Differential Effects of Raloxifene and Estrogen on Body Composition in Growth Hormone-Replaced Hypopituitary Women

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Context: GH deficiency causes reduction in muscle and bone mass and an increase in fat mass (FM), the changes reversed by GH replacement. The beneficial effects of GH on fat oxidation and protein anabolism are attenuated more markedly by raloxifene, a selective estrogen receptor modulator, compared with 17β-estradiol. Whether this translates to a long-term detrimental effect on body composition is unknown.

Objective: Our objective was to compare the effects of 17β-estradiol and raloxifene on FM, lean body mass (LBM), and bone mineral density (BMD) during GH replacement.

Design: This was an open-label randomized crossover study.

Patients and intervention: Sixteen hypopituitary women received GH (0.5 mg/d) replacement for 24 months. One group received 17β-estradiol (2 mg/d) for the first 6 months before crossover to raloxifene (60 mg/d) for the remaining 18 months; the other received the reversed sequence.

Main Outcome Measures: Serum IGF-I and IGF-binding protein-3 concentrations, and FM, LBM, lumbar spine and femoral neck BMD were analyzed at baseline and at 6, 12, and 24 months within and between subjects.

Results: GH therapy significantly increased mean IGF-I during 17β-estradiol and raloxifene cotreatments equally, but elevated IGF-binding protein-3 to a greater extent during raloxifene cotreatment. GH cotreatment with 17β-estradiol increased LBM and lumbar spine and femoral neck BMD and reduced FM to a greater extent than with raloxifene.

Conclusions: In hypopituitary women, raloxifene at therapeutic doses significantly attenuated the beneficial effects of GH on body composition compared with 17β-estradiol. Raloxifene has no metabolic advantage over 17β-estradiol during GH replacement. **(*J Clin Endocrinol Metab* 97: 1005–1012, 2012)**

Adult GH deficiency (GHD) causes an increase in fat mass and a reduction in muscle and bone mass (1, 2). GH replacement reverses these changes by stimulating fat oxidation, protein synthesis, and bone accretion (3–12). We have previously shown in GH-sufficient women that estrogen, when administered orally but not parenterally, reduces fatty acid oxidation and circulating IGF-I levels, which translates into a significant increase in fat mass (FM) and reduction in lean body mass (LBM) over time (13). Thus, orally administered estrogens may counteract

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Abbreviations: BMD, Bone mineral density; CV, coefficient of variation; DXA, dual-energy x-ray absorptiometry; ER, estrogen receptor; FM, fat mass; FN, femoral neck; GHD, GH deficiency; IGFBP-3, IGF-binding protein-3; LBM, lean body mass; LS, lumbar spine; SERM, selective estrogen receptor modulator.

TABLE 1. Subjects' clinical characteristics

Subject	Age (yr)	BMI (kg/m^2)	Diagnosis	Hormone replacement
1	45	33.6	Childhood-onset hypopituitarism	A, T, G
2	59	48.3	Pituitary macroadenoma	G
3	52	32.2	Prolactinoma (S)	A, T
4	49	29.4	Prolactinoma (X)	T, G
5	23	24.3	Childhood-onset hypopituitarism	T, G
6	59	33.6	Sheehan's postpartum necrosis	A, T, G
7	44	32.6	Prolactinoma (S, X)	A, T
8	61	34.7	Pituitary adenoma (S)	A, T
9	58	20.5	Pituitary adenoma	G
10	39	26.9	Cushing's disease (S, X)	A, T, G
11	53	34	Pituitary macroadenoma (S)	T, G
12	49	30.2	Empty sella syndrome	A, T, G, D
13	19	21.1	Hypopituitarism, unknown cause	A, T, G
14	55	33	Pituitary adenoma	A, T
15	22	27.9	Childhood-onset hypopituitarism	G
16	44	33.1	Craniopharyngioma (S)	A, T, G, D

A, Adrenal replacement; BMI, body mass index; D, desmopressin; G, gonadal replacement; S, surgery; T, thyroid replacement; X, irradiation.

the beneficial effects of GH replacement on body composition in hypopituitary women.

