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Protein Metabolism in Acromegaly: Differential Effects of Short- and Long-Term Treatment

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Context: GH acutely increases body protein by stimulating protein synthesis and reducing protein oxidation.

Objective: The objective of the study was to determine whether these changes in protein metabolism are sustained in long-term GH excess and reversed by correction.

Design: We conducted a cross-sectional study in 16 acromegalic and 18 normal subjects and a longitudinal study in which acromegalic subjects were studied before and after short-term (n = 8) or long-term (n = 10) treatment.

Setting: The study was conducted at a clinical research center.

Main Outcome Measures: Whole-body rates of leucine appearance (leucine Ra; an index of protein breakdown), leucine oxidation, and nonoxidative leucine disposal (NOLD; an index of protein synthesis) estimated using infusion of 1-[^{13}C] leucine were measured.

Results: Leucine Ra and NOLD were greater ($P < 0.01$) in acromegalic compared with normal subjects, whereas leucine oxidation did not differ. Leucine oxidation increased significantly ($P < 0.05$) after short-term treatment but returned to baseline after long-term treatment. Both leucine Ra and NOLD decreased significantly ($P < 0.05$) after short- and long-term treatment. Adjustment for body composition did not affect results.

Conclusions: In acromegalic subjects, protein breakdown and synthesis are increased, whereas protein oxidation does not differ from normal subjects. Protein oxidation increases transiently, whereas protein breakdown and synthesis are stably reduced after treatment. Because protein oxidation represents irreversible loss, we conclude that the normal state of protein oxidation found in acromegaly and after long-term treatment represents metabolic adaptation, which maintains protein mass at a steady state after stable changes in GH status. **(*J Clin Endocrinol Metab* 92: 1479–1484, 2007)**

GH ACUTELY EXERTS an anabolic effect by increasing protein synthesis and reducing protein oxidation (1–5). Although the protein metabolic effects of chronic GH excess are not known, the observations that total body nitrogen (6) and body cell mass (BCM) (7) are increased in acromegaly imply that the acute increase in body protein is sustained.

The model of adult GH deficiency provides an insight into how chronic effects of GH differ from acute effects. Using the whole-body leucine turnover technique, which allows accurate estimation of rates of whole-body protein breakdown, oxidation, and synthesis, we have previously shown that protein breakdown and synthesis are equally reduced, therefore, protein loss through oxidation is normal in GH deficient (GHD) adults (8). This observation explains why lean body mass (LBM), although reduced in GHD adults, does not eventually disappear. Similarly, if the anabolic effects observed during acute GH administration were to persist in the setting of chronic GH excess, LBM would indefinitely expand. Because clinical observation and longitudinal studies (9) suggest that this does not occur, homeostatic mechanisms must exist to maintain protein mass at an increased but stable level.

To determine the effects of chronic GH excess on protein metabolism, we have performed a cross-sectional study comparing protein metabolism in acromegalic subjects with normal subjects matched for age and gender. Furthermore, we examined whether the protein metabolic effects of chronic GH excess are reversible, in a longitudinal study, the design of which allowed comparison of short and long-term correction of GH excess. The findings were adjusted for LBM, which we have previously reported to be a major determinant of protein metabolism in both normal and GHD adults (8), and we also attempted to account for the potentially confounding effect of extracellular water (ECW), which is increased in acromegaly (10) and thought to be metabolically inactive.

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Abbreviations: BCM, Body cell mass; BF, body fat; DEXA, dual energy x-ray absorptiometry; ECW, extracellular water; FM, fat mass; GHD, GH deficient; KIC, ketoisocaproic acid; LBM, lean body mass; leucine Ra, rate(s) of leucine appearance; NOLD, nonoxidative leucine disposal.

