IGF-1 Levels Across the Spectrum of Normal to Elevated in Acromegaly: Relationship to Insulin Sensitivity, Markers of Cardiovascular Risk and Body Composition

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Abstract

Purpose—Activity of acromegaly is gauged by levels of GH and IGF-1 and epidemiological studies demonstrate that their normalization reduces acromegaly's excess mortality rate. However, few data are available linking IGF-1 levels to features of the disease that may relate to cardiovascular (CV) risk. Therefore, we tested the hypothesis that serum IGF-1 levels relative to the upper normal limit relate to insulin sensitivity, serum CV risk markers and body composition in acromegaly.

Methods—In this prospective, cross-sectional study conducted at a pituitary tumor referral center we studied 138 adult acromegaly patients, newly diagnosed and previously treated surgically, with fasting and post-oral glucose levels of endocrine and CV risk markers and body composition assessed by DXA.

Results—Active acromegaly is associated with lower insulin sensitivity, body fat and CRP levels than acromegaly in remission. %ULN IGF-1 strongly predicts insulin sensitivity, better than GH and this persists after adjustment for body fat and lean tissue mass. %ULN IGF-1 also relates inversely to CRP levels and fat mass, positively to lean tissue and skeletal muscle estimated (SM^E) by DXA, but not to blood pressure, lipids, BMI or waist circumference (WC). Gender interacts with the IGF-1-lean tissue mass relationship.

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Conclusions—Active acromegaly presents a unique combination of features associated with CV risk, reduced insulin sensitivity yet lower body fat and lower levels of some serum CV risk markers, a pattern that is reversed in remission. %ULN IGF-1 levels strongly predict these features. Given the known increased CV risk of active acromegaly, these findings suggest that of these factors insulin resistance is most strongly related to disease activity and potentially to the increased CV risk of active acromegaly.

Key Terms

Acromegaly; body composition; insulin sensitivity; IGF-1

INTRODUCTION

The evaluation and treatment of acromegaly are directed by measurement of GH and IGF-1 levels, the disease's biochemical markers. Treatment aims to normalize IGF-1 levels and lower GH levels below a certain cut off since achieving these goals is associated with reducing the excess mortality of acromegaly (1,2). The leading cause of death in acromegaly is reported to be cardiovascular disease, which may result from the high prevalence of structural heart disease, hypertension, diabetes mellitus or insulin resistance in acromegaly (3,4). The presence of co-morbidities, including heart disease and disorders of glucose metabolism, increases mortality rates in acromegaly(5), but how disease activity assessed by IGF-1 level, in particular, relates to control of these co-morbidities is incompletely understood. In a prior study (6), we found serum IGF-1 levels, when measured with a now unavailable IGF-1 radio-immunoassay, correlated better than GH with insulin sensitivity in acromegaly patients. Using currently available GH and IGF-1 assays, this study extends these findings to examine, in a large cohort of acromegaly patients, the relationships of disease activity biomarkers to body composition, both fat and lean tissues, insulin sensitivity and other markers of CV risk. We also examine how gender and hypogonadism influence these relationships. We aimed to test our hypothesis that IGF-1 levels across the normal to elevated spectrum predict clinical endpoints for acromegaly therapy that may contribute to the increased CV risk of acromegaly and to the reduction of this risk as acromegaly is treated.

SUBJECTS AND METHODS

Study Subjects

Newly diagnosed and previously surgically treated acromegaly patients were studied. Acromegaly was diagnosed by IGF-1 level above the age-adjusted normal range, nadir GH after oral glucose > 1 µg/L, clinical characteristics of acromegaly and if prior surgery, pathological confirmation of a GH secreting pituitary tumor. From a cohort of 165 consecutively studied subjects, we excluded from this analysis those with diabetes mellitus (n=11), those on acromegaly medications at the time of the visit or within the 3 months prior (long acting somatostatin analog (n=10), pegvisomant (n=2), somatostatin analog and pegvisomant (n=1)), women on oral contraceptives (n=2) and gastric bypass surgery (n=1). In the final study group were 138 subjects (77 males, 61 females) of whom 40 were newly diagnosed, 90 had prior pituitary surgery, 7 surgery and radiotherapy and 1 RT only.

