Effects of Recombinant Human Growth Hormone Therapy on Bone Mineral Density in Adults With Growth Hormone Deficiency: A Meta-Analysis

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Objective: GH deficiency is associated with decreased bone mineral density (BMD) and increased fracture risk. Because the effects of recombinant human GH (rhGH) therapy on BMD and bone mineral content have not been systematically investigated, we conducted a meta-analysis of pertinent studies.

Design: A thorough search of the literature (MEDLINE, EMBASE, and the Cochrane Register) was performed. Relevant studies were divided and analyzed according to their design (randomized/controlled or prospective/retrospective) and duration of rhGH therapy ($\leq$12 months and $>$ 12 months).

Results: Administration of rhGH led to a significant increase in lumbar spine (LS) and femoral neck (FN) BMD in randomized/controlled studies of more than 1 year [weighted mean difference (95% confidence interval)] of 0.038 g/cm^2 (0.011–0.065) and 0.021 g/cm^2 (0.006–0.037) at the LS and FN, respectively, and a nonsignificant drop at the same sites in studies of shorter duration. In prospective studies, a significant increase in the LS and FN BMD was obtained. On meta-regression, a negative association was observed between the change in LS and FN BMD and subjects' age and a positive association between the BMD change and treatment duration. In a subgroup analysis, the increase in LS and FN BMD was significant in men [0.048 g/cm^2 (0.033–0.064) and 0.051 g/cm^2 (0.003–0.098), respectively] but not in women.

Conclusion: This meta-analysis suggests a beneficial effect of rhGH replacement on BMD in adults with GH deficiency. This effect is affected by gender, age, and treatment duration. Larger studies are needed to evaluate the effect of rhGH on fracture risk. (***J Clin Endocrinol Metab*** **99: 852–860, 2014)**

The role of GH in bone biology has been a subject of interest for many decades. Both in vitro and in vivo studies have shown that GH, acting directly and indirectly through IGF-I, has an important anabolic role in skeletal growth and bone maintenance. Early experiments in animals revealed that GH deficiency (GHD) is associated with decreased bone mass and body length, which can be successfully restored by hormone replacement (1).

In humans, the effects of GHD on bone have also been well described. In children, GHD leads to short stature and has been associated with low bone mineral density (BMD) (2). In adults, GHD results in a clinical syndrome that includes abnormalities in body composition, exercise capacity, and general well-being along with decreased BMD and increased fracture risk (3, 4). When compared with non-GHD control populations, adults with GHD and hypopituitarism have been shown to have 2- to 5-fold higher fracture rates, which may be attributed to pituitary hormone deficiencies, (including GHD and hypogonadism) and/or excess replacement therapies (5–7).

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Abbreviations: BMC, bone mineral content; BMD, bone mineral density; CD, Cushing's disease; CI, confidence interval; DXA, dual-energy x-ray absorptiometry; FN, femoral neck; GHD, GH deficiency; LS, lumbar spine; rhGH, recombinant human GH; SDS, SD score; TB, total body; TF, total femur.

Since the advent of recombinant human GH (rhGH) therapy in 1985, GH replacement became a routine clinical practice in children with GHD and growth delay (8, 9). In adults, the precise therapeutic role of GH replacement remains a matter of debate. GH replacement therapy can be beneficial with regard to exercise capacity, body composition, serum lipids, and quality of life (3). However, the effects of rhGH on bone metabolism and bone density seem more complex and have been the subject of multiple studies with contradictory results due to several factors, including variable duration of replacement therapy.

The long-term effects of rhGH replacement on BMD are mainly derived from prospective trials, extending up to 15 years that showed a biphasic change in BMD in response to GH replacement, with an initial decrease around 6 months after therapy initiation, followed by a subsequent increase after at least 1 year of replacement (10). The results of short-term (12 mo or less) randomized controlled trials of GH replacement were, indeed, mostly negative, revealing a decrease or no change in BMD with rhGH (11). Benefits of rhGH replacement in terms of bone health were also addressed in two meta-analyses with contradictory conclusions, with one showing overall BMD increase and the other reporting no significant change in BMD (11, 12). In both meta-analyses, the effect of GH replacement on BMD was not evaluated with regard to patients' age, gender, baseline or on-therapy IGF-I levels, or treatment duration. Available literature is also unclear with regard to the effect of GH replacement on fracture risk because there are no clinical trials of rhGH replacement with fracture end points (6, 7).

In the present study, we have conducted a separate, comprehensive meta-analysis of either randomized or prospective clinical studies examining the effects of rhGH therapy on bone densitometric end points in adult patients with GHD, aiming at better understanding the effect of such replacement therapy on bone health. To characterize the impact of patients' demographics and treatment characteristics on the effects of GH replacement on BMD, we have conducted additional subgroup analyses and meta-regression analyses.

