Journal of the Endocrine Society, 2025, **9**, bvaf072
https://doi.org/10.1210/jendso/bvaf072
Advance access publication 28 April 2025
Clinical Research Article

Growth Hormone Replacement in Craniopharyngioma: Analysis of the Hypopituitary Control and Complications Study (HypoCCS)

Odelia Cooper[1] **and Sungjin Kim**[2]

[1]Pituitary Center, Cedars-Sinai Medical Center, Los Angeles, CA, 90048 USA
[2]Biostatistics Research Center, Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA 90048, USA

Correspondence: Odelia Cooper, MD, Pituitary Center, Division of Endocrinology, Diabetes and Metabolism, Cedars-Sinai Medical Center, 127 S. San Vicente Blvd, A6600, Los Angeles, CA 90048, USA. Email: odelia.cooper@cshs.org.

Abstract

Context: Patients with adult-onset craniopharyngioma (CP) show metabolic dysfunction and panhypopituitarism. Growth hormone (GH) deficiency is often left unaddressed despite the benefits of GH replacement on body composition and lipoprotein metabolism in the general population.

Objective: The aim was to analyze data from Hypopituitary Control and Complications Study (HypoCCS), a global prospective surveillance study of adult GH replacement, and assess the impact of GH replacement on metabolic outcomes in adult-onset CP.

Methods: Primary outcome was a composite endpoint of adverse hepatic outcomes including metabolic dysfunction-associated steatotic liver disease; secondary outcomes included body composition, lipids, blood pressure, glycemic measures, mortality, bone density, and cardiovascular endpoints.

Results: In total, 592 patients with adult-onset CP were identified; 544 received GH for a median of 4.03 years (IQR 2.28-7.82). The 3972 patients with pituitary adenoma (3346 receiving GH) were analyzed for context. GH replacement did not impact hepatic outcomes in either cohort. In adult-onset CP, bone mineral content was significantly lower with GH replacement (estimated mean [est]: 324.90 g; 95% CI −574.49, −75.31; $P = .034$); lower waist–hip ratio and less dyslipidemia medication use were also seen. In pituitary adenomas, fasting blood glucose (est 6.45; 95% CI 3.24, 9.66; $P < .001$), diastolic blood pressure (est 1.44; 95% CI 0.45, 2.43; $P = .005$), and mean arterial pressure (est 1.20; 95% CI 0.14, 2.26; $P = .027$) were significantly higher.

Conclusion: GH led to decreased waist–hip ratio and lipid medication use but adversely impacted bone mineral content in adult-onset CP. Prospective studies of GH replacement in adult-onset CP can further define the benefits on metabolic outcomes in these patients.

Key Words: craniopharyngioma, growth hormone deficiency, metabolic dysfunction-associated steatotic liver disease, glucose metabolism

Abbreviations: ANOVA, analysis of variance; BMI, body mass index; CP, craniopharyngioma; DBP, diastolic blood pressure; DXA, dual-energy x-ray absorptiometry; est, estimated mean; GH, growth hormone; GHD, growth hormone deficiency; HTN, hypertension; IGF, insulin-like growth factor; MAP, mean arterial pressure; MASLD, metabolic dysfunction–associated steatotic liver disease; NFPA, nonfunctioning pituitary adenoma; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus.

Craniopharyngioma (CP), a rare parasellar tumor of embryonic origin, confers significant morbidity from pituitary and hypothalamic failure and mass effects. CP incidence has a bimodal distribution, with a first peak in children aged 0-19 years and a second in adults aged 40-79 [1]. Patients with adult-onset CP show rapid weight gain in the first 6 to 12 months after surgery [2], and half develop metabolic syndrome [3], with a 9-fold increase in development of type 2 diabetes mellitus (T2DM) over time [4, 5]. Rates of metabolic dysfunction–associated steatotic liver disease (MASLD) and its advanced form metabolic dysfunction–associated steatohepatitis are also increased, and further progression to cirrhosis, hepatocellular carcinoma, liver transplantation, and liver-related death have all been reported [6, 7]. There is no current therapy known to prevent or halt progression of serious metabolic dysfunction in these patients.

Up to 80% of patients with adult-onset CP show panhypopituitarism [8], further increasing the risk for metabolic sequelae [9]. Yet, effects of growth hormone deficiency (GHD) in adult-onset CP are not well-appreciated, as delayed growth is not a concern in adults. Indeed, GHD in adult-onset-CP typically remains untreated, and growth hormone (GH) replacement may first be initiated many years after surgery [10] or not at all. Some of this clinical inertia may be due, at least in part, to concerns surrounding potential growth of residual tumor and of the risk for new-onset T2DM with GH replacement, even though evidence for both risks are conflicting [11-14].

In the general population, GH replacement in adults with GHD has confirmed benefits for improving metabolic outcomes commonly impaired in CP, specifically body composition and lipoprotein metabolism [10, 15-22], and may also influence hepatic outcomes, particularly MASLD [23].

Received: 3 January 2025. **Editorial Decision:** 22 April 2025. **Corrected and Typeset:** 14 May 2025

The few studies of GH replacement in patients with adult-onset CP have shown mixed effects on metabolic outcomes, including body mass index (BMI), fat mass, cholesterol, and glucose homeostasis [10, 24, 25]. The effect of GH replacement on hepatic enzymes, steatosis, and fibrosis is similarly unclear [23, 26-28]. Whether untested confounding factors are impeding accurate assessment of GH effect on these measures is unknown.

We sought to assess the impact of GH replacement on metabolic outcomes in patients with adult-onset CP using data from the Hypopituitary Control and Complications Study (HypoCCS), an open-label, global prospective surveillance study of GH replacement in patients with GHD [17]. We also analyzed HypoCCS data on patients with pituitary adenomas to provide additional context to our findings.

Materials and Methods

Data Source

HypoCCS was an observational research surveillance program that collected information on day to day management and clinical experience of adult patients with GHD due to adult-onset hypothalamic or pituitary disease or persistent childhood-onset GHD (registered with ClinicalTrials.gov, NCT01088399). Worldwide, 10 673 patients from 18 countries were enrolled. Patients were recruited from Austria, Belgium, Canada, Czech Republic, Denmark, France, Germany, Hungary, Iceland, Italy, Japan, Norway, Slovakia, Spain, Sweden, The Netherlands, the United Kingdom, and the United States. Of 6840 patients in the database with GHD, the distribution was as follows: 3165 from the United States, 833 from Italy, 462 from the United Kingdom, 439 from The Netherlands, 435 from Germany, 348 from Sweden, 151 from Denmark, and 1007 from other countries. Patients had 1 or 2 study visits per year with a typical interval of 6 to 12 months between visits. No form of intervention was imposed on enrolled patients. All treatment decisions for GH replacement were at the discretion of the site investigator, as was the starting dose and method of dose titration.

The primary objective of HypoCCS was to determine the safety of GH replacement as used in clinical practice in adults with GHD.

Study Cohorts

We extracted data from HypoCCS on patients with adult-onset CP and adult-onset pituitary adenoma and at least 6 months of follow-up on GH replacement. The GH-treated group comprised patients who received GH at any time during participation in HypoCCS, including those who were untreated at enrollment and then started GH replacement while on the study, as well as those who were receiving GH replacement at enrollment and stopped during the study. Patients who did not receive GH at any time during the study were defined as untreated.

Study Endpoints

The primary outcome of our study was a composite hepatic outcome based on adverse event reporting per the Medical Dictionary of Regulatory Activities (MedDRA) version 14.0 [29] for incidence of MASLD, defined as steatosis on imaging or biopsy and ≥1 cardiometabolic criteria [30], hepatitis, cirrhosis, any liver abnormality, or abnormal liver enzymes.

Secondary outcomes included changes in fasting glucose from baseline to the last visit; development of new-onset T2DM; change in percentage fat and lean body mass on bioelectrical impedance analysis and dual-energy x-ray absorptiometry (DXA); change in BMI, waist–hip ratio, bone mineral content on DXA, systolic blood pressure (SBP) and diastolic blood pressure (DBP), mean arterial pressure (MAP), and lipid profiles; development or worsening of hypertension (HTN), hyperlipidemia, stroke, and heart attack; and mortality.

Baseline variables considered included patient demographics (age and sex), metabolic characteristics (BMI, percent body fat, fat mass index, lean BMI, waist–hip ratio, HbA1C, and fasting blood glucose), endocrine characteristics (insulin-like growth factor [IGF]-I level and number of hormone deficits), comorbidities (T2DM, HTN, hyperlipidemia, coronary artery disease, and stroke), current therapies (insulin, oral antidiabetics, dyslipidemia medications, antihypertensives, weight loss medications, estrogen and/or progesterone, and androgen), and therapy prior to enrollment (GH replacement and radiotherapy).

The study was determined to be exempt from institutional review board regulation.

Statistical Analyses

Analyses were performed separately for CP and pituitary adenoma cohorts. Data are presented as frequency (percentage, %) for categorical variables and mean (± SD) or median (interquartile range [IQR]) for continuous variables. Spearman rank correlation coefficient was used to examine associations between GH dose at study end and body composition outcomes. Baseline characteristics and the primary and secondary outcomes were compared between GH treated and untreated groups using analysis of variance (ANOVA) or Wilcoxon rank-sum test for continuous variables and the chi-square test or the Fisher exact test for categorical variables as appropriate. Outcomes that were significantly or marginally significantly different between GH treated and untreated groups with P values less than .1 were further examined.