Subjects with prior surgery were studied 6 months postoperatively and those previously treated with medication were studied 3 months after last administration. On pituitary function assessments 13 patients (9 remission, 4 active disease) had hypopituitarism other than hypogonadism (Tables 1 and 2). 84 subjects were eugonadal (including 8 men on testosterone and 1 woman on estrogen/progesterone replacement) and 54 were hypogonadal (including 27 post-menopausal women and 7 pre-menopausal women with secondary amenorrhea not on hormone replacement therapy and 20 men with low testosterone levels not on therapy). Ten subjects with hyperlipidemia on lipid lowering therapy at the visit were not included in lipid analyses. All were ambulatory with normal renal function and no liver disease.

Study Design

In this prospective, cross-sectional study each subject had one visit that included a history, physical examination with anthropometrics (body weight, height, waist and hip circumferences), blood sampling after an overnight fast for IGF-I, GH, insulin, glucose, leptin, CRP and homocysteine and a 100-g oral glucose (OGTT)(Trutol 100*) with samples at 60, 90 and 120 minutes for GH, glucose and insulin. Samples were frozen at -80°C in multiple aliquots until assayed. Also measured were fasting total cholesterol, HDL, LDL, triglyceride (TG) (108 subjects) and lipoprotein (a) (100 subjects). 116 subjects also underwent whole body and regional body composition estimation by Dual-energy X-ray absorptiometry (DXA).

Biochemical Measurements—GH, IGF-1, insulin and CRP were measured by chemiluminescent immunometric assay and homocysteine by competitive immunoassay IMMULITE®(Siemens). Functional sensitivity was for GH 0.05 $\mu\text{g/L}$, CRP 0.3 mg/L and homocysteine 0.5 $\mu\text{mol/L}$. IGF-I levels were compared to age-appropriate normal ranges. Glucose was measured by hexokinase method, leptin by human RIA kit (Millipore, Research, St. Charles, MO) and lipids as previously described (7). Samples were run in duplicate.

Estimates of insulin sensitivity—Hepatic insulin sensitivity was estimated by homeostasis model assessment (HOMA) scores (8) and whole-body insulin sensitivity by a measure derived from the OGTT, the composite insulin sensitivity index (Comp ISI), which correlates highly with the rate for whole-body glucose disposal during the euglycemic insulin clamp (9). Although we used a 100g glucose limiting comparison of our index values to those in other studies, we were able to compare whole-body IS across our subject groups.

DXA—Whole and regional body composition were estimated by dual-energy X-ray absorptiometry (software version 11.4; GE Lunar Prodigy Advance, Madison WI)(DXA) as previously described (10). Mass of lean tissue and fat for the whole body and specific regions was provided by the software. We calculated DXA estimated inter-muscular adipose tissue-free skeletal muscle (SM) mass (IMAT-free SM or SM^{E}) based on a prediction equation previously validated and found to agree highly with total body SM mass by MRI in a variety of patients, including acromegaly (7,11).

The study was approved by the Institutional Review Board of Columbia University Medical Center. All subjects gave written informed consent before participation.

Statistical Analysis—For analysis, IGF-1 levels were expressed as % of the upper limit of normal (%ULN) for the subject's age. Based on %ULN IGF-1, subjects were divided into a remission group (IGF-1 ≤ ULN) and an active group (IGF-1 > ULN). Four patients with Vitamin B12 deficiency were excluded from CRP and homocysteine analyses.