Materials and Methods

Literature search

We conducted a comprehensive literature search for published studies on the effects of rhGH replacement therapy on BMD and/or bone mineral content (BMC) up to September 2012. Our searches were both computerized and manual. The online search included the databases MEDLINE (PubMed), EMBASE, and the Cochrane Register of Controlled Trials using the key words GH, somatotropin, somatropin, somatotrophin, somatrophin, therapeutic use, GH deficiency, and BMD and the

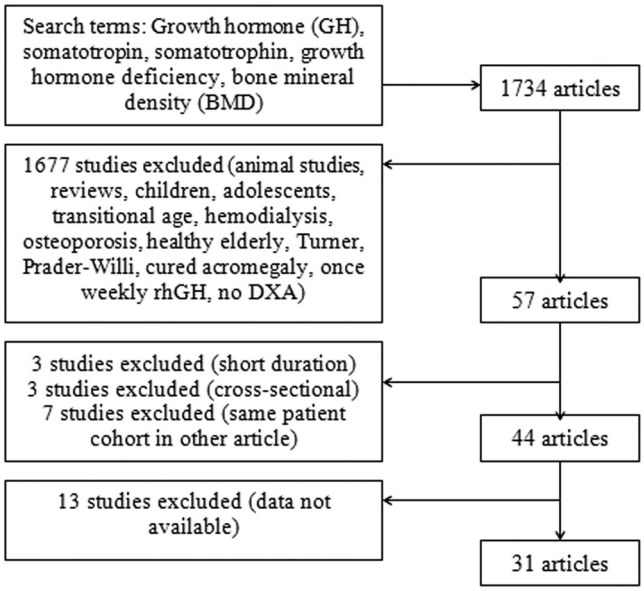


Figure 1. Study flow chart showing search results for studies included in the meta-analysis.

Boolean functions AND and OR. We then did a manual search of the references of both original articles collected and review articles on the topic. In the present meta-analysis, we included all human studies examining the effects of daily rhGH replacement therapy on BMD and/or BMC with no limitation on the study language or the sample size.

The initial literature search identified 1734 articles, of which 1677 were excluded for various reasons (Figure 1), including irrelevant study type (animal studies, reviews), study population (children, adolescents, patients in the transition period to adulthood, Turner syndrome, Prader-Willi syndrome, osteoporosis, healthy elderly, hemodialysis patients, GHD after cured acromegaly), long-acting rhGH replacement treatment (once weekly) and densitometric technique (quantitative computed tomography, ultrasound, single and dual photon absorptiometry because the use of these methods is not as extensively validated as well as dual-energy x-ray absorptiometry (DXA) and cannot be synthesized together with DXA results). Thirteen studies were further excluded because of short-term treatment duration (less than 6 months), cross-sectional design, and nonunique cohorts used in other studies. Among the 44 remaining studies, 17 did not have absolute BMC or BMD data in the published manuscripts so the corresponding authors were contacted. Only four of the authors who responded were able to retrieve and send original data, and thus, 13 studies had to be further excluded.

Data abstraction and analysis

Two authors independently reviewed studies that were included in the meta-analysis. They abstracted data with regard to study design (including the use of intention to treat analyses), year of publication, and number of subjects included and number withdrawn. They also extracted data on the study subject demographics, their underlying disease, and rhGH replacement regimen, including age and gender distribution of patients, age at onset, diagnostic testing and etiology of GHD, duration and dose of rhGH, presence of other anterior pituitary hormone deficiencies and their replacement, baseline body mass index, BMD data and IGF-I levels, the sites imaged by DXA, and the presence of

concurrent diseases and medications that might affect bone. Studies were not scored for quality (eg, using the Jadad scale); however, the authors assessed the quality of all studies included with regard to their design, inclusion and exclusion criteria, patient follow-up, and analysis of end points.

The clinical end points evaluated were the absolute change in BMC and BMD in response to rhGH replacement therapy. Sites examined included total body (TB), posterior anterior lumbar spine (LS), total femur (TF), and femoral neck (FN). The authors of studies that did not include absolute BMC or BMD values in their published manuscripts were contacted. These data were included, depending on author response and data availability. Otherwise, an attempt was made at extracting data from published graphs, when available (13–16). Some studies had to be excluded as a result of lack of adequate data on appropriate end points.

For the purpose of analysis, studies were combined according to their design (randomized/controlled or prospective/retrospective) and the duration of rhGH replacement treatment (up to 12 mo or exceeding 12 mo). Four different data sets were thus synthesized separately: randomized studies of rhGH replacement therapy of 12 months or less, randomized studies of treatment for longer than 12 months, prospective/retrospective studies of 12 months or less, and those exceeding 12 months. The reason for creating such a dichotomy was to increase effect homogeneity between combined studies and account for the hypothesis that significant increases in BMD may need more than 12 months to become apparent. Studies that included a randomized phase followed by a prospective extension were analyzed as two separate studies according to the above classification. The studies that reported data for two time periods (up to 12 mo and longer than 12 mo) were considered separately. Publications reporting data on the same patient cohort within the same time frame were considered as a single study for the purpose of analysis.

