 1.3	105	−2.3 ± 1.8[b]	24	−1.4 ± 1.4	77	−1.1 ± 1.2	28
BMD femoral neck (g/cm^2)	0.87 ± 0.1	100	0.80 ± 0.2	21	0.86 ± 0.1	73	0.89 ± 0.1	27
Z-sc femoral neck	−0.6 ± 1.0	101	−1.1 ± 1.4[a]	22	−0.6 ± 0.9	76	−0.4 ± 0.9	25

[a]$P < 0.05$, treated vs untreated with GH in childhood; [b]$P < 0.01$, treated vs untreated with GH in childhood; [c]$P < 0.05$, persistent GHD vs transient GHD in patients treated with GH in childhood; [d]$P < 0.01$, persistent GHD vs transient GHD in patients treated with GH in childhood.

group had Z-sc LS < −2 in 45.8% and Z-sc FN < −2 in 22.7% at first evaluation.

BMD at LS and FN did not differ statistically between transient and persistent COGHD patients ($P=0.75$ and $P=0.31$, respectively). However, osteocalcin (OC) and beta-cross laps (BCL) levels were significantly higher in patients who have recovered GH/IGF-I axis (Table 4).

The final body height and BMI correlated significantly positively with BMD and Z-sc at LS and FN (data not shown). Duration of rhGH in pediatric age predicted higher bone mass according to BMD LS (rho = 0.20, $P=0.040$), BMD FN (rho = 0.19, $P=0.053$). Duration of pause in rhGH between pediatric and adult care did not predict values of bone parameters. However, age at rhGH treatment cessation before transfer to adult endocrine care correlated negatively with BMD LS and Z-sc LS (r = −0.18, $P=0.05$; r = −0.19, $P=0.03$, respectively) (Fig. 3).

Changes in body composition and BMD during follow-up on rhGH in transition period

Out of 116 subjects on rhGH in TP, we evaluated BC and BMD in 40 (34.4%) of them (32 patients continuing rhGH and 8 patients starting rhGH in TP) after 3 years of treatment. Significant improvement in BC was observed, manifesting as Fat% decrease by 5.2% and LBM increase of 12.1% during 3-year follow-up (Table 6). Changes in bone mass indicated significant increment of BMD LS by 6.9%. BMD increment was additionally demonstrated by Z-sc LS and Z-sc FN improvement (Table 6).

Of these 40 patients, we followed up 15 subjects after 6 years of rhGH in TP (some outgrowing 25 years as the end age for transition period). We detected further trend of increase in LBM and BMD LS. Fat mass and Fat% did not change over this extended follow-up, but BMD FN had tendency of decreasing (data not shown).

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Table 5 Characteristic of patients treated with rhGH during childhood (n = 142) and difference according to etiology of COGHD. Data shown as mean ± S.D.