Continuous variables were summarized by mean ± SD (standard deviation) and categorical variables by frequencies and percentages. For continuous variables, we used Mann-Whitney U-test to test difference in two groups. For categorical variables, Chi-square test was used to compare group difference. Association between two continuous variables was assessed by Spearman's correlation coefficient and simple linear regression analysis. Linear regression models were used to examine predictors of insulin sensitivity including IGF-1 or GH, age, gender, body composition parameters and to investigate predictors of body composition parameters, CRP and leptin levels. Multivariable linear regression models were built with predictors that were significant at 0.1 level in univariable linear regression models. p-values < 0.05 were considered statistically significant. Statistical analyses were performed using GraphPad Prism version 6.0 for Mac and SAS 9.3.

RESULTS

Disease Status of Study Subjects

Remission and active groups characteristics are shown in Table 1 and those of males and females within remission and active groups in Table 2. Sixty-one subjects (44%) were in remission (IGF-1 ≤ ULN) (range 0 to −70% ULN) and 77 (66%) had active disease (IGF-1 > ULN, range 7–493% above ULN). The remission group was older than the active group (p= 0.0007). Overall, ages of males (47 ± 12 yr.) and females (51 ± 12 yr.) did not differ (p=.07) nor did those of males and females within disease groups (Table 2). Remission and active groups did not differ in time elapsed from surgery to the visit, proportions with prior radiotherapy, hypopituitarism or hypogonadism (Table 1).

Relationship of Disease Activity to Insulin Sensitivity, Body Composition & CV Risk Markers

Insulin Sensitivity—Disease status assessed by %ULN IGF-1 was the strongest predictor of insulin sensitivity. HOMA was higher and Comp ISI lower in active vs. remission groups (Table 1). HOMA correlated with %ULN IGF-1 (r = .396, p < 0.00001) (Figure 1A), fasting GH (r = .267, p = .002) and nadir GH (r = .310, p = 0.0003) (Figure 1B). CompISI correlated negatively with %ULN IGF-1 (r = −.380, p < .0001), fasting (r = −.257, p = .003) and nadir GH (r = −.256, p = .003) (Table 3). Insulin sensitivity was related to fat mass; total body fat mass (and similarly trunk fat mass) correlated with HOMA and inversely with CompISI (Table 3). Total body lean mass and skeletal muscle mass estimate by DXA (SME) correlated with HOMA and inversely with CompISI (Table 3). In univariable analysis age was also a significant predictor of insulin sensitivity, but gender, gonadal status and % body or trunk fat were not. In multivariable analysis, after accounting for age, GH levels (fasting

and OGTT nadir) as well as mass of total body and trunk fat and SM^E , only age and %ULN IGF-1 remained independent predictors of HOMA and only %ULN IGF-1 of Comp ISI (Table 4).

Body Composition—Body composition related significantly to disease status. Total body and trunk fat mass and % total body and trunk fat were lower in active disease (Table 1). Lean tissue mass as well as SM^E were higher in active disease overall and in men and women (Tables 1 and 2).

%ULN IGF-1, fasting and nadir GH correlated inversely with total body and trunk fat mass and % total and trunk fat (Table 3)(Figure 2). In univariable analysis, %ULN IGF-1 and GH were predictors of total body and trunk fat and gonadal status also of total body fat mass. However, in multivariable regression, only %ULN IGF-1 and gonadal status remained significant predictors of total body fat mass and only %ULN IGF-1 of trunk fat mass (Table 4). In univariable analysis, %ULN IGF-1, GH, gender and gonadal status were predictors of % total body fat and % trunk fat, but in multivariable analysis only %ULN IGF-1 and gender remained significant predictors of % total body and % trunk fat (Table 4). The slopes of the % body fat - %ULN IGF-1 relationship did not differ in males vs. females ($B = -.04$, $SE = 0.02$, $p = 0.68$) (Figure 2).