Selective estrogen receptor (ER) modulators (SERM) are synthetic estrogen compounds that possess estrogen-agonistic or -antagonistic effects in a tissue-specific manner. In the liver, SERM act like estrogen agonists and therefore may cause similar negative effects to that of estrogen on hepatic GH action, such as reduction in IGF-I synthesis and fatty acid oxidation (14–18). Gibney and co-authors (14) reported that raloxifene, a SERM, reduced IGF-I to a lesser degree than orally administered 17β-estradiol in GH-deficient and in postmenopausal women. This observation suggests that raloxifene may exert lesser attenuation on the hepatic response to GH than 17β-estradiol. Contrary to expectation, we recently observed in a short-term study that raloxifene treatment during GH replacement in hypopituitary women reduced fat oxidation and protein synthesis to a greater extent than 17β-estradiol treatment (19). The aim was to investigate whether these effects on substrate metabolism translate into a corresponding attenuated GH effect on body composition. We compared the effects of 17β-estradiol and raloxifene treatment on body composition in hypopituitary women receiving GH replacement therapy in a randomized crossover trial.

Subjects and Methods

Subjects

Sixteen GH-deficient women were recruited from the Endocrine Outpatient Clinic, St. Vincent's Hospital, Sydney, Australia. Study subjects' clinical characteristics are shown in Table 1. GHD was confirmed by a peak GH response to insulin-induced hypoglycemia of less than 3 ng/ml (20). Subjects were withdrawn from estrogen replacement for at least 2 months before commencement of the study. Before and throughout the study, patients received standard thyroid hormone and cortisol replacement for thyroid and adrenal deficiencies, respectively, and doses were unchanged throughout the study. All subjects were instructed to follow their usual diet and physical activity as well as continuing their usual medications or supplements throughout the study.

The Human Research Ethics Committee of St. Vincent's Hospital approved the study. The study was conducted in accordance with the principles of the Declaration of Helsinki. All subjects gave written informed consent before entering the study. The study was registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12605000532606).

Study design

All patients were commenced on GH replacement therapy (Humatrope; Eli Lilly Australia, West Ryde, Australia; 0.5 mg/d sc injection) and randomized into two groups in a parallel open-label crossover study. One group received 17β-estradiol (2 mg/d) for the first 6 months before crossover to raloxifene (Evista; Eli Lilly Australia; 60 mg/d) for the remaining 18 months (group 1); the other received the reversed sequence (group 2; Fig 1). Medroxyprogesterone acetate (10 mg/d) was administered for the last 10 d of each estrogen treatment month to induce withdrawal bleeding. The dose of GH was not changed in any patients throughout the study, and compliance was monitored by return of used GH cartridges.

The endpoint measures of GH action during raloxifene and 17β-estradiol treatment phases were 1) IGF-I and IGF-binding protein-3 (IGFBP-3) and 2) body composition including FM, LBM, and lumbar spine (LS) and femoral neck (FN) bone mineral density (BMD). The rationale for the study design was to allow a balanced 6-month crossover two-period evaluation of the effects of raloxifene and 17β-estradiol on biochemical variables, FM, and LBM (crossover phase; Fig 1). Because the effect of GH replacement on BMD takes longer to become apparent, at the end of the second period, subjects continued on treatment for an additional 12 months allowing between-group analysis to be carried out after 18 months of continuous cotreatment of GH with either raloxifene or 17β-estradiol (extension phase; Fig 1).

Subjects were studied in the Clinical Research Facility, Garvan Institute of Medical Research. Studies were undertaken at