To examine associations between change in continuous outcomes from baseline to study end and GH replacement, a generalized additive model for location, scale and shape (GAMLSS) [31] was employed using Box–Cox Cole and Green (BCCG), Box–Cox-t (BCT), t-family (TF) or log-normal distribution with an identity link function, including each outcome at the study end as a response variable and its baseline measurement and GH treated vs untreated as covariates after adjusting for prior GH replacement, age, sex, BMI, duration of GHD, and time in study. The goodness of fit of each model was examined using residuals [32] and generalized Akaike information criterion such that the most adequate response distribution was chosen. Binary outcomes were examined using a logistic regression model including GH treated vs untreated as a covariate after adjusting for prior GH replacement, age, sex, BMI, pituitary adenoma subtype, and duration of GHD. Missing data on categorical variables were summarized as "unknown" and excluded from analyses for continuous variables.

All analyses were performed using R package version 4.3.2 [33] with 2-sided tests at a significant level of .05. Significance was not adjusted for multiple tests.

Results

A total of 4564 patients were identified, including 592 patients with adult-onset CP and 3972 patients with pituitary adenoma.

Craniopharyngiomas

Of 592 patients with adult-onset CP identified, 544 were treated with GH replacement and 48 were untreated.

Baseline Characteristics

The GH-treated group had a longer median duration of GH replacement and follow-up vs the untreated group (4.03 [IQR 2.28-7.82] vs 3.13 [IQR 1.63-4.99] years, respectively; $P = .016$), more females (47% vs 38%), younger median age at enrollment (42.9 [IQR 33.6-52.4] vs 53.6 [IQR 43.4-61.3] years; $P < .001$), and earlier median age of GHD diagnosis (37.5 [IQR 27.3-48.6) vs 49.8 [IQR 36.2-59.5] years; $P < .001$) although duration of GHD was similar in the 2 groups (median 1.86 [IQR 0.31-7.01] vs 3.26 [IQR 0.33-7.5] years, respectively; $P = .739$) (Table 1).

Metabolic measures of BMI, waist–hip ratio, and lean body mass were similar at baseline between the GH-treated and untreated groups, while fasting blood glucose levels were lower in the GH-treated group (median 84.7 [IQR 75.7-94] vs 92 [IQR 83-104] mg/dL; $P = .025$) (Table 1).

Comorbidity rates were also similar between the groups at baseline, except that the GH-treated group had lower rates of HTN (3% vs 15%; $P = .009$). GH-treated patients had more hormone deficits than untreated patients ($P < .001$), with 58% and 29%, respectively, showing 4 hormone deficits. Rates of hypogonadism (91% vs 78%, $P = .019$), adrenal insufficiency (88% vs 74%, $P = .011$), and arginine vasopressin deficiency (68% vs 46%, $P = .008$) were all higher in GH-treated vs untreated patients (data not shown). In addition, 21% of GH-treated patients were on estrogen and/or progesterone replacement compared with 6% in untreated patients ($P = .013$) (Table 1).

Prior use of radiotherapy was similar in the 2 groups (26% vs 38%) and approximately 85% were naïve to GH replacement at baseline in both the GH-treated and untreated groups (84% vs 85%).

Outcomes

The composite hepatic outcome was not different between GH-treated and untreated patients, with 19% showing adverse hepatic events with GH replacement compared with 27% without treatment ($P = .219$). On univariate analysis, treatment of GH was not associated with hepatic outcomes (odds ratio [OR] 0.65; 95% CI 0.32, 1.30; $P = .222$) (Table 2 and Table 3).

Examination of metabolic and body composition outcomes showed only a few outcomes were significantly different from baseline with GH treatment. Lean mass on DXA increased by mean 2047.27 (±4209.61) g in GH-treated patients compared with −4247.33 (±4438.79) g in untreated patients ($P = .032$). Rates of osteoporosis on DXA did not differ with and without GH use (8.8% vs 11.1%, respectively; $P = .173$), and no fractures were recorded in untreated patients (0% vs 5.5%; $P = .087$). Waist–hip ratio decreased by 0.01 (IQR −0.03-0.03) in GH-treated patients but increased by 0.03 (IQR 0-0.06) in untreated patients ($P = .006$). SBP remained unchanged with GH replacement but increased in untreated patients (0 [IQR −10-10] vs 5.5 [IQR 0-17] mmHg, respectively; $P = .036$). Similarly, MAP was unchanged (0 [IQR −6.67-6.67] mmHg in treated patients but increased in untreated patients (3.33 [IQR −0.67-8.33] mmHg; $P = .056$).

GH replacement did not impact other metabolic and body composition outcomes, or any cardiovascular outcomes (Table 2). Mortality was similar in GH-treated and untreated patients during the surveillance period (5.9% vs 3.5%; $P = .367$). GH dose at study end was not associated with body composition outcomes (Table 4).

On univariate analysis (Table 3), GH replacement was associated with decreased waist–hip ratio ($P = .010$), decreased SBP ($P = .032$), and lower rates of new-onset HTN ($P = .031$). GH replacement was associated with decreased bone mineral content on DXA $P = .018$), but too few cases of osteoporosis and fracture were reported to determine correlation with GH replacement use. The increase in lean body mass on bioelectrical impedance analysis ($P = .054$) and on DXA ($P = .065$) as well as the decrease in MAP ($P = .064$) in GH-treated patients were not significant.

On multivariable analysis, GH replacement remained associated with decreased bone mineral content (estimated mean [est] −324.90 g; 95% CI −574.49, −75.31; $P = .034$) after adjusting for baseline bone mineral content, or potential confounders, including prior GH replacement, age, sex, BMI, duration of GHD, and time in study (Table 3). Waist–hip ratio (est −0.02; 95% CI −0.05, 0.00; $P = .067$) and rate of dyslipidemia medication use (OR 0.48; 95% CI 0.20-1.14; $P = .097$) were lower in GH-treated vs untreated patients although these associations were not statistically significant. All other outcome measures were not associated with GH use.

Pituitary Adenomas

Of 3972 patients with pituitary adenomas included, 3346 were treated with GH replacement and 626 untreated.

Baseline Characteristics

GH-treated patients with pituitary adenomas had a longer median follow-up (4.3 [IQR 2.1-7.9] years) (3.0 [IQR 1.8-5.0] years; $P < .001$) and shorter median duration of GHD (1.47 [IQR 0.23-6.02] vs 2.28 [IQR 0.28-7.36] years; $P = .012$) than untreated patients (Table 5). GH-treated patients were also younger both at enrollment (median 52.3 [IQR 43.4-60.9] vs 59.6 [IQR 50.1-69.9] years; $P < .001$) and at GHD diagnosis (median 48.1 [IQR 38.2-57.3] vs 55 [IQR 44.3-65.2] years; $P < .001$). Fifteen percent of GH-treated patients with pituitary adenoma had prior use of GH replacement compared with only 7% of untreated patients ($P < .001$).

Patients with pituitary adenoma treated with GH had lower median waist–hip ratio (0.9 [IQR 0.0-0.99] vs 0.9 [IQR 0.9-0.99]; $P = 0.04$), lower median fasting blood glucose (86 [IQR 78-95) vs 90 [IQR 82-103.5] mg/dL; $P < 0.001$), and lower median HbA1C levels (5.6 [IQR 5.3-6.1] vs 5.8 [5.4-6.4]; $P < .001$) at baseline than untreated patients (Table 5). GH-treated patients also had lower rates of T2DM (3% vs 8%; $P < .001$), HTN (11% vs 19%, $P < .001$), hyperlipidemia (16% vs 26%, $P < .001$), coronary artery disease (1% vs 4%, $P < .001$), and stroke (1% vs 2%, $P < .001$). Fewer GH-treated patients were on oral antidiabetic ($P < .001$) and dyslipidemia medications ($P = .015$), while more GH-treated patients were on androgens ($P = .02$). Prior use of radiotherapy rates was more common in GH-treated than untreated patients (34% vs 26%, $P < .001$).

Outcomes

Rates of hepatic adverse events were similar in GH-treated and untreated patients with pituitary adenomas (17.3% vs

Table 1. Baseline characteristics in GH-treated and untreated patients with adult-onset CP