%ULN IGF-1 and fasting and nadir GH correlated with total body lean mass and SM^E (Table 3). In multivariable regression, age, gender and %ULN IGF-1 were significant predictors of lean mass and gender and %ULN IGF-1 of SM^E (Table 4). In addition to expected gender differences in lean and SM^E mass, higher in males in both active and remission groups (Table 2), we found an interaction of gender with the relationship between total body lean mass and %ULN IGF-1 ($B = .038$, $SE = .015$, $p = 0.012$)(Figure 3), and a trend for this between SM^E and %ULN IGF-1 ($B = .013$, $SE = .01$, $p = 0.18$)(Figure 3). Thus, lean mass and somewhat SM^E , increased more per percentage increase in IGF-1 in men than in women. BMI, WC and waist-hip did not correlate with %ULN IGF-1 (Figure 4).

Leptin levels were lower in active disease vs. remission (Table 1). Leptin levels were higher in women than men in both active and remission groups (Table 2). There was a trend for leptin to correlate with %ULN IGF-1 (Table 2). Leptin correlated inversely with GH, more strongly in women than men and with total body and trunk fat mass as well as % body fat in men (Table 2). In multivariable analysis only gender and total body fat mass remained significant predictors of leptin levels (Table 4).

Cardiovascular Risk Markers—CRP levels were lower in active disease vs. remission (Table 1). CRP correlated inversely with %ULN IGF-1 and GH (Table 3). CRP was also strongly related to fat mass, correlating positively with total body and trunk fat mass, % total and trunk fat and waist circumference (Table 3). In univariable analysis there was a trend for gonadal status to also predict CRP levels (eugonadal vs. hypogonadal, $B = -.765$, $p = .067$), but age and gender did not. In a multivariable regression model, after accounting for gonadal status and body composition, only %ULN IGF-1 remained as a significant predictor of CRP levels (Table 4).

Homocysteine levels were lower in active vs. remission groups (Table 1). Homocysteine correlated with age ($r=0.396$, $p<0.00001$), inversely with %ULN IGF-1 ($r=-0.240$, $p=0.008$), basal GH ($r=-.290$, $p<0.001$), nadir GH ($r=-0.329$, $p<0.0003$) and HOMA ($r=-.199$, $p=0.03$) and positively with CompISI ($r=.193$, $p=0.03$).

Systolic (SBP) and diastolic (DBP) blood pressure did not differ in active and remission groups (Table 1) nor did these correlate with %ULN IGF-1 or GH levels. SBP correlated with age ($r=.306$, $p=.0003$) as did DBP ($r=.204$, $p=0.018$). Lipid levels did not differ in active vs. remission groups (Table 1). TG correlated with HOMA ($r=.487$, $p<0.0001$) and inversely with CompISI ($r=-.473$, $p<0.0001$). HDL correlated inversely with HOMA ($r=-.435$, $p<0.0001$) and positively CompISI ($r=.432$, $p<0.0001$).

DISCUSSION

This study, the largest to assess body composition in acromegaly and to relate this to insulin sensitivity and cardiovascular risk markers, has found that acromegaly presents a unique combination of CV risk parameters; in active acromegaly insulin sensitivity is reduced yet body fat and CRP are lower and in remission this pattern is reversed. %ULN IGF-1 strongly predicts, and better than GH levels, these CV risk factors. IGF-1 levels remained the strongest predictor of insulin sensitivity after accounting for body fat. We also found an interaction between gender and lean tissue mass. Lean tissue mass increased more in males than females for the same increment in %ULN, suggesting a clinically relevant gender difference in the relationship of disease activity to body composition.