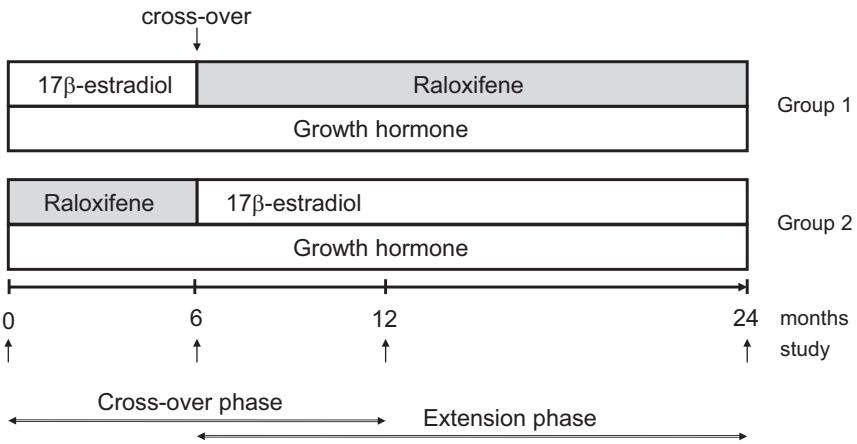

FIG. 1. Study design. Hypopituitary women underwent GH (0.5 mg/d) treatment for 24 months. Group 1 received 17β-estradiol (2 mg/d) for the first 6 months before crossover to raloxifene (60 mg/d) for the remaining 18 months; group 2 received a reversed sequence. Studies were undertaken at baseline and at 6, 12, and 24 months.

baseline and at 6, 12, and 24 months. Body composition was measured by dual-energy x-ray absorptiometry (DXA) at each visit. Study blood samples were collected and placed on ice, and plasma was separated and stored at −80 C until analysis.

One subject from group 2 was not compliant as indicated by no change in IGF-I levels during GH therapy and return of unused GH cartridges and therefore was excluded from the analysis. Body composition measurements by DXA were not undertaken in one subject from group 1 due to technical difficulties, and therefore the subject was excluded from the analysis. Thus, seven patients comprised each group for full comparison.

Body composition

Body composition (LBM and FM) and BMD (LS BMD and FN BMD) were measured using DXA scan (Lunar model DPX, software version 3.1; Lunar Corp., Madison, WI) at the Nuclear Medicine Department, St. Vincent's Hospital, Sydney, Australia. At our institution, the coefficients of variation for LBM, FM, and BMD are 1.4, 2.9, and 1.5%, respectively (13).

Assays

All samples for any individual were measured in the same assay run for each analyte. Serum IGF-I levels were measured by RIA after acid ethanol extraction as previously described (3, 14, 21). The coefficients of variation (CV) for IGF-I were 8.3% at 14.7 nmol/liter and 7.4% at 28.6 nmol/liter. Serum IGFBP-3 levels were measured by RIA using antiserum R-100 in an in-house assay as previously described (22). The within-assay CV for IGFBP-3 were 6.2% at 2.5 μg/ml, 5.5% at 5.7 μg/ml, and 4.5% at 12.6 μg/ml. The between-assay CV were 11.9% at 2.9 μg/ml, 14.5% at 6.3 μg/ml, and 13.1% at 12.7 μg/ml. Conversion factor for IGF-I is 1 μg/liter = 0.131 nmol/liter, and for IGFBP-3 is 1 μg/liter = 0.035 nmol/liter.

Statistical analysis

Comparison of treatment effects between raloxifene and 17β-estradiol was undertaken within and between groups. Analysis of within-group treatment effects was undertaken in a crossover analysis incorporating sequence and period effects in the model (23). Analysis of between-group treatment effects was undertaken at the end of the study comparing the change from the crossover using unpaired two-sample *t* tests. Results are expressed as mean ± SEM and a *P* value <0.05 was considered to be significant. Statistical analysis was undertaken using the statistical software package StataSE version 9.2 (Stata Corp., College Station, TX).

Results

The mean age of the subjects was 46.6 ± 3.1 yr, and mean body mass index was 31.6 ± 1.6 kg/m^2. At baseline, there was no significant difference in IGF-I, IGFBP-3, FM, LBM, or BMD between the groups assigned to 17β-estradiol and raloxifene treatments (Table 2).