Variable	Congenital COGHD (n = 71)	n	Tumor related COGHD (n = 28)	n	Idiopathic COGHD (n = 43)	n
Body weight (kg)[a]	64.9 ± 18.4	71	72.7 ± 14.0	28	65.5 ± 15.0	43
Body height (cm)	169.3 ± 10.8	71	172.3 ± 10.2	28	173.5 ± 7.2	43
BMI (kg/m^2)[a]	22.4 ± 5.3	71	24.4 ± 4.0	28	21.5 ± 4.1	43
Waist circumference (cm)[a]	83.9 ± 15.1	68	87.2 ± 5.8	24	75.7± 5.9	38
Age at start of rhGH[b]	9.3 ± 3.8	71	10.8 ± 2.9	28	12.8 ± 2.2	43
Duration of rhGH[a]	7.9 ± 4.7	71	6.5 ± 4.2	28	5.7 ± 2.0	43
Duration of rhGH treatment gap between pediatric and adult care	2.3 ± 2.8	71	2.0 ± 2.5	28	0.8 ± 1.2	43
Age at cessation of rhGH before transfer to adult care	17.1 ± 2.0	71	18.0 ± 1.8	28	17.4 ± 1.2	43
Fasting glucose (mmol/L)[a]	4.4 ± 0.6	61	4.5 ± 0.5	24	4.7 ± 0.3	34
Fasting insulin (mU/L)	16.4 ± 14.6	47	23.1 ± 19.1	19	13.4 ± 6.1	33
Peak glucose in OGTT (mmol/L)[b]	7.0 ± 1.6	44	7.4 ± 1.6	21	8.3 ± 1.9	30
Peak insulin in OGTT (mU/L)[b]	78.0 ± 42.8	45	137.4 ± 84.5	19	83.8 ± 40.8	31
AUC glucose in OGTT (mmol/L/120 min)	23.1 ± 5.0	44	25.0 ± 5.1	21	25.5 ± 4.7	30
AUC insulin in OGTT (mU/L/120 min)[b]	215.6 ± 122.9	42	390.1 ± 274.0	19	220.2 ± 115.6	31
HbA1c (%)	5.0 ± 0.3	40	5.2 ± 0.4	17	5.1 ± 0.2	23
HOMA index	2.9 ± 2.2	45	4.8 ± 4.3	19	2.7 ± 1.3	32
Total cholesterol (mmol/L)[b]	4.6 ± 1.0	63	5.3 ± 1.7	25	3.9 ± 0.6	34
HDL cholesterol (mmol/L)	1.3 ± 0.4	56	1.2 ± 0.3	24	1.4 ± 0.3	34
LDL cholesterol (mmol/L)[b]	2.7 ± 1.0	54	3.1 ± 1.3	24	2.0 ± 0.5	30
Triglycerides (mmol/L)[b]	1.0 ± 0.6	61	1.9 ± 1.4	25	1.0 ± 0.8	33
OCL (ng/mL)[b]	45.5 ± 35.6	22	38.1 ± 20.0	10	73.3 ± 42.0	20
BCL (pg/mL)[a]	1133.9 ± 737.2	22	771.5 ± 473.3	9	1472.2 ± 1076.3	19
Fat%[b]	30.4 ± 9.2	50	29.8 ± 7.7	23	19.3 ± 6.3	24
FM (kg)[b]	21.4 ± 10.3	50	21.3 ± 7.8	23	13.7 ± 8.9	24
LBM (kg)[a]	42.8 ± 11.5	50	46.7 ± 8.8	22	48.4 ± 8.3	23
TBMC (kg)	2.1 ± 0.5	49	2.2 ± 0.4	23	2.3 ± 0.2	24
BMD lumbar spine (g/cm^2)	0.90 ± 0.1	54	0.86 ± 0.1	22	0.90 ± 0.1	27
Z-sc lumbar spine[a]	−1.31 ± 1.4	55	−1.72 ± 1.3	23	−0.95 ± 1.3	27
BMD femoral neck (g/cm^2)	0.85 ± 0.1	52	0.86 ± 0.1	22	0.90 ± 0.1	26
Z-sc femoral neck	−0.67 ± 1.1	54	−0.65 ± 1.1	22	−0.39 ± 1.0	25

[a]P < 0.05, difference between three etiologies of COGHD; [b]P < 0.01, difference between three etiologies of COGHD.

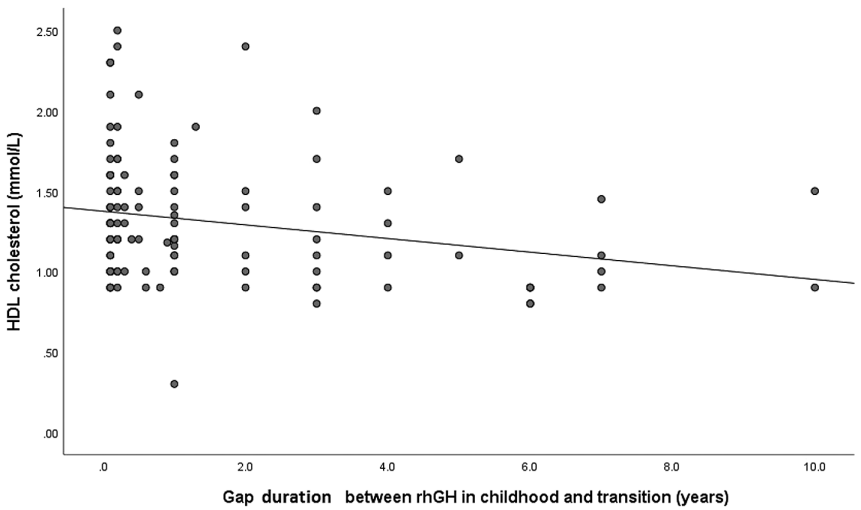

Figure 2
Gap duration between rhGH in childhood and transition correlated negatively with HDL levels (n = 142).