This study confirms our prior findings (6), which were confirmed by others (12), that IGF-1 levels are a stronger predictor of insulin sensitivity than GH levels. The metabolic phenotype in acromegaly is that of GH's insulin-antagonistic actions (13–17). Although IGF-1's insulin sensitizing effect may partially offset those of GH, clinically, GH effects predominate with insulin resistance and disorders of glucose tolerance being common in patients with acromegaly. It is interesting, therefore, that IGF-1 levels, potentially reflecting the integrated degree of GH excess (17) are more predictive of the extent of impaired insulin sensitivity due to GH excess than GH levels themselves. We further these findings to show that IGF-1 levels remained the strongest predictor of insulin sensitivity after accounting for GH levels, age, body fat and skeletal muscle estimated by DXA. Thus, in acromegaly, the mechanisms responsible for impaired insulin sensitivity seem not to depend on the degree of adiposity in contrast to the strong relationship of increasing adipose tissue mass to insulin resistance in the general population (18). As we have previously shown visceral adipose tissue mass is reduced below predicted levels in patients with active acromegaly yet adipose tissue deposition in muscle is increased (15), potentially the latter is a greater contributor to insulin resistance in acromegaly than central adiposity. These relationships warrant further study. In our study, gender did not predict insulin sensitivity, but in another study metabolic syndrome was more prevalent in women than men with acromegaly (19).

We found, as have others, that body and trunk fat are reduced in active acromegaly (20–22). The reduced fat mass of acromegaly is explained by GH's modulation of fat metabolism and its potent lipolytic effect (23–25). We further these findings and show that %ULN IGF-1 is

a negative predictor of fat mass and % fat and that % ULN IGF-1 levels are a stronger predictor than GH levels of body composition changes in acromegaly. By contrast, in another study of 60 subjects (20 on medical therapy), GH predicted fat mass better than IGF-1 (26) and in another IGF-1 levels did not correlate with fat mass determined by cross-sectional CT (27). In our study, as in the general population, % body and trunk fat are higher in women than men with acromegaly, and after accounting for fat mass and other variables, gender along with %ULN IGF-1 remain significant predictors of % fat. However, increasing disease activity related similarly to decreasing % body fat in males as it did in females. One study suggested that with regard to adipose tissue mass males with acromegaly have greater changes than women (22), but another found similar deviations from normal in men and women (28). Hypogonadism may influence body fat changes in acromegaly. In one study, % body fat was higher in hypo- than eugonadal patients (29). In our study, hypogonadism was a positive predictor of total body fat mass, but not of % body fat. GH deficiency in treated acromegaly can be associated with increased body fat (27), in our study very few subjects had other hypopituitarism and none had sub-normal IGF-1 levels, which would be suggestive of GH deficiency.

We also investigated the relationship of lean tissue mass to disease activity in acromegaly and found lean tissue mass and SM^E to be higher in active vs. remission acromegaly and to strongly relate to the degree of IGF-1 elevation. Prior studies found elevated lean tissue mass in acromegaly that correlated with IGF-1 levels (27), which is not surprising because DXA lean tissue estimates are influenced by the known increased tissue hydration of acromegaly (21). Thus, DXA lean tissue changes may not necessarily parallel those of SM mass in acromegaly. We found SM^E , which agrees highly with SM quantified by total body MRI (10,11), to be higher in active acromegaly and to relate to disease activity even after accounting for age and gender. This suggests that acromegaly increases SM mass, although we did not find this in a prior smaller study (10) and in other studies body cell mass (BCM) was not increased in acromegaly compared to controls (30). We also found that as SM^E rose, insulin sensitivity fell, which contrasts with a positive relationship between insulin sensitivity and SM mass in the general population (31). Although rising SM mass and decreasing insulin sensitivity occurring together may be due to the independent relationships of these factors to increasingly active acromegaly, rising IMAT in active acromegaly (15), which does vary positively with SM mass, could contribute to reducing insulin sensitivity.

We also found evidence of a gender difference in the relationship between increasing disease activity and increasing lean tissue mass in acromegaly since total body lean mass increased more per % increase in IGF-1 in men than women; SM^E showed a trend for this difference. Prior studies found the expected gender differences in lean mass, greater BCM and extracellular water (ECW) per body weight in men (21) and we also found the expected higher lean and SM mass in men. A recent study found DXA lean tissue mass was greater in males with acromegaly compared to controls matched for gender and age, but not females (26). However, height and weight are important determinants of mass of lean tissue and skeletal muscle and should be considered when comparing these parameters in acromegaly and control subjects. Lack of difference in females was attributed in this study to older age of the females (26). In our study, our males and females were similar in age. Excess lean tissue in acromegaly reflects not only increases in ECW (20), which correlates with GH and