Within-group effects: 0, 6, and 12 months

To examine whether there were group, treatment, or sequence effects, we performed a crossover analysis, assessing effects at 12 months, allowing for a balanced 6-month crossover two-period evaluation. There was no significant sequence effect for any of the biochemical and body composition measures, except for a small effect on mean IGF-I ($P < 0.05$). There was a greater increase in IGF-I levels in the first 6 months followed by a greater reduction in the next 6 months in group 2 compared with group 1. The analysis revealed significantly different within-group treatment effects. Mean IGFBP-3 concentration was lower ($P < 0.01$) during cotreatment with 17β-estradiol, whereas IGF-I levels were no different between treatments. Cotreatment with 17β-estradiol also resulted in lower FM and higher LBM ($P < 0.05$) than cotreatment with raloxifene. There was no significant within-group treatment effect in any of the BMD measures. During the first 6 months of treatment, there was a trend in an increase in FN BMD with 17β-estradiol and in a fall with raloxifene resulting in a significant difference between treatments ($P = 0.01$). Thus, crossover analysis revealed that cotreatment with 17β-estradiol resulted in significantly lower circulating IGFBP-3 levels, lower FM, and higher LBM than cotreatment with raloxifene.

Between-group comparison: 6–24 months (Table 2)

Biochemistry

We next undertook a study extension to 18 months after crossover to determine whether significant differences occurred between the 17β-estradiol (group 2) and raloxifene (group 1) cotreatments. During GH therapy, there was no significant difference in mean IGF-I levels

TABLE 2. Effects on GH markers, body composition, and bone of GH therapy during 17β -estradiol and raloxifene treatment phases

Outcome measures	Baseline	6 months	12 months	24 months
Group 1				
Treatment	Nil	Estradiol	Raloxifene	Raloxifene
Weight (kg)	82.9 ± 4.1	84.9 ± 3.9	86.0 ± 3.9	88.8 ± 4.2
IGF-I (nmol/liter)	9.6 ± 1.4	21.7 ± 3.0[a]	19.9 ± 3.4[a]	16.7 ± 3.2[a]
IGFBP-3 (nmol/liter)	75.0 ± 11.6	104.2 ± 11.6[a]	109.2 ± 8.3[a]	101.3 ± 10.9
IGF-I/BP-3 ratio	0.14 ± 0.02	0.21 ± 0.02[a]	0.18 ± 0.02	0.16 ± 0.02
LBM (%)	48.8 ± 2.0	49.1 ± 2.2	47.0 ± 2.0	47.6 ± 1.9
FM (%)	47.9 ± 2.0	47.0 ± 2.1	48.7 ± 1.9	48.7 ± 1.8
LS BMD (g/cm^2)	1.08 ± 0.05	1.12 ± 0.04	1.1 ± 0.06	1.1 ± 0.05
FN BMD (g/cm^2)	1.0 ± 0.03	1.03 ± 0.04	1.02 ± 0.04	0.97 ± 0.05
Group 2				
Treatment	Nil	Raloxifene	Estradiol	Estradiol
Weight (kg)	78.8 ± 6.0	78.6 ± 6.0	78.6 ± 6.4	77.8 ± 7.3
IGF-I (nmol/liter)	11.6 ± 3.6	31.7 ± 9.0[a]	20.1 ± 4.2[a]	23.6 ± 6.4[a]
IGFBP-3 (nmol/liter)	92.3 ± 15.5	120.0 ± 9.6	98.3 ± 12.6[b]	95.3 ± 9.7[c]
IGF-I/BP-3 ratio	0.12 ± 0.03	0.26 ± 0.06[a]	0.22 ± 0.04[a]	0.24 ± 0.05[a,b]
LBM (%)	47.5 ± 2.9	49.9 ± 3.5	50.8 ± 4.1[b]	52.6 ± 4.2[a,b]
FM (%)	48.5 ± 2.8	46.1 ± 3.7	45.3 ± 4.5	43.1 ± 4.8[b]
LS BMD (g/cm^2)	1.06 ± 0.07	1.05 ± 0.07	1.08 ± 0.06	1.13 ± 0.07[a,b]
FN BMD (g/cm^2)	0.96 ± 0.05	0.93 ± 0.06[b]	0.95 ± 0.05	1.02 ± 0.04[b]

[a] $P < 0.05$ *vs.* baseline.

[b] $P < 0.05$ *vs.* group 1.