Variable	No GH replacement (n = 48)	GH replacement (n = 544)	*P* value
Demographics			
Follow-up, median years (IQR)	3.13 (1.63-4.99)	4.03 (2.28-7.82)	.016
Age at enrollment, median years (IQR)	53.64 (43.42-61.33)	42.87 (33.55-52.39)	<.001
Age at GHD diagnosis, mean years (IQR)	49.82 (36.21-59.46)	37.49 (27.27-48.64)	<.001
Duration of GHD, median years (IQR)	3.26 (.33-7.5)	1.86 (.31-7.01)	.739
Duration of GH replacement, median years (IQR)		4.03 (2.28-7.82)	
GH dose at study end, median mg/d (IQR)	0 (0-0)	.4 (.21-0.7)	<.001
Female sex, n (%)	18 (37.5)	256 (47.06)	.203
Caucasian race, n (%)	29 (60.42)	362 (66.67)	.409
Metabolic			
BMI, median kg/m^2 (IQR)	29.61 (26.53-34.67)	30.09 (26.3-35.16)	.853
Body fat, median % (IQR)	35.26 (32.6-36.22)	35.25 (28.73-40.08)	.552
Fat mass index, median kg/m^2 (IQR)	11.14 (10.43-14.19)	9.83 (7.85-12.52)	.226
Lean body mass, median kg/m^2 (IQR)	20.18 (16.41-26.98)	17.03 (14.58-19.78)	.208
Waist–hip ratio, median (IQR)	0.94 (0.88-1.01)	0.94 (0.88-0.99)	.603
HbA1C, median % (IQR)	5.8 (5.6-7.7)	5.5 (5.2-6)	.145
Fasting blood glucose, median mg/dL (IQR)	92 (83-104)	84.67 (75.66-94)	.025
Endocrine			
IGF-1, median ng/mL (IQR)	71.5 (52-112)	85 (55.2-135)	.085
No. of hormone deficits, n (%)			<.001
0	2 (4.17)	10 (1.84)	
1	4 (8.33)	23 (4.23)	
2	10 (20.83)	38 (6.99)	
3	18 (37.5)	160 (29.41)	
4	14 (29.17)	313 (57.54)	
Current comorbidities, n (%)			
T2DM	2 (4.17)	17 (3.13)	.779
Hypertension	7 (14.58)	17 (3.13)	.009
Hyperlipidemia	10 (20.83)	85 (15.63)	.711
Coronary artery disease	1 (2.08)	3 (0.55)	.115
Stroke	1 (2.08)	2 (0.37)	.382
Osteoporosis	2 (4.17)	26 (4.78)	1.000
Fracture	1 (2.08)	2 (0.37)	.241
Current therapy, n (%)			
Insulin	0 (0)	15 (2.76)	0.614
Oral antidiabetics	4 (8.33)	34 (6.25)	.525
Dyslipidemia medications	10 (20.83)	74 (13.6)	.174
Antihypertensives	12 (25)	55 (10.11)	.004
Weight loss medications	0 (0)	2 (0.37)	1.00
Estrogen and/or progesterone	3 (6.25)	115 (21.22)	.013
Androgen	16 (33.33)	146 (26.94)	.341
Prior therapy, n (%)			
GH replacement	7 (14.58)	87 (15.99)	.798
Radiotherapy	18 (37.5)	143 (26.29)	.094

Abbreviations: BMI, body mass index; CP, craniopharyngioma; GH, growth hormone; GHD, growth hormone deficiency; IGF, insulin-like growth factor; IQR, interquartile range; T2DM, type 2 diabetes mellitus.
P value is calculated by analysis of variance or Wilcoxon rank-sum test for continuous and ordinal variables; and the hi-square test or the Fisher exact test for categorical variables.

18%, respectively). On univariate analysis, GH treatment was not associated with the composite hepatic outcome (OR 0.97; 95% CI 0.77, 1.23; $P = .807$) (Table 6 and Table 7).

Examination of metabolic and body composition outcomes showed that fasting blood glucose increased more in GH-treated patients than in untreated patients (6 [IQR 0-13] vs 1 [IQR −10-7] mg/dL, respectively; $P = .04$), while mean

Table 2. Outcomes in GH-treated and untreated patients with adult-onset CP

Outcome	No GH replacement (n = 48)	GH replacement (n = 544)	*P* value
Composite hepatic outcome, n (%)	12 (26.67)	93 (19.06)	.219
Metabolic and body composition			
Change in fasting blood glucose, mean mg/dL (SD)	1.33 (19.66)	5.63 (16.32)	.737
Change in HbA1C, mean % (SD)	NA	0.15 (0.76)	NA
New diagnosis of T2DM, n (%)	0 (0)	19 (5.05)	.628
Worsening of T2DM, n (%)	0 (0)	14 (3.73)	.612
Change in percent body fat, mean (SD)	1.86 (2.15)	−2.33 (4.48)	.130
Change in fat mass index, mean kg/m^2 (SD)	0.38 (0.98)	−0.63 (1.82)	.362
Change in lean body mass/fat mass, mean kg/kg (SD)	−0.15 (0.14)	0.19 (0.43)	.197
Diagnosis of osteoporosis on DXA, n (%)	5 (11.1)	43 (8.81)	.173
Diagnosis of fracture on DXA, n (%)	0	27 (5.53)	.087
Change in BMI, median kg/m^2 (IQR)	1200.33 (2241.78)	−1757.77 (4812.56)	.312
Change in total cholesterol, mean mg/dL (SD)	NA	−18.61 (20.25)	NA
Change in high-density lipoproteins, mean mg/dL (SD)	4 (0.01)	1.62 (17.07)	.895
Change in triglycerides, mean mg/dL (SD)	−67.67 (100.17)	−20.13 (83.86)	.221
Change in diastolic blood pressure, median mmHg (IQR)	0 (−5-10)	0 (−10-5)	.231
Cardiovascular			
Myocardial infarction, n (%)	0 (0)	2 (0.53)	1.00
Worsening of coronary heart disease, n (%)	0 (0)	5 (1.34)	1.000
Stroke, n (%)	1 (3.7)	8 (2.13)	.469
Worsening hypertension, n (%)	2 (7.41)	12 (3.22)	.242
Peripheral vascular disease, n (%)	0 (0)	9 (2.42)	1.000
Mortality, n (%)	2 (5.88)	11 (3.49)	.367

Abbreviations: BMI, body mass index; CP, craniopharyngioma; DXA, dual-energy x-ray absorptiometry; GH, growth hormone; IQR, interquartile range; T2DM, type 2 diabetes mellitus.
P value is calculated by ANOVA or Wilcoxon rank-sum test for continuous variables, and chi-square test or Fisher's exact test for categorical variables.

HbA1C decreased less (−0.12% [±1.94] vs −1.95% [±1.84], respectively; $P = .037$) (Table 6). Median BMI increased in GH-treated patients (0.23 [IQR −0.99-1.56] kg/m^2) and remained unchanged in untreated patients ($P = .002$), while DBP (80 [IQR 70-84] vs 76 [IQR 70-82] mmHg; $P < .001$) and MAP (94.67 [IQR 87.33-101.67) vs 93.33 [IQR 86.67-100] mmHg; $P = .007$) were both higher in GH treated patients. Lipid medication use was less frequent (46% vs 56%; $P < .001$), and mortality was lower (2.85% vs 5.05%; $P = .015$) in GH-treated patients vs untreated patients. Patients in the pituitary adenoma cohort who underwent DXA showed no significant difference in the change in bone mineral content, osteoporosis, or fracture in GH-treated vs untreated patients (Table 6).

On univariate analysis, GH replacement was associated with higher BMI at study end (est .33; 95% CI 0.11, 0.55; $P = .004$), reduced use of dyslipidemia medication (OR 0.67; 95% CI 0.50, 0.84; $P = .031$), and increased DBP (est 1.32; 95% CI 0.38, 2.25; $P = .006$). Mortality was also lower in GH-treated vs untreated patients (OR 0.55; 95% CI 0.34, 0.90; $P = .017$) (Table 7). GH dose at study end was not associated with any body composition outcome (Table 8).

On multivariable analysis, increased fasting blood glucose (est 6.45; 95% CI 3.24, 9.66; $P < .001$), increased DBP (est 1.44; 95% CI 0.45, 2.43; $P = .005$), increased MAP (est 1.20; 95% CI 0.14, 2.26; $P = .027$), and lower rate of dyslipidemia medication use (OR 0.73; 95% CI 0.57, 10.93; $P = .010$) were associated with GH replacement after adjusting for prior GH replacement, age, sex, BMI, duration of GHD, and pituitary adenoma subtype (Table 7).

Discussion

In a secondary analysis of the HypoCCS registry database, we found no significant impact of GH replacement on hepatic outcomes in patients with adult-onset CP, although we did see lower waist–hip ratio and dyslipidemia medication use. Of note, we found that GH replacement was associated with a significant decrease in bone mineral content in patients with CP. There was no significant difference in rates of osteoporosis or fractures between the groups, and few events of each were recorded. In the comparator cohort of patients with pituitary adenoma, data from HypoCCS show that GH replacement had no significant effect on hepatic outcomes, but fasting blood glucose as well as blood pressure worsened among those treated with GH replacement (Table 9).

Hepatic Outcomes

The primary aim of our study was to assess whether GH replacement improves a composite hepatic outcome including MASLD, hepatitis, cirrhosis, and abnormal liver enzymes. GH has been demonstrated in preclinical and clinical studies to contribute to the pathogenesis of hepatic steatosis through multiple pathways, including hepatic lipogenesis and inflammation.