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Subjects and Methods

Subjects

There were 16 acromegalic patients (seven men and nine women) and 18 normal subjects (eight men and 10 women) of similar age distribution (Table 1) recruited after obtaining informed written consent. Inclusion criteria for acromegalic patients were: age 18–75 yr; acromegaly defined on the basis of typical history and clinical findings, a nonsuppressed postglucose GH level and an elevated serum IGF-I level; and stable

TABLE 1. Clinical characteristics of patients with acromegaly and normal subjects who participated in the protein turnover studies

	Acromegaly (n = 16)	Normal (n = 18)
Age (yr)	51 (29–67)	52 (27–73)
Gender (male/female)	7/9	8/10
Estimated duration of disease (yr)	6 (2–16)	
Height (cm)	170 (158–192)	166 (148–189)
Weight (kg)	83 (58–117)	71 (53–110)
Body mass index (kg/m^2)	27 (23–41)	25 (20–36)
LBM (kg)	51 (41–80)[a]	44 (29–60)
LBM (%)	71 (47–80)	64 (50–78)
FM (kg)	21 (13–50)	19 (10–45)
FM (%)	27 (20–49)	32 (19–47)
ECW (liters)	25 (19–44)[a]	19 (12–29)
BCM (kg)	28 (18–45)	27 (18–42)
IGF-I (ng/ml)	440 (339–990)[a]	166 (60–176)

Values are expressed as median (range).
[a] $P < 0.01$ *vs.* normal.

pituitary hormone replacement (if required) for 12 months before entry to the study. Patients were excluded from the trial if they had: diseases likely to influence protein metabolism (ischemic heart disease, peripheral vascular disease, uncontrolled hypertension, significant respiratory disease, or arthritis' chronic renal or liver failure); other drugs or alcohol intake thought to impair muscle function; and history of malignancy. Of the 16 patients, nine had undergone previous pituitary surgery, and of these six, had additional radiotherapy. One patient had previously been treated with radiotherapy only. Of the patients who had received previous treatment, four were receiving stable hormone replacement therapy for other deficiencies. All patients had active disease, including the 10 who had received prior treatment, as confirmed by elevated plasma IGF-I, with a range of 339–990 ng/ml (median 440; normal < 240). The control group was comprised of normal volunteers on no medications, recruited from the general population.

Study design

Two studies were performed. The first study was a cross-sectional comparison of protein turnover in all 16 acromegalic and 18 normal subjects. The second study was a longitudinal study in two subgroups of acromegalic patients designed to investigate the effects on protein metabolism after short and long-term treatment (Fig. 1). All patients in the longitudinal study had participated in the cross-sectional study of protein metabolism. The first subgroup (n = 8) was studied before and after 6 weeks of treatment with octreotide LAR (Sandostatin LAR, 20 mg/d; Novartis Pharmaceuticals Corp., East Hanover, NJ). The second subgroup (n = 10) was studied before and at least 3 months (median 14, range 4–24) after transsphenoidal surgery (n = 5) or octreotide (n = 5). Of the subjects in the long-term octreotide group, four had previously taken part in the short-term study. Pituitary replacement therapy was maintained and unaltered throughout the study. The Research Ethics Committee of St. Vincent's Hospital (Sydney, Australia) approved all studies.

Clinical protocol

Dual energy x-ray absorptiometry (DEXA) estimated body composition in 15 acromegalic subjects and all of the normal subjects in the cross-sectional study, and in seven subjects after long-term treatment. DEXA scanning was not performed in the short-term studies because we have previously shown that changes in LBM after octreotide treatment of this duration are entirely attributable to changes in ECW (10). DEXA was performed using a total body scanner (Lunar model DPX, software version 3.1; Lunar Corp., Madison, WI) to determine LBM and fat mass (FM). At our institution, the coefficients of variation for LBM and FM are 1.5 and 2.9%, respectively (10).

An attempt was made to estimate ECW from dilution studies using radioactive sodium, in which we showed that ECW was increased in acromegalic subjects, and that the excess ECW was highly correlated