[c] $P = 0.09$ *vs.* group 1.

between the groups or in the changes from baseline. There was a significantly greater increase in circulating IGFBP-3 levels with raloxifene cotreatment ($P < 0.05$). The IGF-I to IGFBP-3 ratio was lower in group 1 ($P = 0.08$) and in comparison with baseline, this group showed a significantly blunted GH-induced increase in the IGF-I to IGFBP-3 ratio ($P < 0.01$) during this cotreatment phase with raloxifene. Thus, between-group comparison revealed a significantly greater increase in IGFBP-3 levels and lower IGF-I to IGFBP-3 ratio with raloxifene cotreatment during the 18-month extension phase.

Body composition (Figs. 2–4)

After 18 months of GH treatment, the mean percent FM was significantly lower and LBM significantly higher in group 2 cotreated with 17β-estradiol ($P < 0.05$). There was a 3.1 ± 1.8% reduction and a 1.7 ± 1.3% increase from crossover in FM with 17β-estradiol and raloxifene treatments, respectively. Over this duration, there was a corresponding 2.7 ± 1.5% increase of LBM with 17β-estradiol in contrast to a 1.5 ± 1.3% decrease with raloxifene cotreatment. The divergent effect between 17β-estradiol and raloxifene treatments was evident also in comparison with baseline values. Overall, there was 5.4 ± 2.4% reduction in FM and 5.1 ± 1.9% increase in LBM with 17β-estradiol and 0.8 ± 1.6% increase in FM and 1.2 ± 1.8% reduction in LBM with raloxifene cotreatment. These were significant opposite changes in FM and LBM between treatments ($P < 0.01$).

After 18 months of GH treatment, the mean LS BMD was significantly higher in group 2 cotreated with 17β-estradiol ($P < 0.01$). Similarly, FN BMD was also significantly higher with 17β-estradiol compared with raloxifene cotreatment ($P < 0.05$). There was a progressive increase in BMD only with 17β-estradiol cotreatment at these sites. In LS BMD, there was 8.2 ± 1.6% increase from crossover and 5.2 ± 2.0% increase in FN BMD with 17β-estradiol cotreatment and 2.5 ± 1.3% reduction in LS BMD and 0.7 ± 1.2% reduction in FN BMD with raloxifene cotreatment with the changes significantly different ($P < 0.05$) between treatments.

In summary, cotreatment with 17β-estradiol resulted in a greater reduction in FM and greater increases in LBM and in LS and FN BMD compared with concurrent raloxifene treatment during GH replacement.

Discussion

This study compared the long-term effects of 17β-estradiol and raloxifene on body composition and BMD in hypopituitary women during GH replacement. GH therapy in both groups cotreated with either 17β-estradiol or raloxifene resulted in a significant increase in circulating IGF-I, IGFBP-3, and the molar ratio of IGF-I to IGFBP-3. No significant changes in body composition occurred during the first 6 months of GH therapy. Over an additional 18 months of GH replacement, cotreatment with 17β-