Statistical analysis

Data was combined using the DerSimonian-Laird method, that is, random effects model (17). This model provides a more conservative estimate of overall treatment effect, which may be especially relevant when studies are of different design and duration of follow-up (17). With this method, we estimated weighted mean differences and 95% confidence intervals (CIs) for the end points used. Standardized mean differences and the 95% CI were also calculated.

Both funnel plots as well as Duval and Tweedie's trim and fill analyses were used to examine possible existing publication biases. In addition, the presence of heterogeneity between studies was examined using the Cochran Q test and the I^2 index (18). In cases in which heterogeneity was present ($P < .05$ on the Q test), subgroup analysis was pursued.

Statistical analyses were performed using the statistical package Comprehensive Meta-Analysis (version 2.2.046, 2007; Bio-

Table 1. Characteristics of Subjects of Studies Included in the Meta-Analysis

First Author, Year	Study Design	Age, y	Gender, % M/F	Onset of GHD, % Childhood/Adult	Hypopituitarism, %
Thoren et al, 1993 (30)	R, PC	42 (22–65)	55/45	0/100	
Sartorio et al, 1996 (29)	Pros OL	29.6 ± 3.4 SD	100/0	100/0	
Finkenstedt et al, 1997 (22)	R, DB, PC	44.0 ± 3.1	78/22	0/100	
Cuneo et al, 1998 (21)	R, DB, PC	40.5 ± 1.5	56/44	33/67	71 (TSH), 74 (ACTH), 79 (FSH/LH)
Janssen et al, 1998 (24)	Pros OL	50 ± 2	42/58	0/100	83 (TSH), 83 (ACTH), 95.7 (FSH/LH)
Kotzmann et al, 1998 (26)	Pros OL	45 ± 2.6 SD	21/79	0/100	57.8 (TSH), 52.6 (ACTH), 31.6 (FSH/LH)
Rodriguez-Arnao et al, 1998 (28)	R, DB, PC (6 m) Pros OL (12 m)	39.8 (21.1–59.9)	51/49	20/80	42.8 (TSH), 45.7 (ACTH), 51.4 (FSH/LH)
Johansson et al, 1999 (25)	R, PC	46 ± 7 SD	58/42	6/94	
Luisetto et al, 1999 (27)	R, DB, PC (6 m) Pros OL (12 m)	28.9 ± 2.6 SD	90/10	80/20	90 (TSH), 80 (ACTH), 100 (FSH/LH)
Longobardi et al, 1999 (15)	Pros OL	27.0 ± 4.4 SD	56/44	50/50	
Biller et al, 2000 (20)	R, DB, PC (18 m) (ITT)	median 51 (24–64)	100/0	0/100	82.5 (TSH), 65 (ACTH), 82.5 (FSH/LH)
	Pros OL (18 m)	49.5 ± 2.3	100/0	0/100	75 (TSH), 65 (ACTH), 65 (FSH/LH)
Gomez et al, 2000 (23)	Pros OL	40.3 ± 10.9 SD	70/30	0/100	85 (TSH), 80 (ACTH), 70 (FSH/LH)
Beckers et al, 2001 (19)	Pros OL	41.1	33/67	24/76	71.4 (TSH), 38.1 (ACTH), 47.6 (FSH/LH)
Clanget et al, 2001 (35)	Pros OL	42.5 ± 11.7 SD	67/33	25/75	66.7 (TSH), 66.7 (ACTH), 84.6 (FSH/LH)
Drake et al, 2001 (36)	Pros OL	Median 46 (28–64)	54/46	8/92	61.5 (TSH), 69.2 (ACTH), 76.9 (FSH/LH)
Gotherstrom et al, 2001 (37)	Pros OL (ITT)	49.3 ± 1.0	59/41	0/100	86.4 (TSH), 75 (ACTH), 91.5 (FSH/LH)
Sartorio et al, 2001 (39)	Pros OL	45.0 ± 2.3	78/22	0/100	72.2 (TSH), 50 (ACTH), 72.2 (FSH/LH)
Bex et al, 2002 (32)	R (ITT)	49.7 (25–65)	59/41	0/100	58 (TSH), 55 (ACTH), 74 (FSH/LH)
Johannsson et al, 2004 (14)	Pros OL (ITT)	CD 51.9 ± 2.9	87/13	0/100	46.7 (TSH), 60 (ACTH), (FSH/LH)
		NFA 50.0 ± 3.9	87/13	0/100	60 (TSH), 46.7 (ACTH), (FSH/LH)
Arwert et al, 2005 (31)	Pros OL, controlled	28.6 ± 4.2 SD	100/0	100/0	69.6 (TSH), 60.9 (ACTH), 52.2 (FSH/LH)
Boguszewski et al, 2005 (33)	Pros OL	40.6 ± 11.2 SD	61/39	22/78	100 (TSH), 83.3 (ACTH), 88.9 (FSH/LH)
Bravenboer et al, 2005 (34)	Pros OL	28 ± 4 SD	100/0	100/0	63.2 (TSH), 50 (ACTH), 52.6 (FSH/LH)
Tanriverdi et al, 2005 (41)	Pros OL	49.4 ± 7.9	0/100	0/100	100 (TSH), 78.6 (ACTH), 100 (FSH/LH)
Colson et al, 2006 (13)	Pros OL	48 (17–75)	38/62	0/100	67 (TSH), 52 (ACTH), 53 (FSH/LH)
Snyder et al, 2007 (40)	R, DB, PC (ITT)	49.8	60/40	0/100	
Rota et al, 2008 (38)	Pros OL	36.5 ± 1.13	55/45	0/100	70.3 (TSH), 54.6 (ACTH), 56.3 (FSH/LH)
Zaninelli et al, 2008 (42)	Pros OL	50.5 ± 13.2 SD	33/67	22/78	
Cabo et al, 2011 (43)	Retrospective	45 ± 13 SD	88/12	35/65	
Jorgensen et al, 2011 (44)	Pros OL	49.2 ± 9.2 SD	64/36	0/100	79.5 (TSH), 79.5 (ACTH), 66.7 (FSH/LH)
Rossini et al, 2011 (16)	Retrospective	34 (18–64)	69/31	37.5/62.5	81.3 (TSH), 78.1 (ACTH), 84.4 (FSH/LH)
Elbornsson et al, 2012 (10)	Pros OL (ITT)	49.4 (22–74)	57/43	0/100	(FSH/LH)