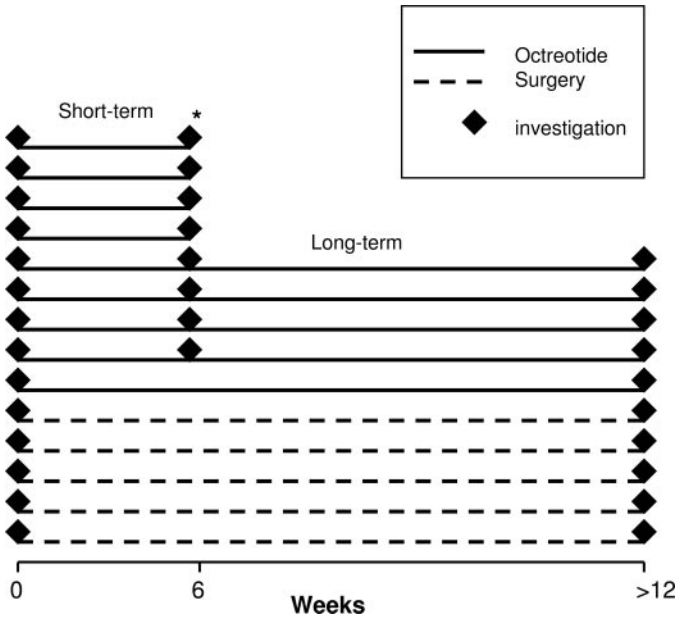

FIG. 1. Treatment flow chart of the 14 acromegalic patients studied during octreotide (n = 9) and after surgery (n = 5). In the octreotide group, seven participated in the short-term evaluation, four in both the short and long-term evaluation, and one after long-term evaluation. The data from one short-term octreotide-treated patient (*) was excluded from analysis because of a lack of IGF-I response. Thus, short-term data were available in seven and long-term data in 10 acromegalic subjects.

with log GH and IGF-I (r = 0.80) after adjustment for percent body fat (BF) measured using DEXA scanning (10). Briefly, 25 μCi ^{24}NaCl (Australian Nuclear Science and Technology Organisation, Sydney, Australia) were injected iv, and a venous blood sample was obtained after a 22-h equilibrium phase. After adjusting for urinary loss, ECW was calculated as previously described (11, 12). In our laboratory, the reproducibility of this technique for five normal subjects studied on three separate occasions is 5.1%. Because the closest correlation was found with IGF-I, a model that included percent BF and IGF-I and predicted 83% of the variance in percent ECW was used to estimate ECW. The equations used were ECW = 35.066 − 0.293 (percent BF) in normal subjects and ECW = 35.066 − 0.293 (percent BF) + 0.011 (IGF-I) in acromegalic subjects, where ECW is expressed in liters, and IGF-I is expressed in ng/ml. BCM, the metabolically active component of LBM, was calculated as the difference between LBM, measured by DEXA scanning, and ECW.

Whole-body protein turnover was undertaken using a primed constant infusion of 1-[^{13}C] leucine, as previously described (8, 13). 99% $NaH^{13}CO_3$ was obtained from Cambridge Isotope Laboratories (Woburn, MA), and 99% 1-[^{13}C] leucine was obtained from Mass Trace (Woburn, MA). Solutions of each were prepared under sterile conditions using 0.9% saline.

Subjects were studied in the Clinical Research Facility after an overnight fast, as previously described (8, 13). A 0.1 mg/kg priming dose of $NaH^{13}CO_3$ was followed immediately by 1-[^{13}C] leucine (prime, 0.5 mg/kg; infusion, 0.5 mg/kg·h). Blood and breath samples were collected before (−10, 0 min) and at the end of a 3-h infusion (140, 160, and 180 min). Blood was placed on ice, and plasma was separated and stored at −80 C until analysis. CO_2 production rates were measured with an open circuit, ventilated hood system (Deltatrac monitor; Datex Instrumentation Corp., Helsinki, Finland). The monitor was calibrated against standard gases before each study. Measurements were averaged over 20–40 and 160–180 min. The coefficient of variation was 4%.

Calculation of whole-body protein turnover

Leucine Ra, leucine incorporation into protein, and leucine oxidation were calculated as previously described (8). The reciprocal pool model

TABLE 2. Leucine Ra, leucine oxidation, and NOLD (μmol/min) in 16 patients with acromegaly (Acro) and 18 normal subjects

	Leucine Ra			Leucine oxidation			NOLD		
	Acro (n = 16)	Normal (n = 18)	*P* value	Acro (n = 16)	Normal (n = 18)	*P* value	Acro (n = 16)	Normal (n = 18)	*P* value
Unadjusted	165 ± 9	124 ± 7	0.001	31 ± 2	26 ± 1	0.10	135 ± 8	98 ± 6	0.001
LBM adjusted	150 ± 7	143 ± 6	0.11	28 ± 2	28 ± 2	0.89	122 ± 6	107 ± 5	0.09
BCM adjusted	161 ± 7	126 ± 6	0.001	30 ± 2	26 ± 2	0.12	131 ± 6	100 ± 5	0.0005