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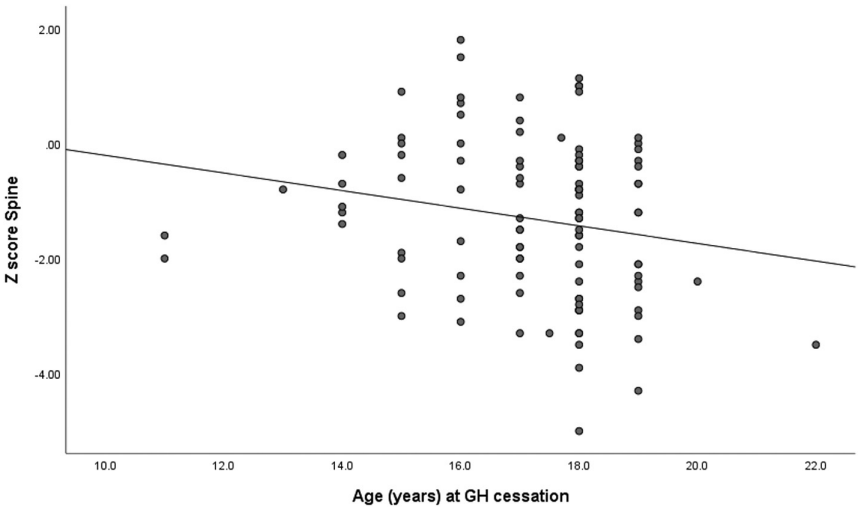

Figure 3
Z-sc at the lumbar spine correlated negatively with age at discontinuation of rhGH therapy before retesting in transition (n = 142).

Discussion

In this study, we analyzed 170 patients with COGHD recruited over the last 15 years and referred to a single adult neuroendocrine unit from two pediatric centers after completion of linear growth. More than a half of enrolled patients had congenital etiology of GHD, while tumor caused and idiopathic COGHD were represented about one-fourth each. The observed distribution is in agreement with the results of our earlier study relating to the etiology of hypopituitarism in Serbia (12). In a monocentric French study on 112 COGHD patients in transition, acquired GHD was recorded in 56% of subjects, congenital in 33%, and idiopathic in 11% (6). In the KIMS database study involving 314 young adult COGHD patients, the most common single cause of GHD was idiopathic (in 33%) followed by craniopharyngioma (in 20%) (13). A Scottish multicentric study focusing on the management of COGHD in 130 young adults, structural abnormalities were detected in 30%, tumor-related COGHD in 40% while GHD cause was unknown in 11% (5).

Cranial tumor and ALL were behind COGHD in 23.5% of patients in our study. Cranial surgery and/or radiotherapy, experienced by a majority of these patients, made them prone to develop hypothalamic damage presenting as a higher prevalence of MPHD and metabolic deterioration. We demonstrated that TUMC had notably more pituitary hormone deficits and a higher incidence of diabetes insipidus compared to the other two etiological groups. Subjects belonging to TUMC demonstrated worse metabolic outcomes according to higher values of insulin in OGTT and worse lipid profile than CONG and IDOP groups. They had increased Fat% and FM compared to IDOP, but similar to the CONG group. Most numerous patients in the TUMC group were those treated for craniopharyngioma in childhood. Yuen *et al.* analyzed 260 adults with COGHD caused by craniopharyngioma and showed that they had higher prevalence of MPHD and greater BC alterations but comparable fasting glucose, HbA1c, cholesterol levels as the patients with other causes of COGHD (14). Subjects with a history of medulloblastoma tend to develop MPHD dependent on the received craniospinal radiation dose (15). Metabolic syndrome was reported in 23% as a late effect in childhood ALL survivors treated with cranial irradiation (16). Our tumor-related group included five patients who experienced medulloblastoma and two subjects who underwent chemotherapy and cranial irradiation due to ALL. These underlying diseases probably contributed to the poorer metabolic profile of this group. Hoybye *et al.* observed that patients with the organic pituitary disease

Table 6 Effects of 3 years of rhGH replacement in transition period on body composition and BMD (n = 40).