IGF-1 levels (20), but also in soft tissues, and metabolically active tissues including skeletal muscle and organs (32,33). The apparent greater increase in lean tissues as IGF-1 increases in men does not seem to be due only to increases in SM since we found only a trend for an interaction of gender with SM^E. Although it is known that females are less sensitive to GH effects with regard to IGF-1 production(34,35) and in patients with acromegaly the GH/IGF-1 ratio is higher in women than men (36), IGF-1 levels are generally similar in men and women as they were in our study. Therefore, anabolic effects of IGF-1 alone on skeletal muscle would not explain the gender difference we observed. Rather, a synergistic effect of androgen and IGF-1 on lean tissues and skeletal muscle in men may occur. In hypopituitary men, administration of GH and testosterone produced independent and additive effects to increase ECW as well as suppress protein oxidation and stimulate protein synthesis (37–39). Additive effects of testosterone and IGF-1 could thus explain the apparently greater lean tissue increase to rising IGF-1 levels in men than women with acromegaly.

We found, as have others, lower leptin levels in active acromegaly (7,40,41). Our data suggest that observed leptin changes are due primarily to fat mass changes, but are also influenced by leptin's known sexual dimorphism (7,40,42); in multivariate analysis, gender and fat mass remained significant predictors of leptin levels. In prior studies leptin correlated with fat mass (41), but we found this highly significant only in men. Interestingly, leptin correlated with GH and not IGF-1, but in other studies leptin correlated with IGF-1(41) and neither GH nor IGF-1 (43). The determinants of serum leptin levels in acromegaly and the relationship of body composition and disease activity to leptin levels are complex and require further study.

In our study, BMI, WC and waist/hip ratio did not correlate strongly with %ULN IGF-1, suggesting that these measures which perform well to predict body composition in normal populations, cannot be used to assess body composition changes relating to disease activity in acromegaly.

We found serum CV risk markers to relate inversely to disease activity, CRP most strongly to %ULN IGF-1 and homocysteine to GH. CRP levels are lower in active than controlled acromegaly (44,45) and rise as acromegaly is treated (7). The cause of the reciprocal relationship between CRP and acromegaly disease status is unclear. CRP may be reduced in active acromegaly because GH suppresses the hepatic acute-phase response of CRP through cross-talk of cytokine signalling or through reduced fat mass production of IL-6, a stimulator of CRP (46,47). In our study, fat mass was very significantly related to CRP, but %ULN IGF-1 remained significant after adjusting for fat mass suggesting a role for disease activity beyond fat mass changes to CRP changes in acromegaly. Although we have shown prospectively that successful surgical therapy lowers SBP, DBP, triglyceride and lipoprotein a levels and raises HDL (7), we did not detect differences in these other CV risk markers in active vs. remission groups in this cross-sectional study. Possibly, older age of our remission group or the less robust cross-sectional design obscured the differences.

Our study has certain limitations. Its' cross sectional design limits our ability to determine causality in our associations. We also limited our study to patients not receiving medical therapy, which can alter GH/IGF-1 relationships and might have altered study results (48).

Our findings do therefore require reassessment in medical therapy specific groups. Additional studies are needed in patients with diabetes mellitus since our study excluded them as well as in patients with pre-diabetes since the rate of this was also too low to examine this subgroup separately in our study. Additional studies are also needed in patients with hypopituitarism other than hypogonadism since the rate of this was too low in our cohort to examine this group separately.