Data are presented as unadjusted and after adjustment, LBM, and BCM by analysis of covariance. Values are expressed as mean ± SEM.

was used in which enrichment of α-ketoisocaproic acid (KIC) is used as a surrogate measure of true intracellular leucine enrichment (14). Because leucine represents 8% of total body protein, or 590 μmol leucine represents 1 g of protein, rates of protein turnover may be estimated using these constants (15, 16).

Analytical methods

α-KIC, a metabolite of leucine, was extracted by the method of Nissen *et al.* (17). As previously described (8), KIC enrichment was measured as the butyldimethylsilyl derivative by gas chromatography (model 5890; Hewlett-Packard Co., Palo Alto, CA)-mass spectrometry (MSD 5971A; Hewlett-Packard Co.), with selective monitoring of ions 301 and 302 (14). CO_2 enrichment in breath was measured on a SIRA Series II isotope ratio mass spectrometer (VG Isotech, Cheshire, UK). RIA measured IGF-I after acid-ethanol extraction using recombinant human IGF-I as standard. The intraassay and interassay coefficients of variation for IGF-I were 8.2 and 13.0%, respectively (8, 10).

Statistics

At the commencement of the study, no data were available concerning protein turnover in subjects with acromegaly. Therefore, sample size was based on previous studies from our unit comparing subjects with GH deficiency and normal subjects, in which clear differences were observed using smaller study groups than those in the current study (8). The Mann-Whitney *U* test was used to compare the effects between groups. Results are expressed as median (range) and the Wilcoxon signed rank sum test was used to compare paired changes from baseline after treatment. Correction of whole-body leucine turnover for LBM and BCM was made using analysis of covariance after validating that the actual data were normally distributed using the Kolmogorov-Smirnov test. This approach was undertaken because while the relationship between LBM and components of metabolism is linear, the regression line does not cross the y-axis at zero [*i.e.* the relationship is best expressed as y = a (LBM) + b], where y is the component of metabolism (*e.g.* leucine Ra), a is the slope of the regression line, and b is where the regression line intercepts with the y-axis. For this reason, as we and others (8, 18–22) previously described, we have used a regression-based approach to adjust for the effects of body composition rather than simple division. Results are expressed as median (range) unless otherwise stated, and statistical significance was set at an α level of 0.05.

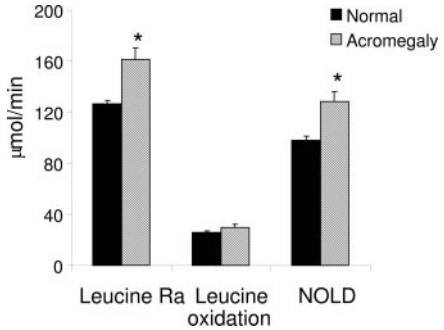

FIG. 2. Leucine Ra, leucine oxidation, and NOLD in 18 normal subjects and 16 patients with acromegaly. Results are adjusted for BCM by analysis of covariance and expressed as μmol/min. *, $P < 0.01$ between groups.

Results

The mean age, gender distribution, and height did not differ significantly between subjects with acromegaly and normal subjects (Table 1). Subjects with acromegaly tended to be heavier ($P = 0.08$) and had a greater LBM ($P < 0.01$) compared with normal subjects. Estimated ECW was significantly elevated ($P < 0.001$; Table 1), while estimated BCM tended to be higher in acromegaly, although the difference was not statistically significant. Three acromegalic subjects were receiving glucocorticoid replacement, four were receiving thyroxine replacement, and two were receiving testosterone replacement.

Comparison of protein turnover in subjects with acromegaly and normal subjects

LBM correlated significantly with leucine Ra ($R^2 = 0.62$; $P < 0.001$), leucine oxidation ($R^2 = 0.37$; $P < 0.001$), and NOLD ($R^2 = 0.59$; $P < 0.001$) in normal and acromegalic subjects. LBM is composed in part by metabolically inactive ECW, therefore, we reanalyzed the relationship for BCM. BCM also correlated significantly with leucine Ra ($R^2 = 0.38$; $P < 0.0001$), leucine oxidation ($R^2 = 0.16$; $P < 0.02$), and NOLD ($R^2 = 0.38$; $P < 0.0001$), but the goodness of fit of the relationship was not improved by substituting BCM for LBM.