Abbreviations: AO, adult onset; CD, Cushing's disease; CO, childhood onset; DB, double blind; ITT, intention to treat; M month; NFA, nonfunctioning adenoma; OL, open label; PC, placebo controlled; PRL, prolactinoma; Pros, prospective; R, randomized. Data are shown as mean ± SEM or mean (range) if not otherwise specified.

[a] Excluding women of menopausal age (>50 y).

stat, Inc). Data are presented as mean ± SD, mean and 95% CI, or mean and range, as appropriate. Values of $P < .05$ were considered statistically significant.

Results

There were 31 studies used for synthesis in the present meta-analysis (10, 13–16, 19–44). There were nine randomized placebo-controlled studies (six of which were double blind) and one controlled study. Six of the randomized studies included subjects treated for 12 months or less, three included patients followed up for 18–24 months, and one study reported data on both time periods. There were two retrospective studies, 19 prospective studies, and four randomized studies with a separate prospective extension. Among those, 13 studies included data on rhGH replacement treatment for 12 months' duration or less and 18 for longer than 12 months, ranging between 18 and 180 months.

Baseline demographic and clinical characteristics of the study subjects are detailed in Table 1. There were a total of 1403 patients in 31 studies. Of these, 138 withdrew, 75 of whom were counted by intention-to-treat analysis, leaving 1340 subjects whose data were reported. There were 247 subjects in randomized studies of more than 12 months' duration, and 365 subjects in randomized studies of 12 months or less. In prospective or retrospective studies, data were available for 662 subjects treated for more than 12 months and for 390 treated for 12 months or less.

The mean age of study participants ranged from 27.0 to 51.9 years and their mean body mass index from 21.5 to 30.0 kg/m^2. Four studies included only men, one study included only women, and six studies presented separate data for men and women. Separate data were thus available for 336 men and 150 women. In 6 of 31 studies, patients with conditions or on medications that might affect bone were excluded.

The onset of GHD varied between study populations. Sixteen studies enrolled subjects with adult-onset GHD, three studies had patients with childhood-onset GHD who were treated in adulthood, and 12 studies included subjects with both adult-onset and childhood-onset disease. In all studies, the diagnosis of GHD was well established based on provocative testing. The etiology of GHD in