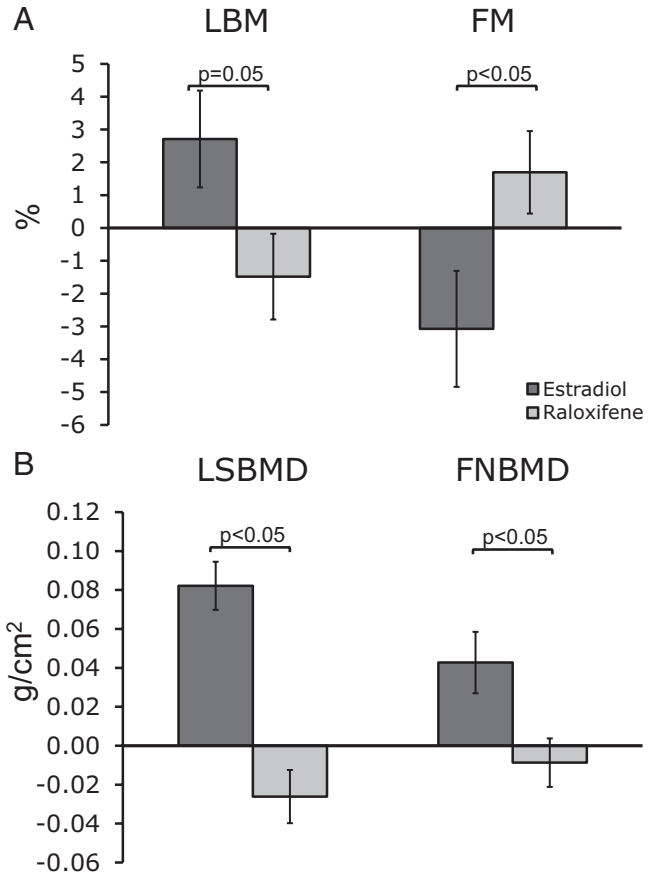

FIG. 2. Change in body composition measures at 18 months after crossover in hypopituitary women during GH therapy receiving cotreatment with 17β-estradiol and raloxifene. A, Change in LBM and FM, presented as a percentage of body weight; B, change in LS BMD and FN BMD. Data are expressed as a mean change from the crossover point ± SEM.

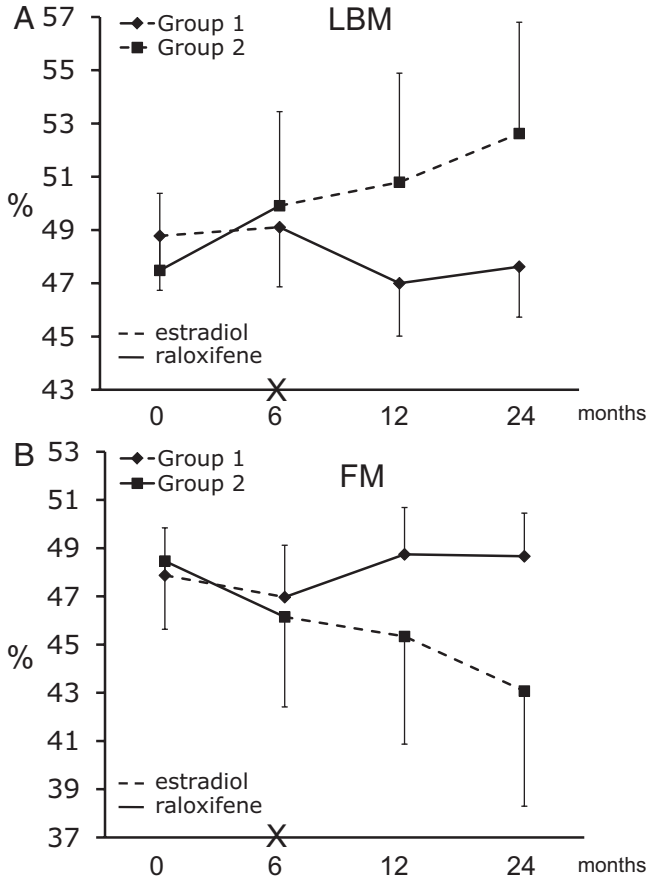

FIG. 3. LBM (A) and FM (B) in hypopituitary women over 24 months of GH therapy in group 1 and group 2. Data are presented as a percentage of body weight and expressed as mean ± SEM. The 6-month mark indicates the crossover point.

estradiol resulted in significantly lower IGFBP-3 levels, higher IGF-I to IGFBP-3 ratio and a significantly greater reduction in FM and increase in LBM and BMD at the LS and FN, compared with raloxifene cotreatment.

This study provides strong evidence that 17β-estradiol cotreatment imparts lesser detrimental effects on body composition during GH replacement compared with raloxifene cotreatment. These findings are somewhat surprising because we have previously reported that in healthy and GHD women, the magnitude of raloxifene-induced reduction in IGF-I level was less than that of estrogen (14). Therefore, raloxifene should have exerted a lesser suppressive effect on GH action, and this could translate into smaller negative effects on body composition than 17β-estradiol. However, we found the opposite. The present findings are in line with the results from our short-term study where we compared the metabolic effects of GH alone or GH coadministered with 17β-estradiol or with raloxifene in GH-deficient women employing identical dosage regimens (19). In the short-term study, raloxifene muted the stimulation by GH of fat oxidation to a greater extent than 17β-estradiol. In addition, raloxifene treatment exerted an inhibitory effect on GH-induced protein anabolism and on bone formation markers (19). In the current study, over the long-term GH replacement, cotreatment with raloxifene resulted in a lesser increase in LBM and BMD and lesser reduction in FM compared with 17β-estradiol cotreatment. Collectively, these data indicate that in the doses used, raloxifene blunts the effects of GH on substrate metabolism and on body composition to a greater extent than oral 17β-estradiol in hypopituitary women.