In conclusion, acromegaly presents a pattern of CV risk markers opposite to that seen in the general population, lower insulin sensitivity along with lower fat mass and serum CV risk markers in active disease and the opposite pattern in remission. These factors strongly relate to disease activity measured by %ULN IGF-1. Since active acromegaly is associated with increased CV risk, our results suggest that reduced insulin sensitivity, of the factors we studied, could be the more significant contributor to this increased risk. Although we did not see changes in blood pressure or lipids related to disease activity in this study, these improve in patients evaluated prospectively and are likely significant contributors to the increased CV risk of acromegaly. The relative contributions of CV risk factors to outcome in acromegaly warrants further study. We also provide novel data that gender interacts with the relationship of disease activity to components of lean tissue mass. Further investigation into the nature of this gender difference and its response to acromegaly treatment is warranted. This study, the largest to examine body composition in acromegaly and its relationship to disease activity, metabolic and clinical markers finds IGF-1 levels across the normal to elevated spectrum to be important predictors of features relevant to cardiovascular risk in active and treated acromegaly patients.

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Figure 1.

Univariable regression plots of % upper limit of normal (%ULN) IGF-1 and HOMA score (Figure 1A), log nadir GH and HOMA (Figure 1B).

Figure 2. Univariable regression plots of %ULN IGF-1 and total body % fat in males and females (Figure 2A) and %ULN IGF1 and trunk fat mass (Figure 2B).

Figure 3.

Univariable regression plots of %ULN IGF-1 and total body lean mass in males and females (Figure 3A) and %ULN IGF-1 and SM^{E} (skeletal muscle mass estimated by DXA) in males and females (Figure 3B).

Figure 4.
Univariable regression plots of %ULN IGF-1 and BMI and waist circumference.

Table 1

Clinical characteristics, endocrine, metabolic and body composition parameters in remission and active groups

	Remission Group	Active Group	
	n = 61	n = 77	p-value
Age (yr) mean (range)	52.7 ± 10.7	46 ± 13.5	0.0007
Gender (F/M)	29/32	32/45	0.49
Newly Diagnosed (#)		40	
Surgery to Visit (yr.)	7.03 ± 6.7	5.4 ± 5.7	0.15
Radiotherapy (#)	3	5	0.69
Hormone replacement (#)	GC(4),T4(8),T(2),E(1)	GC(3), T4(3), T(3)	0.08
Gonadal Function (#)	F: PM(17), H(3),Eu(9). M: H(7), Eu (27).	F: PM(10),H(4), Eu(18). M: H(13), Eu(30).	0.69
Lipid Lowering Drugs (#)	5	9	
IGF-1 (ng/ml)	173 ± 49	595 ± 211	
IGF-1 % ULN	-29 ± 16	127 ± 87	
GH Fasting (µg/L)	0.92 ± 1.16	20 ± 37	<0.0001
GH Nadir OGTT (µg/L)	0.25 ± 0.25	14 ± 25	<0.0001
HOMA-IR Score	1.73 ± 1.3	3.14 ± 2.6	0.0002
Comp ISI	7.39 ± 5.3	5.82 ± 5.2	0.0048
CRP (mg/L)	2.14 ± 3.2	0.63 ± 0.64	<.0001
HCY (µmol/L)	9.7 ± 2.6	9.2 ± 4.9	0.032
Leptin (ng/ml)	14 ± 10.5	9.9 ± 9.4	0.0024
Lipoprotein a (mg/dl)	27.6 ± 28	31.1 ± 37	0.68
TC (mg/dL)	194 ± 34	183 ± 37	0.44
LDL (mg/dL)	120 ± 33	113 ± 32	0.07
HDL (mg/dL)	53 ± 15	48.6 ± 15	0.1
TG (mg/dL)	104 ± 44	108 ± 55	0.89
Systolic Blood Pressure	123 ± 12	124 ± 14	0.84
Diastolic Blood Pressure	82 ± 8	83 ± 8	0.85
BMI (kg/m ²)	29.7 ± 5.6	28.8 ± 5.0	0.19
Waist circumference (cm)	98 ± 21	95.6 ± 14	0.13
WAIST/HIP Ratio	0.908 ± 0.12	1.023 ± 0.95	0.79
Total Body Fat mass (kg)	32.1 ± 11.5	23.6 ± 11.9	0.0003
Total Body Lean mass(kg)	54.8 ± 12.7	62.5 ± 14.6	0.005
Total Body % Fat	36.6 ± 8.2	26.7 ± 10.4	<0.0001
Trunk Fat mass(kg)	17.9 ± 5.8	12.9 ± 6.8	0.0001
Trunk Lean mass (kg)	26.3 ± 5.9	30.45 ± 7.5	0.0029
Trunk % Fat	39.9 ± 7.4	28.7 ± 11	<0.0001
IMAT free SM (kg)	26.3 ± 8.2	31.2 ± 8.4	0.0043