Table 1. Characteristics of Subjects of Studies Included in the Meta-Analysis

Hypogonadal Subjects on Replacement, %	Subjects, n	Withdrawn, n	Approximate Mean Target rhGH Dose, IU/d (mg/d)	Duration of Therapy, mo	End Points
	20	0	0.036/kg (0.012/kg)	6	BMD TB, LS, FN
	8	0	0.036/kg (0.012/kg)	6	BMD TB, LS, TF
	18	0	(2.4 ± 0.2) 0.8	6	BMD TB, LS, FN
100[a]	163	13	2.4 ± 0.8 (0.8)	6	BMD TB
100[a]	47	7	1.6 ± 0.1 (0.5)	24	BMD LS
35	19	0	0.036/kg (0.012/kg)	18	BMD LS, FN
	35	2	0.036/kg (0.012/kg)	6	BMC and BMD TB, LS, FN
	19	4		12	BMC and BMD TB, LS, FN
100 (M)/53.3 (F)	36	0	1.25 U/m^2	9	BMC and BMD TB
100	10	0	0.036/kg (0.012/kg)	6	BMC and BMD LS
	5	0	0.036/kg (0.012/kg)	12	BMC and BMD LS
	36	6	CO 0.025/kg (0.008/kg) AO 0.0125/kg (0.004/kg)	24	BMD FN
	40	7	0.012/kg (0.004/kg)	18	BMD TB, LS, TF, FN
	20	5	0.0123/kg (0.0041/kg)	18	BMD TB, LS, TF, FN
100	10	0	0.036/kg (0.012/kg)	24	BMD LS, FN
100	21	0	1.4 (0.5)	78	BMC LS and BMD TB, LS
100	12	0	2.4 (0.8)	72	BMD LS
100	13	0	Median 1.6 M/F 1.5/2 (0.5 M/F 0.5/0.7)	58 (median)	BMD LS, FN
100 (M)/70 (F)	118	10	1.44 (0.48 ± 0.02)	60	BMC and BMD TB, LS, FN
77	18	0	0.036/kg (0.012/kg)	12	BMD TB
90 (M)/100(F)[a]	98	8	M 2 ± 0.6 (0.67 ± 0.2) F 2 ± 0.6 (0.67 ± 0.2) SD	24	BMC LS and BMD LS, TF, FN
100 (M)/73 (F)	15	1	1.32 (0.44 ± 0.05)	24	BMC and BMD LS
100 (M)/50 (F)	15	0	1.47 (0.49 ± 0.03)	24	BMC and BMD LS
100	42	0	1.2 (0.4)	120	BMD LS, FN
100[a]	18	0	0.6 (0.2)	12	BMD LS, TF, FN
100	50	12	0.43 ± 0.1 mg/m^2 · d SD	60	BMC TB and BMD LS, FN
100[a]	14	4	2 (0.66)	18	BMD LS, FN
100[a]	124	12	NFA 1.26 (0.42 ± 0.2), PRL 1.62 (0.54 ± 0.3), CD 1.74 (0.58 ± 0.23)	Mean 36–50	BMD LS, FN
	67	13	M 1.23 (0.41 ± 0.26), F 1.95 (0.65 ± 0.22) SD	24	BMD LS, TF, FN
100 (M) / 59 (F)	64	0	M 1.62 (0.54 ± 0.034), F 2.01 (0.67 ± 0.034)	24	BMD LS, FN
	18	4	1.35 (0.45)	48	BMD LS, TF, FN
	17	0	CO 2.28 (0.76 ± 0.1) SD, AO 2.1 (0.70 ± 0.2) SD	60	BMD LS, TF
100	39	3	M 1.68 (0.56 ± 0.22), F 2.88 (0.96 ± 0.56) SD	42	BMC and BMD TB, LS, TF
86.4 (M)/ 93 (F)	64	0	M 0.0098/kg (0.00327/kg), F 0.011/kg (0.00365/kg)	36	BMC and BMD LS, TF, FN
100 (M)/31 (F)	126	36	1.23 (0.41 ± 0.01)	180	BMC and BMD TB, LS, FN

most of the studies was diverse, except for one study that included only patients with GHD secondary to Sheehan's syndrome and two studies that separately reported subjects with cured Cushing's disease (CD), nonfunctioning adenomas, and prolactinomas. Most subjects included had additional anterior pituitary hormone deficiencies and were on stable replacement for at least 6 months before study entry. However, data on replacement doses of additional deficiencies and corresponding serum hormone levels were available only for a minority of studies. PTH levels were measured only in four studies and were not abnormally high (when available). Serum IGF-I levels were available in 11 studies. They ranged between −4.7 and −0.4 SD score (SDS) at baseline and between −3.1 and 2 on therapy. When the data were presented, changes (from baseline) in IGF-I levels on GH replacement were statistically significant.

Patients with GHD were usually treatment naïve. Those who received prior therapy, namely in childhood, were at least 1 year off GH replacement before study entry. All treated patients with GHD were receiving daily rhGH injections. Treatment duration ranged from 6 to 180 months. There was a wide range of GH doses. Older studies mainly used weight-based dosing regimens. In the rest of the studies, rhGH dose ranged from 0.2 to 0.96 mg/d, with higher doses prescribed to women and subjects with childhood-onset GHD.