Table 3. Univariate and multivariable analyses of outcomes in GH-treated and untreated patients with adult-onset CP

Outcome	Univariate		Multivariable	
	Estimate (95% CI)	*P* value	Estimate (95% CI)	*P* value
Composite hepatic outcome[a]				
GH replacement	0.65 (0.32, 1.30)	.222	0.56 (0.27, 1.18)	.130
No GH replacement	1 (Reference)		1 (Reference)	
Lean body mass index on BIA[b]				
GH replacement	1.14 (1.01, 1.28)	.054	1.12 (0.98, 1.28)	.144
No GH replacement	1 (Reference)		1 (Reference)	
Lean body mass on DXA, g[b]				
GH replacement	1.13 (1.00, 1.28)	.065	1.07 (0.94, 1.23)	.334
No GH replacement	1 (Reference)		1 (Reference)	
Total bone mineral content on DXA, g[c]				
GH replacement	−323.66 (−561.62, −85.71)	.018	−324.90 (−574.49, −75.31)	.034
No GH replacement	0 (Reference)		0 (Reference)	
Waist–hip ratio[d]				
GH replacement	−0.03 (−0.06, −0.01)	.010	−0.02 (−0.05, 0.00)	.067
No GH replacement	0 (Reference)		0 (Reference)	
New onset hypertension[a]				
GH replacement	0.48 (0.25 0.94)	.031	0.82 (0.38, 1.73)	.597
No GH replacement	1 (Reference)		1 (Reference)	
Systolic blood pressure, mmHg[d]				
GH replacement	−5.99 (−11.44, −0.54)	.032	−3.71 (−9.08, 1.66)	.176
No GH replacement	0 (Reference)		0 (Reference)	
Mean arterial pressure, mmHg[d]				
GH replacement	−3.55 (−7.29, 0.19)	.064	−1.86 (−5.55, 1.82)	.322
No GH replacement	0 (Reference)		0 (Reference)	
Dyslipidemia medication use[a]				
GH replacement	.52 (0.23, 1.13)	.100	0.48 (0.20, 1.14)	.097
No GH replacement	1 (Reference)		1 (Reference)	

All multivariable models were adjusted for prior GH replacement, age, sex, BMI, and duration of GH deficiency. For continuous outcomes, time in study was additionally included in the multivariable model.
Abbreviations: BIA, bioelectrical impedance analysis; BMI, body mass index; CP, craniopharyngioma; DXA, dual-energy X-ray absorptiometry; GH, growth hormone.
[a]Modeled with a logistic regression model; estimate is an odds ratio for GH treated group compared to the untreated group.
[b]Modeled with GAMLSS using a log-normal distribution with an identity link function; estimate is expressed as the ratio of estimated means of the outcome of interest for GH treated group compared with the untreated group.
[c]Modeled with GAMLSS using a BCCG distribution with an identity link function; estimate is an estimated effect of GH treatment on the outcome of interest compared to the untreated group.
[d]Modeled with GAMLSS using a BCT distribution with an identity link function; estimate is an estimated effect of GH treatment on the outcome of interest compared to the untreated group.

Table 4. Associations between GH dose at study end and change in body composition outcomes in patients with adult-onset CP

Outcome	Correlation coefficient	*P* value
Percent body fat	−0.144	.546
Fat mass index	−0.156	.510
Lean body mass/fat mass	−0.227	.435
Lean body mass index on BIA	−0.006	.986
Body mass index	0.041	.452
Fat mass on DXA	−0.065	.781
Lean body mass on DXA	0.095	.747
Total bone mineral content on DXA	0.106	.706
Waist–hip ratio	−0.132	.068

P value is calculated by Spearman rank correlation.
Abbreviations: BIA, bioelectrical impedance analysis; DXA, dual-energy X-ray absorptiometry.

GH stimulates lipolysis in white adipose tissue which increases circulating free fatty acids and acts on skeletal muscle to enhance free fatty acid mobilization and uptake [34]. Free fatty acids are then available for hepatic uptake and storage and subsequent intrahepatic lipid accumulation [35].

GH and IGF-1 also directly act on the liver by targeting hepatocytes, macrophages, and hepatic stellate cells to prevent MASLD [36]. Hepatocyte-specific knockout of GH receptor and downstream signals (JAK2, STAT5) in mice led to development of hepatic steatosis and insulin resistance [37-39]. Hepatic steatosis was observed in a model of adult-onset hepatocyte GHR knockdown, with enhanced hepatic de novo lipogenesis and reduced β-oxidation [40] as well as reduced insulin metabolism and increased gluconeogenesis [41]. Similarly, a GHD rat model demonstrated hepatic steatosis and fibrosis, with increased oxidative stress and abnormal mitochondria morphology that reversed with GH and IGF-1 administration [42].

Table 5. Baseline characteristics GH-treated and untreated patients with pituitary adenoma

Variable	No GH replacement (n = 626)	GH replacement (n = 3346)	*P* value
Demographics			
Follow-up, median years (IQR)	2.98 (1.75-4.98)	4.26 (2.1-7.89)	<.001
Age at enrollment, median years (IQR)	59.56 (50.14-69.92)	52.32 (43.42-60.89)	<.001
Age at GHD diagnosis, median years (IQR)	55 (44.3-65.23)	48.07 (38.15-57.25)	<.001
Duration of GHD, median years (IQR)	2.28 (0.28-7.36)	1.47 (0.23-6.02)	.012
Duration of GH replacement, median years (IQR)		4.26 (2.1-7.89)	
GH dose at study end, median mg/d (IQR)	0 (0-0)	0.4 (0.2-0.6)	<.001
Female sex, n (%)	223 (35.62)	1430 (42.74)	<.001
Caucasian race, n (%)	381 (60.96)	2428 (72.67)	<.001
Type of adenoma/diagnosis, n (%)			
Nonfunctioning adenoma	400 (72.6)	1956 (61.66)	<.001
Cushing disease	34 (5.43)	392 (11.72)	<.001
Acromegaly	23 (3.67)	165 (4.93)	.174
Prolactinoma	100 (15.97)	686 (20.5)	.009
Metabolic			
BMI, median kg/m^2 (IQR)	28.86 (26.22-32.92)	29.05 (25.79-32.76)	.683
Body fat, % (IQR)	30.27 (24.94-37.62)	32.17 (26.42-39.8)	.321
Fat mass index, median kg/m^2 (IQR)	8.24 (6.87-12.31)	9.06 (6.91-11.92)	.645
Lean body mass index, median kg/m^2 (IQR)	18.03 (16.52-19.4)	17.63 (15.63-19.36)	.186
Waist–hip ratio, median (IQR)	0.94 (0.89-0.99)	0.93 (0.88-0.99)	.040
HbA1C, median % (IQR)	5.8 (5.4-6.35)	5.6 (5.3-6.1)	<.001
Fasting blood glucose, median mg/dL (IQR)	90 (82-103.5)	86 (78-95)	<.001
Endocrine			
IGF-I, median ng/mL (IQR)	73 (47-102)	94 (63-143)	<.001
No. of hormonal deficits, n (%)			.213
0	440 (11.08)	65 (10.38)	
1	686 (17.27)	115 (18.37)	
2	876 (22.05)	149 (23.8)	
3	1569 (39.5)	255 (40.73)	
4	401 (10.1)	42 (6.71)	
Current comorbidities, n (%)			
T2DM	48 (7.67)	111 (3.32)	<.001
Hypertension	119 (19.01)	384 (11.48)	<.001
Hyperlipidemia	160 (25.56)	538 (16.08)	<.001
Coronary artery disease	26 (4.15)	43 (1.29)	<.001
Stroke	11 (1.76)	24 (0.72)	<.001
Osteoporosis	42 (6.71)	158 (4.72)	.536
Fracture	14 (2.24)	34 (1.02)	.084
Current therapy, n (%)			
Insulin	16 (2.56)	52 (1.55)	.318
Oral antidiabetics	70 (11.18)	175 (5.23)	<.001
Dyslipidemia medications	165 (26.36)	579 (17.30)	.015
Antihypertensives	209 (33.39)	908 (27.14)	.416
Weight loss medications	1 (0.16)	10 (0.3)	.701
Estrogen and/or progesterone	49 (7.93)	507 (15.22)	<.001
Androgen	147 (23.79)	944 (28.34)	.02
Prior therapy, n (%)			
GH replacement	41 (6.6)	490 (14.6)	<.001
Radiotherapy	165 (26.36)	1129 (33.74)	<.001

P value is calculated by analysis of variance or Wilcoxon rank-sum test for continuous and ordinal variables; and chi-square test or Fisher exact test for categorical variables.
Abbreviations: BMI, body mass index; GH, growth hormone; GHD, growth hormone deficiency; IQR, interquartile range; T2DM, type 2 diabetes mellitus.

Table 6. Outcomes in GH-treated and untreated patients with pituitary adenoma

Outcome	No GH replacement (n = 626)	GH replacement (n = 3346)	*P* value
Composite hepatic outcome, n (%)	103 (17.67)	530 (17.25)	.808
Metabolic and body composition			
New diagnosis of T2DM, n (%)	13 (3.16)	66 (2.82)	.702
Worsening of T2DM, n (%)	12 (2.92)	69 (2.96)	.963
Change in percent body fat, median (IQR)	−1.13 (−3.4-0.57)	−1.75 (−4.25-1.49)	.847
Change in fat mass index kg/m^2, median (IQR)	−0.59 (−1.16-0.22)	−0.57 (−1.61-0.73)	.809
Change in lean body mass index kg/m^2, (SD)	0.24 (± 0.99)	0.53 (± 1.31)	.521
Change in DXA fat mass, median g (IQR)	−1183 (−3451-297)	−1655 (−4275-1625)	.955
Change in lean mass on DXA, mean g (SD)	420 (± 2921.37)	1637.8 (± 3855.56)	.367
Change in total bone mineral content on DXA, mean g (SD)	100 (± 110.26)	−14.75 (± 181.2)	.105
Diagnosis of osteoporosis on DXA, n (%)	73 (12.52)	316 (10.29)	.109
Diagnosis of fracture on DXA, n (%)	30 (5.15)	189 (6.15)	.348
Change in waist–hip ratio, median (IQR)	0 (−0.02-0.05)	0 (−0.03-0.04)	.584
Change in total cholesterol, mean mg/dL (SD)	−3.21 (± 19.39)	−17.69 (± 46.26)	.543
Change in high-density lipoproteins, mean mg/dL (SD)	−2 (± 5.57)	4.84 (± 10.48)	.270
Change in triglycerides, median mg/dL (IQR)	−5 (−60-33)	−3 (−53-35.43)	.772
Change in systolic blood pressure, median mmHg (IQR)	0 (−10-12)	0 (−10-12)	.485
New onset hypertension, n (%)	235 (40.59)	1213 (39.68)	.682
Cardiovascular			
Myocardial infarction, n (%)	5 (1.22)	24 (1.02)	.609
Worsening of coronary heart disease, n (%)	10 (2.44)	43 (1.84)	.412
Stroke, n (%)	8 (1.95)	40 (1.71)	.732
Peripheral vascular disease, n (%)	7 (1.71)	50 (2.14)	.573
Mortality	23 (5.05)	62 (2.85)	.015

P value is calculated by ANOVA or Wilcoxon rank-sum test for continuous variables and chi-square test or Fisher's exact test for categorical variables.
Abbreviations: DXA, dual X-ray absorptiometry; GH, growth hormone; IQR, interquartile range; T2DM, type 2 diabetes mellitus.