In adults, GH plays an important role in regulating bone mass (24). BMD is lower and nonvertebral fracture risk is increased 3-fold in adults with GHD (25–27). GH therapy increases markers of bone resorption and formation, changes indicative of an enhancement of bone remodeling (28). Over a 10-yr period of GH replacement, this amounts to a net increase of about 7% in LS and 4% in FN BMD in GH-deficient adults (29). Previous studies have also reported that adequate estrogen replacement is required for an optimal increase in BMD in GHD women (29, 30). Both estrogen and raloxifene exert potent anti-

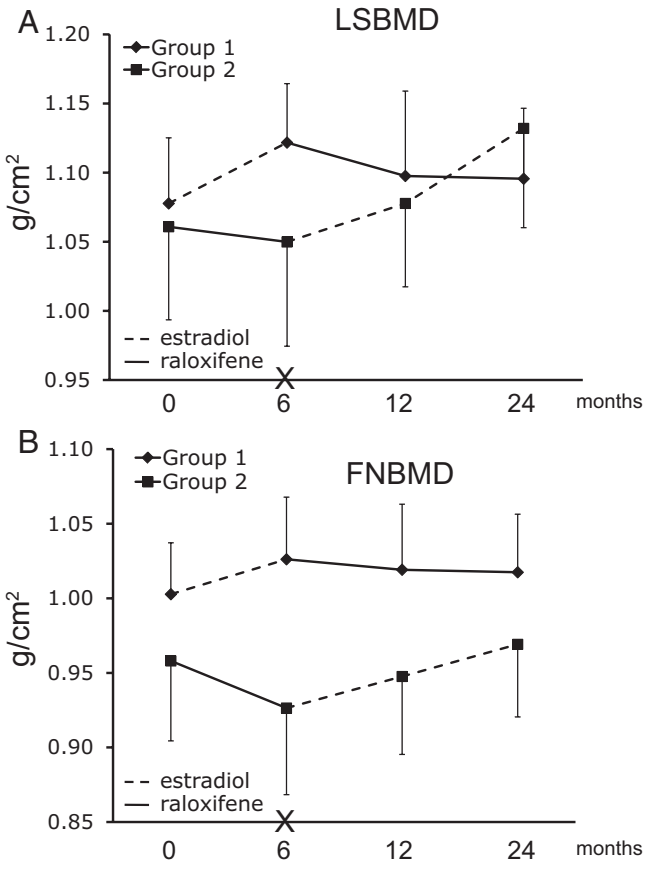

FIG. 4. LS BMD (A) and FN BMD (B) in hypopituitary women over 24 months of GH therapy in group 1 and group 2. Data are expressed as mean ± SEM. The 6-month mark indicates the crossover point.

resorptive effects (31, 32). In our short-term study, GH replacement for 1 month significantly elevated serum PINP, ICTP, and CTX levels (19), changes in agreement with previous findings (28, 30). Cotreatments with 17β-estradiol and raloxifene did not significantly alter bone turnover markers during GH therapy; however, raloxifene induced a trend toward a reduction in the formation marker PINP (19). It is conceivable that the blunting of PINP during GH-raloxifene cotreatment contributed in part to a reduced bone-anabolic effect compared with 17β-estradiol cotreatment in the present long-term study. Our results indicate that cotreatment with estrogen favors greater bone anabolism than cotreatment with raloxifene during GH replacement.