BMD was measured by DXA scans. All studies used a single type of machine throughout the study (14 studies used Hologic, 10 used Lunar, and one used Norland) except for one that changed machines throughout the study and two that combined data from two different machines (multicenter trials). Baseline Z-scores were available in 13 studies and were mostly in the normal range for age, except for two studies that reported scores consistent with osteopenia.

There was no evidence of publication bias, based on funnel plots and Duval and Tweedie's trim and fill analysis (data not shown). The results of Q test and I^2 index suggested that data were likely heterogeneous with regard to treatment effects on several end points (Table 2), which further justified the choice of the random-effects model for data analysis and subgroup analyses.

Efficacy end points

The results of the meta-analysis are summarized in Table 2, including weighted mean differences, 95% CIs, and *P* values for each end point synthesized.

In randomized/controlled studies, we found a significant increase in BMD at both the LS and FN in patients who received rhGH replacement therapy for more than 12 months (n = 247) and a nonsignificant increase in BMD at the TF. The change in BMD ranged between 1% and 7% (CI) at the spine and 0.6% and 4% at the FN. In randomized studies extending for 12 months or less (n = 282), there was a decrease in both BMC and BMD at the LS as well as in BMD at the FN, but this finding did not reach statistical significance.

In prospective studies, there was a significant increase in LS BMD and a trend (statistically nonsignificant) toward an increase in FN BMD in subjects on up to 12 months of rhGH therapy. Moreover, there was a nonsignificant increase in TB and LS BMC. In prospective studies of longer duration (>12 mo), there was a significant increase in LS and FN BMD.

On meta-regression analysis of randomized studies of rhGH therapy of more than 12 months, we found a weak negative association between the change in LS BMD and subjects' age (β-coefficient = −.004; 95% CI −0.007 to −0.0008; P = .01). A similar association was also found between the change in FN BMD and age (β-coefficient = −.006; 95% CI −0.008 to −0.003; $P < .0001$). Further analysis revealed a weak positive association between the change in LS BMD and the study duration (β-coefficient = .0008; 95% CI 0.0002–0.0015; P = .01). Similar data were obtained with regard to the relationship between the change in FN BMD and the study duration (β-coefficient = .001; 95% CI 0.0006–0.0018); $P < .0001$). No statistically significant association was found between the change in the BMD and rhGH replacement dose (data not shown).

In prospective studies extending more than 12 months, there was a negative association between baseline Z-score and treatment effect at the FN (β-coefficient = −0.35; 95% CI −0.60 to −0.11; P = .005). Similarly, a negative association was observed between baseline IGF-I SDS and FN BMD change (β-coefficient = −.15; 95% CI −0.28 to −0.01; P = .03). No statistically significant relation was obtained between both baseline variables and the LS BMD change. At the LS (but not at the FN), a positive association was detected between on-therapy IGF-I SDS and treatment effect (β-coefficient = .14; 95% CI 0.03–0.24; P = .01). Similar findings were not noted in randomized studies (data not shown).

Subgroup analysis

The effect of gender on the change in BMD under rhGH replacement therapy was further studied in a subgroup analysis. When data were analyzed separately in men (n = 181) and women (n = 68) treated for more than 12 months in randomized studies, a significant increase in LS BMD was observed in men, with a mean change (95% CI) of 0.048 (0.033–0.064, $P < .001$) but not in women [0.008 (−0.008 to 0.025), P = .3]. Similarly, the increase in FN BMD was significant only in men, with a mean change

Table 2. Results of Meta-Analysis of the Effects of rhGH Replacement Therapy in Adults, Including Bone Densitometric End Points

Randomized/Controlled Studies up to 12 Months in Duration

Endpoint	Weighted Mean Difference	95% CI	*P* Value	No. of Studies	No. of Subjects (GH)	No. of Subjects (placebo)	Total No. of Subjects	Q Test *P* Value	I^2 Index (%)
BMC LS	-0.008	-0.247 0.232	.951	2	73	37	110	.720	0
BMD TB	0.008	-0.025 0.041	.628	5	96	96	192	.064	55
BMD LS	-0.002	-0.025 0.020	.841	5	108	74	182	0	91
BMD FN	-0.001	-0.015 0.013	.843	4	103	68	171	*.003*	75

BMC, Bone Mineral Content, BMD, Bone Mineral Density, LS, Lumbar Spine, TB, Total Body, FN, Femoral Neck. *P* values < .05 are shown in italics.

Randomized/Controlled Studies over 12 Months in Duration

Endpoint	Weighted Mean Difference	95% CI	*P* Value	No. of Studies	No. of Subjects (GH)	No. of Subjects (placebo)	Total No. of Subjects	Q Test *P* Value	I^2 Index (%)
BMD LS	0.038	0.011 0.065	*.006*	4	144	105	249	0	94
BMD FN	0.021	0.006 0.037	*.008*	4	144	105	249	*.001*	76
BMD TF	0.014	-0.007 0.034	.188	3	121	86	207	0	90

BMD, Bone Mineral Density, LS, Lumbar Spine, TF, Total Femur. *P* values < .05 are shown in italics.