GH and IGF-1 regulation of inflammation may also contribute to development of hepatic steatosis. GH treatment of M1 proinflammatory macrophages switches them to M2 anti-inflammatory macrophages [43], while knock out of IGF1 receptors in macrophage precursor cells leads to increased M1 macrophages and metabolic dysfunction in diet-induced obese mice [44]. Clinically, these shifts manifest in adults with GHD as increased inflammatory markers [45], which are decreased in patients with acromegaly [46].

MASLD has been reported in up to 50% of patients with GHD [47, 48], and IGF-I levels were shown to predict hepatic steatosis [49]. However, whether GH replacement can reverse or mitigate progression of MASLD is unclear. In a cohort of 66 patients with GHD, 19 patients who were assessed before and after 6 to 12 months of GH replacement showed improvements in liver enzymes, while histologic markers of hepatic steatosis and fibrosis improved in 5 patients who underwent repeat biopsies [23]. Other studies similarly suggest improvement in liver enzymes and fibrosis markers after more than 24 months of GH replacement [28], as well as increased rates of MASLD with cessation of GH replacement in adults with childhood-onset GHD [50]. Even in patients with intact GH function, 6 months of GH administration led to small but significant reductions in hepatic fat fraction [51, 52]. By contrast, in a cohort of 22 patients with GHD, 36% of whom had steatosis on imaging, 6 months of GH replacement did not impact standard measures of liver fat quantification on FibroScan [26].

The mixed findings in published studies and the lack of benefit in our study in patients with CP could be attributed to the other factors that drive hepatic steatosis, including hypothalamic obesity, insulin resistance, dyslipidemia, glucocorticoid over-replacement, hypogonadism, and hypothyroidism, all of which are present in many patients with CP [36, 53]. Indeed, patients with CP are observed to have higher rates of hepatic steatosis on imaging, elevated transaminases, and/or histologic liver changes consistent with MASLD compared with patients with GHD and other pituitary lesions [7, 54-57], suggesting such additional contributors may play a role in MASLD development in CP. Accordingly, these factors may dilute the isolated impact of GH replacement on hepatic outcomes and undermine our ability to detect a significant benefit with GH treatment.

Further, the design of HypoCCS limited us to analysis of outcomes based on hepatic adverse event reporting rather than results of standardized, routine hepatic imaging. Likely this underestimated the true incidence of MASLD and the impact of GH on this outcome. Rigorous, prospective studies are needed to confirm benefits of GH replacement on hepatic outcomes in adult-onset CP.

Metabolic Outcomes and Body Composition

Metabolic syndrome is up to 2-fold more prevalent in patients with GHD compared with the general population [58]. This translates to increased cardiovascular mortality if GH is not

Table 7. Univariate and multivariable analyses of outcomes in GH-treated and untreated patients with pituitary adenoma

Outcome	Univariate		Multivariable	
	Estimate (95% CI)	*P* value	Estimate (95% CI)	*P* value
Composite hepatic outcome[a]				
GH replacement	0.97 (0.77, 1.23)	.807	0.94 (0.73, 1.21)	.626
No GH replacement	1 (Reference)		1 (Reference)	
Fasting blood glucose[b]				
GH replacement	4.05 (−0.86, 8.97)	.100	6.45 (3.24, 9.66)	<.001
No GH replacement	0 (Reference)		0 (Reference)	
HbA1C[b]				
GH replacement	0.26 (−0.39, 0.91)	.449	0.20 (−0.09, 0.49)	.192
No GH replacement	0 (Reference)		0 (Reference)	
Body mass index, kg/m^2[b]				
GH replacement	0.33 (0.11, 0.55)	.004	0.19 (−0.04, 0.42)	.105
No GH replacement	0 (Reference)		0 (Reference)	
Lean body mass/fat mass, kg[b]				
GH replacement	0.05 (−0.16, 0.27)	.630	−0.09 (−0.33, 0.15)	.474
No GH replacement	0 (Reference)		0 (Reference)	
Dyslipidemia medication use[a]				
GH replacement	0.67 (0.50, 0.84)	.031	0.73 (0.57, 0.93)	.010
No GH replacement	1 (Reference)		1 (Reference)	
Worsening of hypertension[a]				
GH replacement	1.64 (0.94, 2.88)	.083	1.79 (0.99, 3.26)	.055
No GH replacement	1 (Reference)		1 (Reference)	
Diastolic blood pressure, mmHg[b]				
GH replacement	1.32 (0.38, 2.25)	.006	1.44 (0.45, 2.43)	.005
No GH replacement	0 (Reference)		0 (Reference)	
Mean arterial pressure, mmHg[b]				
GH replacement	0.74 (−0.25, 1.74)	.103	1.20 (0.14, 2.26)	.027
No GH replacement	0 (Reference)		0 (Reference)	
Osteoporosis				
GH replacement	0.79 (0.60, 1.04)	.087	0.21 (0.05, 1.00)	.0496
No GH replacement	1 (Reference)		1 (Reference)	
Fracture				
GH replacement	1.19 (0.80, 1.77)	.39	1.28 (0.84, 1.95)	.247
No GH replacement	1 (Reference)		1 (Reference)	
Mortality[a]				
GH replacement	0.55 (0.34, 0.90)	.017	0.82 (0.48, 1.42)	.485
No GH replacement	1 (Reference)		1 (Reference)	

All multivariable models were adjusted for prior GH replacement, age, sex, body mass index, pituitary adenoma subtype, and duration of GH deficiency. For continuous outcomes, time in study was additionally included in the multivariable model.
Abbreviation: GH, growth hormone.
[a]Modeled with a logistic regression model; estimate is an odds ratio for the GH treated group compared with the untreated group.
[b]Modeled with GAMLSS using a BCT distribution with an identity link function; estimate is an estimated effect of GH replacement on the outcome of interest compared with the untreated group.

replaced [59-61], and a return to normal with GH replacement [62]. Furthermore, randomized controlled clinical trials of GH replacement in adults with GHD show reduced fat mass and increased lean body mass [18, 19, 63-65]. Benefits are seen as early as 6 months after treatment initiation [19, 63], and long-term follow-up in both HypoCCS and the observational Pfizer International Metabolic Database (KIMS) confirm these benefits [17, 66]. Indeed, meta-analysis of blinded, randomized placebo-controlled trials showed dose-related changes in body composition with GH replacement, including increased lean body mass and reduced total and low-density lipoprotein cholesterol, fat mass, fasting blood glucose, and insulin, despite no change in BMI [67, 68].

However, the effects of GH replacement on body composition in patients with adult-onset CP is less clear. Studies from other groups comparing adults with CP vs nonfunctioning pituitary

Table 8. Associations between GH dose at study end and change in body composition outcomes in patients with pituitary adenoma

Outcome	Correlation coefficient	*P* value
Percent body fat	−0.078	.450
Fat mass index	−0.135	.184
Lean body mass/fat mass	0.079	.561
Lean body mass index on BIA	0.007	.960
Body mass index	0.01	.646
Fat mass on DXA	−0.137	.172
Lean body mass on DXA	0.013	.925
Total bone mineral content on DXA	0.121	.360
Waist–hip ratio	−0.04	.163

P value is calculated by Spearman rank correlation.
Abbreviations: BIA, bioelectrical impedance analysis; DXA, dual-energy X-ray absorptiometry; GH, growth hormone.

Table 9. Summary of effects of GH replacement on outcomes in patients with adult-onset CP and pituitary adenoma

Outcome	Effect of GH replacement vs no replacement	
	CP	Pituitary adenoma
Hepatic outcomes	No difference	No difference
Waist–hip ratio	Trend toward improvement	No difference
Bone mineral content	Lower	No difference
Fasting blood glucose	No difference	Worse
Dyslipidemia medication use	Trend toward improvement	No difference
Blood pressure	No difference	Worse
Mortality	No difference	No difference

Abbreviations: CP, craniopharyngioma; GH, growth hormone.

adenoma (NFPA) suggest small improvements are seen in both cohorts. In a study of 19 patients with CP and 19 with NFPA treated with GH, percent body fat and total cholesterol decreased only in the NFPA cohort after 1 year; after 5 years, patients with CP still did not experience improved body composition even though insulin sensitivity decreased [24]. In the KIMS database, improved fat free mass, lipids, and quality of life measures were seen in 183 patients with CP and 209 patients with NFPA after 2 years of GH treatment, although decreased body fat was seen only in NFPA [10]. Finally, a Dutch registry study of 291 patients with CP and 778 with NFPA showed BMI increased with GH replacement in patients with CP and was unchanged in patients with NFPA [25].