Parameter	Visit 0	Visit 1	Absolute change	Percent of change	*P* value
Fat%	30.7 ± 8.9	29.1 ± 9.1	−1.62	5.2	0.043
FM (kg)	20.7 ± 9.5	21.1 ± 9.1	0.40	1.9	0.571 (NS)
LBM (kg)	42.9 ± 10.5	47.3 ± 10.9	4.38	12.1	0.001
TBMC (kg)	2.14 ± 0.5	2.33 ± 0.5	0.19	8.8	0.001
BMD lumbar spine (g/cm^2)	0.87 ± 0.2	0.93 ± 0.2	0.06	6.9	0.001
BMD femoral neck (g/cm^2)	0.85 ± 0.2	0.86 ± 0.2	0.01	1.2	0.456 (NS)
Z-sc lumbar spine	−1.58 ± 1.7	−1.25 ± 1.5	0.33		0.005
Z-sc femoral neck	−0.77 ± 1.3	−0.50 ± 1.3	0.27		0.007

Visit 0, first DXA evaluation at admission on adult care unit; Visit 1, second DXA evaluation after 3 years of rhGH replacement in transition period.

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are commonly overweight with adverse lipid profiles (17). Survivors of childhood brain tumors are recognized as a high-risk population for decreased BMD due to the neoplasia itself, treatments and their sequelae, hypopituitarism, malnutrition, and lifestyle – all likely to negatively affect bone metabolism (18). Results of our study support this, as TUMC patients had lower Z-sc LS and bone turnover compared to two other etiology-dependent groups. We enrolled four patients with a history of intracranial germinoma, who contributed to the reduced BMD in TUMC group. Low BMD was reported as prevalent in patients with a history of intracranial germinoma (19, 20).

Comparison of COGHD patients treated with rhGH in childhood (before age of 16, for at least 2.5 years) with those deprived of rhGH demonstrated worse metabolic profile in the untreated group regarding adverse lipid profile and higher insulin resistance. Benefits of rhGH in childhood were manifested by increased TBMC, BMD LS, Z-sc LS, and Z-sc FN, tendency to increased LBM and parallel Fat% reduction in TP. Upon reaching the final height, approximately 20% of GHD children treated with rhGH had a BMD LS between –1 and –2S.D. of the normal mean (21). Kaufman *et al.* indicated that COGHD presents with a lower bone mass despite prior to rhGH treatment in childhood (22). Cohen *et al.* analyzed BMD in 36 post-pubertal adolescents with cranial tumor-related COGHD on rhGH in childhood and found that treated subjects had a higher BMD Z sc LS and Z-sc FN than untreated subjects (18). Similarly, we detected Z-sc LS < –2 in 31.4% of patients adequately replaced with rhGH in childhood, contrary to 45.8% in the GH-untreated COGHD group. We observed that a longer duration of rhGH replacement correlated positively with BMD in both investigated skeletal sites. On the other hand, older age at rhGH cessation before transfer to adult endocrine care was associated with lower BMD LS and Z-sc LS. Tritos *et al.* showed that a longer gap between pediatric and adult age rhGH replacement was negatively associated with BMD at FN in adults (13). Conversely, we did not find any influence of duration of the interval between stopping and recommencement of rhGH on bone parameters. However, we detected a negative correlation of the length of that interval (1.7 years) with HDL levels in transition. The similar was observed in the KIMS study in which the duration of rhGH discontinuation between childhood and adulthood (4.4 years) was associated with significantly more detrimental lipid profiles (23).