Prospective Studies Up to 12 Months in Duration

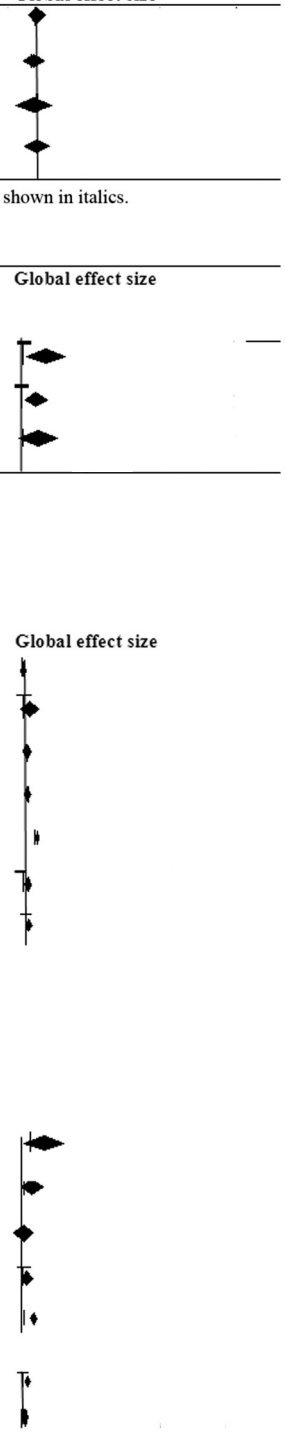
Endpoint	Weighted Mean Difference	95% CI	*P* Value	No. of Studies	No. of Subjects	Q Test *P* Value	I^2 Index (%)
BMC TB	0.010	-0.059 0.078	.778	2	148	.322	0
BMC LS	0.960	-0.476 2.395	.190	3	187	0	84
BMC FN	-0.020	-0.113 0.072	.667	2	182	.074	62
BMD TB	-0.008	-0.029 0.014	.474	5	198	.072	53
BMD LS	0.016	0.004 0.029	*.012*	10	307	.432	1.3
BMD FN	0.021	-0.000 0.041	.054	8	307	0	72
BMD TF	0.019	-0.006 0.043	.133	4	107	.210	30

BMC, Bone Mineral Content, BMD, Bone Mineral Density, TB, Total Body, LS, Lumbar Spine, FN, Femoral Neck, TF, Total Femur. *P* values < .05 are shown in italics.

Prospective Studies Over 12 Months in Duration

Endpoint	Weighted Mean Difference	95% CI	*P* Value	No. of Studies	No. of Subjects	Q Test *P* Value	I^2 Index (%)
BMC TB	0.255	0.020 0.490	*0.033*	2	143	*0.005*	87
BMC LS	2.944	-0.015 5.903	0.051	4	241	0	97
BMC FN	0.041	-0.227 0.308	0.767	2	190	0	96
BMD TB	0.017	-0.005 0.039	0.124	4	203	*0.009*	68
BMD LS	0.046	0.035 0.058	*< 0.001*	17	632	0	83
BMD FN	0.027	0.013 0.042	*< 0.001*	12	499	0	71
BMD TF	0.021	-0.006 0.047	0.129	5	151	*0.028*	55

BMC, Bone Mineral Content, BMD, Bone Mineral Density, TB, Total Body, LS, Lumbar Spine, FN, Femoral Neck, TF, Total Femur. *P* values < .05 are shown in italics.



(95% CI) of 0.051 (0.003–0.098), $P = .04$ vs 0.005 (−0.058 to 0.067, $P = .88$) in women.

In long-term prospective studies, a significant increase in LS BMD was noted in both men (n = 129) and women (n = 68): mean change (95% CI) 0.054 (0.036–0.071, $P < .001$) in men and 0.018 (0.003–0.034, $P = .02$) in women.

Discussion

In the present meta-analysis, we have shown a beneficial effect of rhGH replacement therapy of more than 1 year on BMD in patients with GHD. A statistically significant increase in LS and FN BMD was detected in randomized studies of longer duration and was preceded by an initial decline in BMD in short-term studies. An increase in BMD was also observed in prospective studies of all treatment duration, although statistically significant only in long-term studies and in short-term studies at the LS. The effect of GH replacement on BMD was influenced by patients' demographics (including age and gender), baseline IGF-I level, baseline BMD Z-score, and treatment duration, findings that were not reported in previous meta-analyses.