In our study, BMI did not change in patients with adult-onset CP or pituitary adenoma, possibly because we controlled for confounders that could impact the body composition response to GH including duration of GHD and GH dose. Hypothalamic obesity and the impact of hypothalamic damage on energy expenditure and sympathetic activity may be countering the impact of GH replacement on body composition in our cohort [69, 70].

Glucose metabolism was not impacted by GH use in patients with CP. Although patients with pituitary adenoma experienced worsening fasting blood glucose, rates of new-onset T2DM or worsening of prior T2DM did not differ, consistent with a prior HypoCCS report [12]. In the KIMS database, while fasting glucose increased with GH, it was not clinically significant [71]. Furthermore, a meta-analysis confirmed that while glucose may increase initially with GH replacement, longer duration of treatment beyond 1 year does not impact glucose metabolism [72].

Bone Health

The risk of fracture is 2 to 5 times higher in patients with GHD than in the general population (reviewed in [73]) and fracture prevalence is considerably higher in untreated vs treated patients (78.6% vs 53.8%, $P = .009$) [74]. Furthermore, GH replacement was shown to have a beneficial impact on bone health in adult patients with GHD, including those with CP. For instance, total bone mineral content and increased lumbar and/or femoral neck bone mineral density were seen after 4 to 5 years of GH replacement [75, 76], and long-term GH replacement up to 15 years led to further improvements, particularly in men [77]. In patients with CP, Z-scores of the spine and femoral neck increased with GH replacement [78].

However, GH treatment can lead to a decline in bone mineral density in the first 12 months after initiation, which is thought to be due to an increase in bone resorption before new bone formation starts [79]. Maximum bone mineral density is then achieved at 5 to 7 years from treatment onset [77, 79, 80]. We found a decrease in bone mineral content in patients with CP treated with GH replacement. Although median duration of GH replacement was 4 years, the lowest quartile was treated for only 2.8 years. It is possible that longer durations of treatment would have demonstrated increased bone mineral content.

Interestingly, osteoporosis and fracture rates remained unchanged with GH replacement in our study. A prior HypoCCS analysis had reported a lower incidence of fractures with GH replacement among those without pre-existing osteoporosis, but GH provided neither protection nor increased fractures among those with pre-existing osteoporosis [81]. We did not parse out those with pre-existing osteoporosis, and few cases of osteoporosis and fracture were recorded, precluding an ability to determine whether GH use correlated with these outcomes. A larger cohort and/or longer follow-up would be needed to fully assess the effect of GH on bone health in patients with adult-onset CP.

Blood Pressure

HypoCCS studies of pooled cohorts did not show an impact of GH on BP [17]. Our study demonstrated worsening BP with GH replacement among patients with pituitary adenomas, but unchanged BP outcomes among patients with CP. By contrast, in the Dutch registry study comparing outcomes in CP vs NFPA, DBP was decreased in GH-replaced patients with NFPA but unchanged in those with CP [25]. Factors driving these differences in outcomes are difficult to parse as meta-analyses of randomized controlled trials of GH replacement show variable results [67, 82].

Lipid Profiles and Dyslipidemia Medication Use

In general, lipid profiles improve with GH replacement. In the KIMS study, both total and low-density lipoprotein cholesterol levels improved in patients with NFPAs and CPs [10]

and others also show increases in levels of high-density lipoprotein cholesterol [18, 20]. In the Dutch registry study comparing outcomes in CP vs NFPA, lipid profiles improved in both groups with GH [25]. Subsequent meta-analyses confirmed these findings [68, 82].

Our study demonstrated that fewer patients with CP on GH replacement were on dyslipidemia medications. There were too few reports of lipid levels in patients with CP to analyze the effect of GH replacement.

Limitations

As is typical of studies that use surveillance data such as HypoCCS, we recognize that rigorously testing our primary and secondary outcomes could be challenging. Specifically, patients on GH replacement had longer follow-up time in the study, which may have impacted the amount of data available for analysis. Sample sizes with granular data on laboratory and anthropometric measures were small, and not all outcomes had sufficient data at last follow-up. Data were not necessarily collected on all metabolic outcomes for each patient globally. Most important, as data on hepatic effects were collected to report on adverse events, imaging and screening for MASLD and metabolic dysfunction–associated steatohepatitis were not performed. All of these confounders may impact interpretation and application of our results to patients with CP treated with GH replacement and potentially underestimate the impact of GH replacement on metabolic and hepatic outcomes. Given these limitations, it is difficult to establish a clear effect for GH on changes in these outcomes, and data from more rigorous studies would be needed. However, this global surveillance study reflects real-world data and clinical experience, strengthening its value as a resource for examination of this important issue. Further, prior studies conducting univariate analyses to assess the impact of GH on metabolic outcomes [17-22, 83-90] generally showed improvements in body composition, lipids, and bone mineral density. By contrast, studies that performed multivariable analyses [10, 24, 25] showed similar findings to ours, with an increase in BMI in patients with CP, limited benefit in body composition, or no impact on metabolic syndrome. This suggests further strength to our study given the more rigorous statistical modeling of a global dataset.

Conclusions

In an analysis of HypoCCS data, we did not demonstrate a significant improvement in the composite outcome of hepatic disease among patients with adult-onset CP treated with GH replacement compared with untreated patients. Patients with CP replaced with GH showed decreased bone mineral content, with no significant increase in osteoporosis and fracture rates noted. Patients with CP replaced with GH also showed decreased waist–hip ratio; this effect was not seen in our comparative analysis of patients with pituitary adenomas. Although glucose metabolism remained unchanged in patients with CP regardless of GH replacement, it worsened with GH replacement in patients with pituitary adenoma. Mortality during this surveillance period was unchanged in both the CP and pituitary adenoma cohorts. The mechanism underlying adverse metabolic outcomes with pituitary adenoma and not with CP is unclear, but it may relate to the sequelae of hypothalamic dysfunction observed in patients with CP that are not adequately addressed with GH replacement. Our results suggest a favorable impact for GH replacement on some metabolic outcomes and a potential benefit for recommending GH replacement in select patients with adult-onset CP. Prospective studies of GH replacement in adult-onset CP can further define the benefits on metabolic outcomes in these patients.

Acknowledgments

We thank Shira Berman for assistance with manuscript editing. This publication is based on research using data from data contributors Eli Lilly and Company that has been made available through Vivli, Inc. Vivli has not contributed to or approved, and Vivli and Eli Lilly and Company are not in any way responsible for, the contents of this publication.

Funding

None

Disclosures

The authors have nothing to disclose.

Data Availability

Restrictions apply to the availability of some or all data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

Clinical Trial Information

ClinicalTrials.gov registration number: NCT01088399 (registered February 25, 2010).

References

1. Zacharia BE, Bruce SS, Goldstein H, Malone HR, Neugut AI, Bruce JN. Incidence, treatment and survival of patients with craniopharyngioma in the surveillance, epidemiology and end results program. *Neuro Oncol*. 2012;14(8):1070-1078.
2. Mende KC, Kellner T, Petersenn S, *et al*. Clinical situation, therapy, and follow-up of adult craniopharyngioma. *J Clin Endocrinol Metab*. 2020;105(1):252-265.
3. Muller HL. Craniopharyngioma. *Endocr Rev*. 2014;35(3):513-543.
4. Yuen KCJ, Mattsson AF, Burman P, *et al*. Relative risks of contributing factors to morbidity and mortality in adults with craniopharyngioma on growth hormone replacement. *J Clin Endocrinol Metab*. 2018;103(2):768-777.
5. Wijnen M, Olsson DS, van den Heuvel-Eibrink MM, *et al*. The metabolic syndrome and its components in 178 patients treated for craniopharyngioma after 16 years of follow-up. *Eur J Endocrinol*. 2018;178(1):11-22.
6. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology*. 2016;64(1):73-84.
7. Adams LA, Feldstein A, Lindor KD, Angulo P. Nonalcoholic fatty liver disease among patients with hypothalamic and pituitary dysfunction. *Hepatology*. 2004;39(4):909-914.
8. Gautier A, Godbout A, Grosheny C, *et al*. Markers of recurrence and long-term morbidity in craniopharyngioma: a systematic