Next, we compared rates of leucine metabolism between the two groups before and after adjusting the data for the effects of LBM and BCM using analysis of covariance. Table 2 shows data before and after adjustment for LBM and BCM. Leucine Ra and NOLD, unadjusted and when adjusted for LBM and BCM (Fig. 2), were greater in acromegalic subjects, although differences when adjusted for LBM do not reach statistical significance. Leucine oxidation was not different between the two groups, either unadjusted or adjusted, for LBM or BCM (Fig. 2 and Table 2).

TABLE 3. Characteristics at baseline of the two groups of acromegalic patients who were studied at baseline and after short-term (octreotide LAR) or long-term (octreotide or surgery) treatment

	Short term (n = 7)	Long term (n = 10)
Age (yr)	57 (33–73)	50 (33–57)
Gender (male/female)	5/2	5/5
Height (cm)	171 (161–192)	171 (161–192)
Body mass index (kg/m^2)	29 (25–37)	29 (26–56)
IGF-I (ng/ml)	398 (325–574)	490 (325–990)

Values are expressed as median (range).

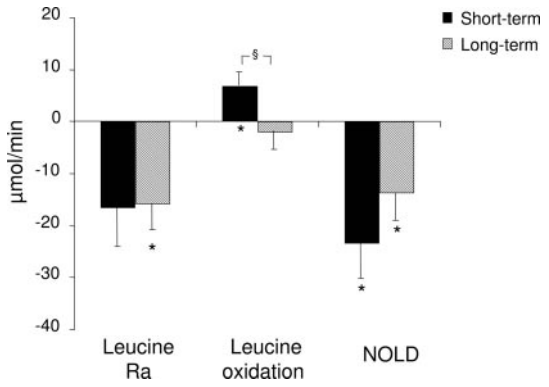

FIG. 3. Change from baseline of leucine turnover after short-term (n = 7) and long-term (n = 10) treatment of acromegaly. *, $P < 0.05$ *vs.* baseline. §, $P < 0.05$ between groups.

Comparison of protein turnover in acromegaly pretreatment and posttreatment

After short-term treatment, IGF-I decreased from 398 (325–574) to 199 ng/ml (40–283), and after long-term treatment, from 490 (325–990) to 226 ng/ml (161–325) ($P < 0.01$) (Table 3). There was no change in IGF-I after octreotide LAR in one subject (range 300–335 ng/ml), who was, therefore, classified as a nonresponder. His results were not included in further analysis. DEXA scanning revealed a significant reduction in LBM [61.3 (40.9–76.3) *vs.* 58.7 kg (39.8–71.5); $P < 0.05$] and a trend toward an increase in FM [23.9 (16.7–33.8) *vs.* 26.1 kg (19.4–38.1); $P = 0.10$] after long-term treatment.

Following short-term treatment, leucine Ra [172 (136–252; mean ± SEM, 180 ± 17) to 159 μmol/min (115–207; 165 ± 12); $P < 0.05$] and NOLD [143 (136–252; 156 ± 17) to 125 μmol/min (114–236; 133 ± 13); $P < 0.05$] decreased, while leucine oxidation increased significantly from 24 (16–29; 24 ± 2) to 34 μmol/min (16–43; 32 ± 4; $P < 0.05$) (Fig. 3). In the patients studied after long-term treatment, both leucine Ra [174 (136–232; 176 ± 12) to 157 μmol/min (112–214; 160 ± 10); $P < 0.05$] and NOLD [146 (114–236; 144 ± 10) to 126 μmol/min (94–183; 130 ± 9; $P < 0.05$] were significantly lower than before treatment. However, no significant change in leucine oxidation was observed [28 (19–59; 31 ± 4) to 30 μmol/min (19–43; 29 ± 3)] after long-term treatment (Fig. 3). There were no differences in the response to treatment between those who were treated with surgery and those who were treated with long-term octreotide (Table 4).