The biphasic effect of rhGH replacement observed in randomized studies has been previously described in the literature and is consistent with the hypothesis that GH stimulates both bone formation and bone resorption (as evidenced by changes in bone markers), which results in increased bone turnover (45). This effect is prominent during at least the first 6 months of GH treatment, resulting in increased number of bone metabolic units and a subsequent decrease in BMC and BMD. Only after this initial period will bone turnover slow down and GH replacement increase bone mass (46). This explains the lack of the beneficial effect on BMD reported in the meta-analysis by Hazem et al (11) that mainly included randomized studies of short duration (70% of included studies were of a duration of 6 mo). Similarly, Davidson et al (12) showed beneficial results on BMD after 18 months of treatment.

A limitation of included studies is the use of different dose regimens of GH, namely use of high doses (based on body weight or body surface area) as compared with the more recent recommendation by The Endocrine Society to use a fixed starting replacement dose of 0.2–0.3 mg/d in adults aged 30–60 years that is further adjusted according to age, gender, and IGF-I levels (47). In the present study, no significant association was found between the rhGH dose and the change in BMD, which can be possibly explained by the wide range of doses used. However, the effect of GH replacement on LS BMD (but not FN BMD) was positively associated with on-therapy IGF-I SDS, raising the possibility that predominantly trabecular (LS) and predominantly cortical bone (FN) may show different sensitivity to GH effects as well as indicating the importance of assuring that GH dose is sufficient to normalize IGF-I levels. This issue can be of particular concern in women on oral estrogen replacement (33). On the other hand, the prescription of lower rhGH doses may likely result in fewer adverse effects, such as peripheral edema (48).

On subgroup analysis, the increase in BMD was consistently higher in men as compared with women and was significant only in men in randomized studies. This observation coincides with results of individual studies that separately evaluated both genders. One explanation is that women require higher replacement GH doses as compared with men because oral estrogen inhibits GH-induced IGF-I synthesis. The need for gender-related dose adjustment has not been taken into account in all studies included in this meta-analysis, namely in randomized studies (32, 40), which could account for the observed difference in BMD between men and women. However, even in studies in which higher rhGH doses were given to women, the change in BMD remained more pronounced in males (16, 36, 38, 44).It may also be noted that it is unclear whether rhGH replacement doses have been sufficient in women study subjects because gender-specific data on IGF-I levels were reported in only one of these studies. Because there were very limited data reported separately for women of menopausal age (with or without sex steroid replacement), it was not possible to conduct pertinent subgroup analyses.

In randomized studies of rhGH replacement of more than 1 year, an inverse association was obtained between patients' age and LS and FN increase in BMD, with more pronounced increase in BMD at younger age. This observation, although small and largely driven by one study (31), is consistent with the existing literature. Patients who develop GHD at a younger age, before they reach peak bone mass, and in whom GH replacement is not maintained beyond puberty, usually have lower BMD and respond more significantly to rhGH replacement (47). In the subset of prospective studies in which baseline BMD Z-scores and IGF-I SDS were available, the increase in FN BMD was, indeed, more pronounced in subjects with lower baseline BMD Z-scores and lower baseline IGF-I SDS, suggesting a greater benefit to patients with lower baseline bone density and more severe GH deficiency. In long-term randomized studies, the increase in LS and FN BMD was positively associated with increase in study duration. This result, however, is to be interpreted cautiously because randomized studies of rhGH replacement combined in this meta-analysis extend only up to 24 months. Only one controlled, nonrandomized study, which extended for 10 years, was available. It showed sustained

improvement in LS BMD in rhGH-replaced patients after 10 years of treatment as compared with controls. In addition, FN BMD increased during the initial 5 years of replacement but returned to baseline levels after 10 years. It remained, however, significantly higher than controls (31). Similarly, rhGH replacement for 15 years resulted in persistent increase in LS BMD, whereas FN BMD increased for only the first 7 years in the longest available prospective study (10).

While reporting data on BMD, available studies lacked fracture end points. A decrease in fracture risk is anticipated as a result of the observed improvement in BMD. In addition, GH replacement is associated with improved muscle performance, increased quality of life, and physical activity, which could further lower fracture rates (11, 49). However, adequately powered studies are needed to definitively evaluate the effect of rhGH replacement therapy on fracture risk in GHD adults.

In conclusion, the findings of the present meta-analysis suggest that rhGH replacement therapy in adults with GHD may lead to improvement in LS and FN BMD that might become apparent after more than 12 months of therapy. The varying doses and treatment durations used in the different studies make it hard to draw a conclusion on the optimal dose and duration of replacement. The available literature also lacks data on the effects of such therapy on fracture risk because the benefits of rhGH replacement may extend beyond the possible gain in BMD. Larger studies are thus needed to evaluate the effect of the currently recommended low doses of rhGH in men and women with GHD on both BMD and fracture risk.

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