analysis of 171 patients. *J Clin Endocrinol Metab*. 2012;97(4):1258-1267.
9. Nyenwe EA, Williamson-Baddorf S, Waters B, Wan JY, Solomon SS. Nonalcoholic fatty liver disease and metabolic syndrome in hypopituitary patients. *Am J Med Sci*. 2009;338(3):190-195.
10. Verhelst J, Kendall-Taylor P, Erfurth EM, *et al*. Baseline characteristics and response to 2 years of growth hormone (GH) replacement of hypopituitary patients with GH deficiency due to adult-onset craniopharyngioma in comparison with patients with nonfunctioning pituitary adenoma: data from KIMS (Pfizer International metabolic database). *J Clin Endocrinol Metab*. 2005;90(8):4636-4643.
11. Beauregard C, Utz AL, Schaub AE, *et al*. Growth hormone decreases visceral fat and improves cardiovascular risk markers in women with hypopituitarism: a randomized, placebo-controlled study. *J Clin Endocrinol Metab*. 2008;93(6):2063-2071.
12. Attanasio AF, Jung H, Mo D, *et al*. Prevalence and incidence of diabetes mellitus in adult patients on growth hormone replacement for growth hormone deficiency: a surveillance database analysis. *J Clin Endocrinol Metab*. 2011;96(7):2255-2261.
13. Hartman ML, Xu R, Crowe BJ, *et al*. Prospective safety surveillance of GH-deficient adults: comparison of GH-treated vs untreated patients. *J Clin Endocrinol Metab*. 2013;98(3):980-988.
14. Stochholm K, Kiess W. Long-term safety of growth hormone-A combined registry analysis. *Clin Endocrinol (Oxf)*. 2018;88(4):515-528.
15. Fleseriu M, Hashim IA, Karavitaki N, *et al*. Hormonal replacement in hypopituitarism in adults: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2016;101(11):3888-3921.
16. Yuen KCJ, Biller BMK, Radovick S, *et al*. American Association of Clinical Endocrinologists and American College of Endocrinology guidelines for management of growth hormone deficiency in adults and patients transitioning from pediatric to adult care. *Endocr Pract*. 2019;25(11):1191-1232.
17. Attanasio AF, Bates PC, Ho KK, *et al*. Human growth hormone replacement in adult hypopituitary patients: long-term effects on body composition and lipid status--3–year results from the HypoCCS database. *J Clin Endocrinol Metab*. 2002;87(4):1600-1606.
18. Hoffman AR, Kuntze JE, Baptista J, *et al*. Growth hormone (GH) replacement therapy in adult-onset gh deficiency: effects on body composition in men and women in a double-blind, randomized, placebo-controlled trial. *J Clin Endocrinol Metab*. 2004;89(5):2048-2056.
19. Salomon F, Cuneo RC, Hesp R, Sonksen PH. The effects of treatment with recombinant human growth hormone on body composition and metabolism in adults with growth hormone deficiency. *N Engl J Med*. 1989;321(26):1797-1803.
20. Elbornsson M, Gotherstrom G, Bosaeus I, Bengtsson BA, Johannsson G, Svensson J. Fifteen years of GH replacement improves body composition and cardiovascular risk factors. *Eur J Endocrinol*. 2013;168(5):745-753.
21. Jorgensen JO, Vahl N, Hansen TB, Thuesen L, Hagen C, Christiansen JS. Growth hormone versus placebo treatment for one year in growth hormone deficient adults: increase in exercise capacity and normalization of body composition. *Clin Endocrinol (Oxf)*. 1996;45(6):681-688.
22. Oi-Yo Y, Yamamoto M, Urai S, *et al*. Long-term metabolic effectiveness and safety of growth hormone replacement therapy in patients with adult growth hormone deficiency: a single-institution study in Japan. *Pituitary*. 2024;27(5):605-613.
23. Nishizawa H, Iguchi G, Murawaki A, *et al*. Nonalcoholic fatty liver disease in adult hypopituitary patients with GH deficiency and the impact of GH replacement therapy. *Eur J Endocrinol*. 2012;167(1):67-74.
24. Profka E, Giavoli C, Bergamaschi S, *et al*. Analysis of short- and long-term metabolic effects of growth hormone replacement therapy in adult patients with craniopharyngioma and non-functioning pituitary adenoma. *J Endocrinol Invest*. 2015;38(4):413-420.
25. Verweij T, Slagboom TNA, van Varsseveld NC, van der Lely AJ, Drent ML, van Bunderen CC. Cardiovascular risk profile in growth hormone-treated adults with craniopharyngioma compared to non-functioning pituitary adenoma: a national cohort study. *Eur J Endocrinol*. 2021;185(6):793-801.
26. Carvalho-Furtado ACL, Carvalho-Louro DM, Regattieri NAT, *et al*. Transient elastography and controlled attenuation parameter (CAP) in the assessment of liver steatosis in severe adult growth hormone deficiency. *Front Endocrinol (Lausanne)*. 2019;10:364.
27. Gardner CJ, Irwin AJ, Daousi C, *et al*. Hepatic steatosis, GH deficiency and the effects of GH replacement: a liverpool magnetic resonance spectroscopy study. *Eur J Endocrinol*. 2012;166(6):993-1002.
28. Matsumoto R, Fukuoka H, Iguchi G, *et al*. Long-term effects of growth hormone replacement therapy on liver function in adult patients with growth hormone deficiency. *Growth Horm IGF Res*. 2014;24(5):174-179.
29. Brown EG, Wood L, Wood S. The medical dictionary for regulatory activities (MedDRA). *Drug Saf*. 1999;20(2):109-117.
30. Rinella ME, Lazarus JV, Ratziu V, *et al*. A multisociety delphi consensus statement on new fatty liver disease nomenclature. *Ann Hepatol*. 2024;29(1):101133.
31. Rigby RA, Stasinopoulos DM. Generalized additive models for location, scale and shape. *J R Stat Soc Ser C Appl Stat*. 2005;54(3):507-554.
32. van Buuren S, Fredriks M. Worm plot: a simple diagnostic device for modelling growth reference curves. *Stat Med*. 2001;20(8):1259-1277.
33. R Core Team. *R: A Language and Environment for Statistical Computing*. R v4.3.2. R Foundation for Statistical Computing; 2023.
34. Moller N, Jorgensen JO. Effects of growth hormone on glucose, lipid, and protein metabolism in human subjects. *Endocr Rev*. 2009;30(2):152-177.
35. Armstrong MJ, Hazlehurst JM, Hull D, *et al*. Abdominal subcutaneous adipose tissue insulin resistance and lipolysis in patients with non-alcoholic steatohepatitis. *Diabetes Obes Metab*. 2014;16(7):651-660.
36. Takahashi Y. The role of growth hormone and insulin-like growth factor-I in the liver. *Int J Mol Sci*. 2017;18(7):1447.
37. Cui Y, Hosui A, Sun R, *et al*. Loss of signal transducer and activator of transcription 5 leads to hepatosteatosis and impaired liver regeneration. *Hepatology*. 2007;46(2):504-513.
38. Fan Y, Menon RK, Cohen P, *et al*. Liver-specific deletion of the growth hormone receptor reveals essential role of growth hormone signaling in hepatic lipid metabolism. *J Biol Chem*. 2009;284(30):19937-19944.
39. Sos BC, Harris C, Nordstrom SM, *et al*. Abrogation of growth hormone secretion rescues fatty liver in mice with hepatocyte-specific deletion of JAK2. *J Clin Invest*. 2011;121(4):1412-1423.
40. Cordoba-Chacon J, Majumdar N, List EO, *et al*. Growth hormone inhibits hepatic De Novo lipogenesis in adult mice. *Diabetes*. 2015;64(9):3093-3103.
41. Rufinatscha K, Ress C, Folie S, *et al*. Metabolic effects of reduced growth hormone action in fatty liver disease. *Hepatol Int*. 2018;12(5):474-481.
42. Nishizawa H, Takahashi M, Fukuoka H, Iguchi G, Kitazawa R, Takahashi Y. GH-independent IGF-I action is essential to prevent the development of nonalcoholic steatohepatitis in a GH-deficient rat model. *Biochem Biophys Res Commun*. 2012;423(2):295-300.
43. Soler Palacios B, Nieto C, Fajardo P, *et al*. Growth hormone reprograms macrophages toward an anti-inflammatory and reparative profile in an MAFB-dependent manner. *J Immunol*. 2020;205(3):776-788.
44. Spadaro O, Camell CD, Bosurgi L, *et al*. IGF1 shapes macrophage activation in response to immunometabolic challenge. *Cell Rep*. 2017;19(2):225-234.
45. Deepak D, Daousi C, Javadpour M, *et al*. The influence of growth hormone replacement on peripheral inflammatory and