Subgroup analysis of the four subjects who took part in the short and long-term studies revealed a similar pattern, with leucine Ra [167 (136–219) to 148 μmol/min (115–196)] and NOLD [142 (114–191) to 128 μmol/min (91–152)] decreasing after 6 wk of treatment and remaining lower than pretreatment levels after 2 yr of treatment [150 (129–195) leucine Ra; 124 (106–167) NOLD]. The increase in leucine oxidation [25 (19–28) to 40 (24–43)] after short-term treatment was no longer apparent after long-term treatment [26 μmol/min (19–34)] (Fig. 4).

Discussion

These cross-sectional and longitudinal studies in acromegaly are the first to investigate the consequences of chronic GH excess and its reversal on whole-body protein metabolism. The results show that absolute leucine Ra and incorporation into protein and synthesis were similarly increased in active acromegaly, while leucine oxidation did not differ from normal subjects. Treatment of acromegaly resulted in a sustained reduction in leucine appearance and incorporation into protein but a transient phase in which leucine oxidation was increased followed by a later phase when oxidation returned to baseline. Thus, while GH regulates all three components of leucine metabolism, its effect was dependent on whether the GH state was stable or changing. Leucine appearance and incorporation into protein were invariably influenced by GH status, being increased in acromegaly and decreasing to a stable level early after treatment. In contrast, leucine oxidation was not perturbed in patients with stable active disease but increased early after treatment before returning to normal.

One previous study has addressed protein metabolism in acromegalic subjects. Using similar techniques to those in the current study, Battezzati *et al.* (23), in a study involving smaller numbers of subjects, observed no difference in any component of protein metabolism, expressed in relation to body weight, under postabsorptive conditions. During a hyperinsulinemic euglycemic clamp, leucine appearance and incorporation into protein decreased significantly, but the decrease in acromegalic subjects was less than that observed in normal subjects. After transsphenoidal surgery, these effects were partially but incompletely reversed. The latter observations are compatible with our finding that successful treatment reverses protein metabolic perturbations in acromegaly. However, the baseline finding that leucine Ra and NOLD are not different in acromegaly is in conflict with ours. To ascertain whether the disagreement occurred from the way the data are expressed, we undertook a reanalysis after dividing the leucine data by body weight. Weight-adjusted leucine turnover (2.00 ± 0.13 *vs.* 1.71 ± 0.05 μmol/kg·min; $P < 0.01$) remained significantly higher in acromegaly, however, NOLD (1.37 ± 0.15 *vs.* 1.40 ± 0.09 μmol/kg·min) did not. Weight-adjusted leucine oxidation (0.38 ± 0.03 *vs.* 0.36 ± 0.02 μmol/kg·min) was not different between the two groups. Although the findings are not entirely consonant when the data are analyzed in the same way, the two studies do agree that leucine oxidation is not perturbed in acromegaly.

These findings in chronic GH excess show similarities and

TABLE 4. The effect of treatment of acromegaly with surgery or long-term octreotide

	Surgery (n = 5)		Octreotide (n = 5)	
	Preoperative	Postoperative	Preoperative	Postoperative
Leucine Ra (μmol/min)	179 (131–232) [186 ± 16]	169 (112–214) [168 ± 15]	142 (136–219) [166 ± 17]	152 (129–195) [152 ± 12]
Leucine oxidation (μmol/min)	33 (24–59) [37 ± 6]	35 (104–189) [33 ± 4]	28 (27–59) [25 ± 2]	23 (19–34) [25 ± 3]
NOLD (μmol/min)	146 (104–189) [145 ± 12]	126 (18–43) [131 ± 13]	141 (114–191) [141 ± 16]	127 (106–167) [127 ± 11]

Values are expressed as median (range) [mean ± SEM].