Clinical studies of bone density in COGHD adolescents reported conflicting findings related to the effect of continuation of rhGH after final height achievement (24, 25). Our results demonstrated a significant increase of BMD LS (6.9%), Z-sc LS, and Z-sc FN in 40 COGHD subjects on rhGH treatment after 3 years during TP. Also, other studies have confirmed that continuation of rhGH is associated with increasing BMD LS by 2 to 6% after 1–2 years of follow-up (2, 3, 7, 26). In addition, a study by Hyldstrup *et al.* showed that 24 months of continuation of rhGH after achievement of final height in young COGHD adults resulted in increased cortical bone thickness (27). However, some studies observed no change in BMD after 6–24 months of rhGH discontinuation after growth completion compared to control subjects (4, 28, 29). Many factors such as gender, height, age at onset, body composition, gonadal status, or GHD severity may contribute to conflicting data on bone mass in patients with COGHD (25).

Similar to the contradictory reports related to bone mass, there are inconsistent findings on the effect of continuing rhGH on body composition in TP. Our study showed the favorable effect of the resumption of rhGH in 40 COGHD subjects after 3 years in TP. We observed a significant decrease in Fat% (5.2%) and an increase in LBM (12.1%). In accordance to our results, other studies demonstrated that recommencement of rhGH in TP with the duration of 1–2 years manifested as significant LBM increase (6–14%) and FM reduction (7–12%). Discontinuation of rhGH treatment for 6–24 months in COGHD adolescents after final height achievement resulted in FM increase (10–17%) and LBM decrease by up to 8% (3, 8, 30, 31, 32, 33, 34, 35). By contrast, a few studies reported no difference in BC parameters after 6–24 months period of rhGH after growth completion (4, 36). At first evaluation after transfer from pediatric care, we showed that final body height correlated negatively with Fat% and positively with LBM and TBMC. However, BMI was predictive of not only higher Fat% and FM but increased LBM and TBMC. In addition, the number of missing pituitary hormones was associated with higher Fat% and FM.

Previous studies reported a prevalence of persistent GHD upon retesting in adulthood ranging from 52 to 94% (5, 6, 37). After retesting we detected 28.2% of patients who recovered GH/IGF-I axis and showed that predictors of persistent GHD included tumor etiology and number of missing pituitary hormones, similarly as reported previously (13). Quigley *et al.* reported that in idiopathic GHD patients, the best predictor of persistent GHD is IGF-I below –5.3 S.D. measured after 6 weeks from rhGH termination (38). In line with that, our transient-GHD group had significantly higher IGF-I compared to persistent-GHD subjects at retesting. In accordance to reports of Bechtold *et al.*, we detected better BC in transient GHD compared to those with persistent GHD (39). However, their fasting

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glucose, peak and AUC glucose in OGTT were higher than in persistent GHD. Observed glucose impairments could have a possible explanation in the predominant origin of these subjects in idiopathic COGHD. Early retesting in idiopathic GHD children before TP was reported to reveal complete GH-secretion normalization in 84% (40). These patients may experience endogenous GH normalization by the time adult height is achieved and possible over-treatment with prolonged rhGH leading to the risk of glucose metabolism impairment.

The advantages of this comprehensive study are a large number of enrolled patients who have been evaluated at the same adult department after transfer from two pediatric centers which resulted in uniform recruitment and evaluation protocol, thus presenting well organized 'transition unit care' (41). The limitation of our study may lay in focusing the follow-up of BMD on the patients with worse baseline values at first evaluation possibly creating some bias in obtained results. Reaching the accepted cut-off response of GH excludes severe GHD, but not a possible lesser degree of GH deficiency. This is an inherent limitation of every assessment of GH secretion by stimulation tests, and a possible source of discrepancies between different studies, in addition to occasional divergence in selected cut-off points.

In conclusion, the effect of growth hormone replacement in childhood is invaluable for metabolism, body composition, and skeletal system during the transition period. Patients with COGHD caused by a cranial tumor are at greatest risk for metabolic abnormalities, altered body composition, and lower BMD. Continuation of rhGH in transition is important for improving body composition and increasing bone mass in patients with persistent GHD.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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