cardiovascular risk markers in adults with severe growth hormone deficiency. *Growth Horm IGF Res*. 2010;20(3):220-225.
46. Ozkan C, Altinova AE, Cerit ET, *et al*. Markers of early atherosclerosis, oxidative stress and inflammation in patients with acromegaly. *Pituitary*. 2015;18(5):621-629.
47. Chalasani N, Younossi Z, Lavine JE, *et al*. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the study of liver diseases. *Hepatology*. 2018;67(1):328-357.
48. Ichikawa T, Hamasaki K, Ishikawa H, Ejima E, Eguchi K, Nakao K. Non-alcoholic steatohepatitis and hepatic steatosis in patients with adult onset growth hormone deficiency. *Gut*. 2003;52(6):914.
49. Nguyen A, Ricolfi F, Lemogne B, *et al*. Liver fat content in people with pituitary diseases: influence of serum IGF1 levels. *Horm Metab Res*. 2018;50(4):303-307.
50. Fukuda I, Hizuka N, Yasumoto K, Morita J, Kurimoto M, Takano K. Metabolic co-morbidities revealed in patients with childhood-onset adult GH deficiency after cessation of GH replacement therapy for short stature. *Endocr J*. 2008;55(6):977-984.
51. Momin AA, Recinos MA, Cioffi G, *et al*. Descriptive epidemiology of craniopharyngiomas in the United States. *Pituitary*. 2021;24(4):517-522.
52. Dichtel LE, Corey KE, Haines MS, *et al*. Growth hormone administration improves nonalcoholic fatty liver disease in overweight/obesity: a randomized trial. *J Clin Endocrinol Metab*. 2023;108(12):e1542-e1550.
53. Hazlehurst JM, Tomlinson JW. Non-alcoholic fatty liver disease in common endocrine disorders. *Eur J Endocrinol*. 2013;169(2):R27-R37.
54. Hong JW, Kim JY, Kim YE, Lee EJ. Metabolic parameters and nonalcoholic fatty liver disease in hypopituitary men. *Horm Metab Res*. 2011;43(1):48-54.
55. Yuan XX, Zhu HJ, Pan H, *et al*. Clinical characteristics of nonalcoholic fatty liver disease in Chinese adult hypopituitary patients. *World J Gastroenterol*. 2019;25(14):1741-1752.
56. Jung SY, Lee YJ, Lee HJ, *et al*. Nonalcoholic fatty liver disease in long-term survivors of childhood-onset craniopharyngioma. *Ann Pediatr Endocrinol Metab*. 2017;22(3):189-196.
57. Hoffmann A, Bootsveld K, Gebhardt U, Daubenbuchel AM, Sterkenburg AS, Muller HL. Nonalcoholic fatty liver disease and fatigue in long-term survivors of childhood-onset craniopharyngioma. *Eur J Endocrinol*. 2015;173(3):389-397.
58. Claessen KM, Appelman-Dijkstra NM, Adoptie DM, *et al*. Metabolic profile in growth hormone-deficient (GHD) adults after long-term recombinant human growth hormone (rhGH) therapy. *J Clin Endocrinol Metab*. 2013;98(1):352-361.
59. Tomlinson JW, Holden N, Hills RK, *et al*. Association between premature mortality and hypopituitarism. West midlands prospective hypopituitary study group. *Lancet*. 2001;357(9254):425-431.
60. Verhelst J, Mattsson AF, Luger A, *et al*. Prevalence and characteristics of the metabolic syndrome in 2479 hypopituitary patients with adult-onset GH deficiency before GH replacement: a KIMS analysis. *Eur J Endocrinol*. 2011;165(6):881-889.
61. Holmer H, Svensson J, Rylander L, *et al*. Nonfatal stroke, cardiac disease, and diabetes mellitus in hypopituitary patients on hormone replacement including growth hormone. *J Clin Endocrinol Metab*. 2007;92(9):3560-3567.
62. Svensson J, Bengtsson BA, Rosen T, Oden A, Johannsson G. Malignant disease and cardiovascular morbidity in hypopituitary adults with or without growth hormone replacement therapy. *J Clin Endocrinol Metab*. 2004;89(7):3306-3312.
63. Chihara K, Kato Y, Kohno H, *et al*. Efficacy and safety of growth hormone (GH) in the treatment of adult Japanese patients with GH deficiency: a randomised, placebo-controlled study. *Growth Horm IGF Res*. 2006;16(2):132-142.
64. Baum HB, Biller BM, Finkelstein JS, *et al*. Effects of physiologic growth hormone therapy on bone density and body composition in patients with adult-onset growth hormone deficiency. A randomized, placebo-controlled trial. *Ann Intern Med*. 1996;125(11):883-890.
65. Carroll PV, Christ ER, Bengtsson BA, *et al*. Growth hormone deficiency in adulthood and the effects of growth hormone replacement: a review. Growth hormone research society scientific committee. *J Clin Endocrinol Metab*. 1998;83(2):382-395.
66. Abs R, Feldt-Rasmussen U, Mattsson AF, *et al*. Determinants of cardiovascular risk in 2589 hypopituitary GH-deficient adults—a KIMS database analysis. *Eur J Endocrinol*. 2006;155(1):79-90.
67. Maison P, Griffin S, Nicoue-Beglah M, Haddad N, Balkau B, Chanson P. Metaanalysis of blinded RP-CT. Impact of growth hormone (GH) treatment on cardiovascular risk factors in GH-deficient adults: a metaanalysis of blinded, randomized, placebo-controlled trials. *J Clin Endocrinol Metab*. 2004;89(5):2192-2199.
68. Newman CB, Carmichael JD, Kleinberg DL. Effects of low dose versus high dose human growth hormone on body composition and lipids in adults with GH deficiency: a meta-analysis of placebo-controlled randomized trials. *Pituitary*. 2015;18(3):297-305.
69. Lustig RH. Autonomic dysfunction of the beta-cell and the pathogenesis of obesity. *Rev Endocr Metab Disord*. 2003;4(1):23-32.
70. Roth CL, McCormack SE. Acquired hypothalamic obesity: a clinical overview and update. *Diabetes Obes Metab*. 2024;26(S2):34-45.
71. Johannsson G, Touraine P, Feldt-Rasmussen U, *et al*. Long-term safety of growth hormone in adults with growth hormone deficiency: overview of 15,809 GH-treated patients. *J Clin Endocrinol Metab*. 2022;107(7):1906-1919.
72. Zhou H, Sun L, Zhang S, Wang Y, Wang G. Effect of long-term growth hormone replacement on glucose metabolism in adults with growth hormone deficiency: a systematic review and meta-analysis. *Pituitary*. 2021;24(1):130-142.
73. Akirov A, Rudman Y, Fleseriu M. Hypopituitarism and bone disease: pathophysiology, diagnosis and treatment outcomes. *Pituitary*. 2024;27(6):778-788.
74. Mazziotti G, Bianchi A, Bonadonna S, *et al*. Increased prevalence of radiological spinal deformities in adult patients with GH deficiency: influence of GH replacement therapy. *J Bone Miner Res*. 2006;21(4):520-528.
75. Gotherstrom G, Svensson J, Koranyi J, *et al*. A prospective study of 5 years of GH replacement therapy in GH-deficient adults: sustained effects on body composition, bone mass, and metabolic indices. *J Clin Endocrinol Metab*. 2001;86(10):4657-4665.
76. Tritos NA, Hamrahian AH, King D, *et al*. Predictors of the effects of 4 years of growth hormone replacement on bone mineral density in patients with adult-onset growth hormone deficiency—a KIMS database analysis. *Clin Endocrinol (Oxf)*. 2013;79(2):178-184.
77. Appelman-Dijkstra NM, Claessen KM, Hamdy NA, Pereira AM, Biermasz NR. Effects of up to 15 years of recombinant human GH (rhGH) replacement on bone metabolism in adults with growth hormone deficiency (GHD): the Leiden cohort study. *Clin Endocrinol (Oxf)*. 2014;81(5):727-735.
78. van Santen SS, Olsson DS, Hammarstrand C, *et al*. Body composition and bone mineral density in craniopharyngioma patients: a longitudinal study over 10 years. *J Clin Endocrinol Metab*. 2020;105(12):dgaa607.
79. Barake M, Klibanski A, Tritos NA. Effects of recombinant human growth hormone therapy on bone mineral density in adults with growth hormone deficiency: a meta-analysis. *J Clin Endocrinol Metab*. 2014;99(3):852-860.
80. Bex M, Abs R, Maiter D, Beckers A, Lamberigts G, Bouillon R. The effects of growth hormone replacement therapy on bone metabolism in adult-onset growth hormone deficiency: a 2-year open randomized controlled multicenter trial. *J Bone Miner Res*. 2002;17(6):1081-1094.
81. Mo D, Fleseriu M, Qi R, *et al*. Fracture risk in adult patients treated with growth hormone replacement therapy for growth hormone deficiency: a prospective observational cohort study. *Lancet Diabetes Endocrinol*. 2015;3(5):331-338.

82. Giagulli VA, Castellana M, Perrone R, Guastamacchia E, Iacoviello M, Triggiani V. GH supplementation effects on cardiovascular risk in GH deficient adult patients: a systematic review and meta-analysis. *Endocr Metab Immune Disord Drug Targets*. 2017;17(4):285-296.
83. Losa M, Beck-Peccoz P, Aimaretti G, *et al.* Characteristics and outcomes of Italian patients from the observational, multicentre, hypopituitary control and complications study (HypoCCS) according to tertiles of growth hormone peak concentration following stimulation testing at study entry. *Clin Endocrinol (Oxf)*. 2015;83(4):527-535.
84. Shimatsu A, Ishii H, Nishinaga H, Murai O, Chihara K. Safety and effectiveness of long-term growth hormone therapy in Japanese patients with adult growth hormone deficiency: a postmarketing, multicenter, observational study. *Endocr J*. 2017;64(7):651-662.
85. Webb SM, Mo D, Lamberts SW, *et al.* Metabolic, cardiovascular, and cerebrovascular outcomes in growth hormone-deficient subjects with previous cushing's disease or non-functioning pituitary adenoma. *J Clin Endocrinol Metab*. 2010;95(2):630-638.
86. Gotherstrom G, Bengtsson BA, Bosaeus I, Johannsson G, Svensson J. A 10-year, prospective study of the metabolic effects of growth hormone replacement in adults. *J Clin Endocrinol Metab*. 2007;92(4):1442-1445.
87. Chrisoulidou A, Beshyah SA, Rutherford O, *et al.* Effects of 7 years of growth hormone replacement therapy in hypopituitary adults. *J Clin Endocrinol Metab*. 2000;85(10):3762-3769.
88. Rochira V, Mossetto G, Jia N, *et al.* Analysis of characteristics and outcomes by growth hormone treatment duration in adult patients in the Italian cohort of the hypopituitary control and complications study (HypoCCS). *J Endocrinol Invest*. 2018;41(11):1259-1266.
89. Spielhagen C, Schwahn C, Moller K, *et al.* The benefit of long-term growth hormone (GH) replacement therapy in hypopituitary adults with GH deficiency: results of the German KIMS database. *Growth Horm IGF Res*. 2011;21(1):1-10.
90. Postma MR, van Beek AP, Jonsson PJ, *et al.* Improvements in body composition after 4 years of growth hormone treatment in adult-onset hypopituitarism compared to age-matched controls. *Neuroendocrinology*. 2019;109(2):131-140.