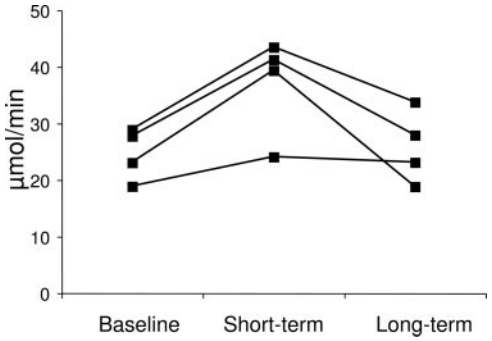

FIG. 4. Leucine oxidation in four patients with acromegaly who were studied after short- (6 wk) and long-term (greater than 4 months) treatment with octreotide.

differences compared with those observed after acute GH administration. Short-term administration of supraphysiological GH increases leucine turnover (4) and incorporation into protein, and reduces oxidation (4, 5). The current study shows that increased leucine appearance and incorporation into protein are also observed in the setting of chronic GH excess but that oxidation does not differ from normal subjects. These findings suggest that in chronic GH excess, a new equilibrium is reached in which protein turnover is increased, but total body protein is stable. This finding is consistent with the maintenance of a stable protein mass and with the clinical observation that while LBM is increased in acromegaly, it does not continue to increase indefinitely (9). It is the corollary of our previous observation that chronic GH deficiency is characterized by reduced protein breakdown and synthesis but unchanged protein oxidation compared with normal controls (8).

Important differences were also observed between short and long-term correction of GH excess. Short-term treatment with octreotide LAR reduced leucine appearance and incorporation into protein but increased leucine oxidation, while after long-term treatment, the reduction in leucine appearance and incorporation into protein was sustained, but oxidation no longer differed from baseline. The findings were the same when only subjects who received octreotide were considered because there was no difference between the long-term effects of surgery and octreotide. Because leucine oxidation represents irreversible protein loss, the combined results of the cross-sectional and longitudinal studies suggest that a decrease in GH leads to a short-term loss of body protein, followed by a sustained phase when body protein mass is stabilized at a new level. This proposal is supported by long-term observational studies, showing that LBM decreases after successful treatment of acromegaly but remains stable after unsuccessful treatment (9).

Body composition is a major determinant of protein metabolism, and because this occurs almost entirely within lean tissue, components of protein metabolism are conventionally adjusted for LBM. However, we and others (7, 9, 10) have previously shown that increased LBM in acromegaly largely reflects increased ECW, and that the excess of ECW is highly correlated with circulating GH and IGF-I levels. Because ECW is metabolically inactive, we were concerned about adjustment for LBM in acromegaly without accounting for changes in the ratio of metabolically active BCM to metabolically inactive ECW. To address this, we developed a model, which included percent FM and IGF-I, and which predicted more than 80% of the variance in ECW in acromegalic subjects. Interestingly, we found that even before adjustment for estimated ECW, LBM was tightly correlated with components of protein turnover and that substituting BCM for LBM did not result in a tighter correlation. These observations imply that LBM measured by DEXA scanning largely reflects metabolically active tissue. Importantly, our findings were not altered whichever way adjustment for body composition was made.

The mechanisms behind the observed effects are not known, and might reflect any combination of increased GH, IGF-I, and insulin, and reduced insulin sensitivity. Like GH (24), IGF-I directly increases whole-body (25) and skeletal muscle (26) protein synthesis, but unlike GH, IGF-I reduces whole-body protein breakdown (26). Although insulin, which is increased in acromegaly, reduces protein breakdown (27), resistance to insulin action may nullify this effect. The study by Battezzati *et al.* (23) has provided further insight into the complex interaction between GH and insulin. In that study, the differences between normal and acromegalic subjects only emerged during hyperinsulinemic conditions, suggesting that the effect of GH to increase protein turnover may result from its insulin-antagonistic effect. More complex studies would help to clarify the interaction between GH, insulin, and substrate availability. The studies reported here were performed in the postabsorptive setting, but there is evidence from GHD subjects that effects of GH post-prandially are also important, particularly in increasing protein synthesis (28). Other studies have used amino acid infusions to show that GH increases protein synthesis in the face of an adequate substrate supply (25).

Conclusions

Acromegaly results in a sustained increase in leucine Ra and NOLD that reverses after successful treatment. In contrast, protein oxidation rates vary in a time-dependent manner. Correction of GH excess leads to transient loss of protein from oxidation, which then reverts to normal, as found in chronic GH excess. We propose that this dynamic time-dependent process represents metabolic adaptation that operates to maintain LBM at a new steady state.

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