The higher IGFBP-3 levels observed during raloxifene treatment raises the possibility of a causal role in the attenuated bone-anabolic effects occurring during GH therapy. IGFBP-3 is a major IGF-I-binding protein that modulates IGF-I activity. Although we did not measure IGF-I bioactivity, higher IGFBP-3 levels may be indicative of a lower free IGF-I. In addition, IGFBP-3 also exerts IGF-I-independent effects (33, 34). We are not aware of any data reporting a negative effect of circulating IGFBP-3 on bone mineral status in humans. However, studies in postmenopausal women with osteoporosis have reported a negative association between cortical bone IGFBP-3 content with BMD (35). In rodents, overexpression of IGFBP-3 results in growth retardation, reduced BMD along with increased osteoclast number and bone resorption, and a significant negative effect on bone formation (36). There are no data reporting an association between circulating and bone content of IGFBP-3 in humans; thus, the pathophysiological significance of the association between higher circulating IGFBP-3 levels and attenuated increases in BMD during GH therapy is unknown.

Higher IGFBP-3 levels during raloxifene treatment was also associated with a smaller increase in LBM and smaller reduction in FM compared with 17β-estradiol treatment. Studies in postmenopausal and GHD women also report that raloxifene increases IGFBP-3 levels in contrast to a lowering effect of estrogen (14, 15, 37). We previously reported that 1 month of GH and raloxifene cotreatment resulted in a lower IGF-I to IGFBP-3 ratio than cotreatment with 17β-estradiol (19). Over the course of the current long-term study, cotreatment with raloxifene showed a significantly blunted GH-induced increase in the IGF-I to IGFBP-3 ratio. Low molar ratio of IGF-I to IGFBP-3 is strongly linked to the metabolic syndrome (38). Detrimental effects of raloxifene on metabolic health are supported by a study in postmenopausal women, in whom raloxifene treatment for 3 yr increased the risk for diabetes (39). Unlike estrogen, which is primarily an ERα agonist, raloxifene acts predominantly through the ERβ receptor (40, 41). In animal models, ERβ activation inhibits glucose transporter 4 activity in skeletal muscle reducing glucose transport, which may result in insulin resistance and subsequent development of obesity (42). In addition, there is evidence that IGFBP-3 levels affect adipose tissue metabolism. IGFBP-3 inhibits insulin-stimulated glucose uptake in adipocytes (43) and adipocyte differentiation (44). There is emerging evidence of IGFBP-3 on skeletal muscle reporting reduced muscle mass in IGFBP-3 transgenic animals (45). In diabetic mice, there are higher levels of skeletal muscle IGFBP-3, which may further disrupt anabolic effects of the GH-IGF-I system (46). Higher IGFBP-3 levels during raloxifene treatment may therefore at least partly contribute to the attenuating effect on LBM. In human skeletal muscle cells, estrogen stimulates (47–49) whereas raloxifene down-regulates the expression of *MyoD* (49), a gene responsible for myoblast differentiation. If this translates to a reduction in muscle mass, it could explain the differences in GH-induced increase on LBM in our hypopituitary women during the different cotreatments. Taken together, the evidence supports a possible role for IGFBP-3 in mediating in part the differences in effects between raloxifene and estrogen on

LBM and FM through effects on muscle and adipocyte differentiation and function.

A weakness of the current study is the small sample size, which is addressed in part by incorporating a crossover design. We did not perform regional analysis of FM distribution or functional studies to assess whether lesser increase in LBM during raloxifene treatment phase associated with lower muscle strength or power. However, this study has important clinical implications. GH and estrogen are standard hormone replacement therapies in hypopituitary women. Raloxifene is a widely prescribed antiresorptive agent in the treatment of osteoporosis and considered an alternative for hypopituitary women who are uncertain about the risks and benefits of estrogen replacement therapy. Our findings caution against the assumed advantage of raloxifene or possibly other SERM in this clinical setting.

In summary, GH replacement significantly increased IGF-I during both 17β-estradiol and raloxifene cotreatments to a similar extent. However, GH therapy increased LBM and BMD and reduced FM to a lesser extent with raloxifene than with 17β-estradiol cotreatment. We conclude that in GHD women during GH replacement, cotreatment with raloxifene offers no metabolic or body compositional advantage over 17β-estradiol.

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