Data are Mean $\pm$ SD. # = Number of subjects. GC=oral glucocorticoid replacement therapy, T4- thyroxine replacement therapy; T-testosterone therapy, E-estrogen therapy. PM- postmenopausal(no HRT). H- hypogonadal with no replacement therapy, Eu- eugonadal. (HOMA-IR) scores = [fasting serum insulin (μ U/ml) $\times$ fasting plasma glucose (mmol/liter)/22.5), Comp ISI = [10,000/square root of (fasting glucose mg/dl $\times$ fasting insulin μ U/ml) $\times$ (mean glucose $\times$ mean insulin oGTT)]; CRP = c-reactive protein; HCY - homocysteine; TC = total cholesterol; LDL = LDL cholesterol; HDL = HDL cholesterol; TG = Triglycerides. Normal IGF-I ranges: age 19, 141–483; 20, 127–424; 21–25 116–358; ages 26–30, 117–329 ng/ml; 31–35, 115–307 ng/ml; 36–40, 109–284 ng/ml; 41–45, 101–267 ng/ml; 46–50, 94–252 ng/ml; 51–55, 87–238 ng/ml; 56–60, 81–225 ng/ml; 61–65, 75–212 ng/ml; 66–70, 69–200 ng/ml.

Table 2

Clinical characteristics, endocrine, metabolic and body composition parameters in males and females in remission and active groups.

	Remission Group		M vs. F p-value	Active Group		M vs. F p-value
	Males (n=32)	Females (n=29)		Males (n = 45)	Females (n=32)	
Age (yr) mean (range)	50.8 ± 12	54 ± 8	0.13	45 ± 12	48 ± 15	0.45
Newly Diagnosed (#)				20	20	
Surgery to Visit (yr.)	6.3 ± 5.6	7.7 ± 7.8	0.88	4.8 ± 6	6.3 ± 5.3	0.28
Radiotherapy (#)		4		5		
Hormone replacement (#)	GC (2), T4(1), T(3)	GC (3), T4(8), E(2)		GC (3), T4(4), T(5)		0.08
Gonadal Function (#)	H(7), Eu(25)	PM(17), H(3), Eu(9)		H(13), Eu(32)	PM(10), H(4), Eu(18)	0.69
Lipid Lowering Drugs (#)		4		4	2	
IGF-1 (ng/ml)	185 ± 48	159 ± 49	0.06	558 ± 206	647 ± 211	0.08
IGF-1 % ULN	-26 ± 13	-32 ± 18	0.21	102 ± 71	153 ± 99	0.02
GH Fasting (µg/L)	0.48 ± 1.1	1.1 ± 1.2	0.04	15.3 ± 29	27 ± 4.6	0.09
GH Nadir OGTT (µg/L)	0.23 ± 0.26	0.27 ± 0.29	0.07	11.2 ± 22	18 ± 31	0.035
Glucose Intolerance (#) ¹	4			5	5	
HOMA-IR Score	1.84 ± 1.3	1.6 ± 1.3	0.26	2.89 ± 2.4	3.4 ± 2.8***	0.24
Comp ISI	7.4 ± 5.1	7.7 ± 5.8	0.99	6.57 ± 5.9	4.4 ± 3.5**	0.12
CRP (mg/L)	1.4 ± 1.5	3.0 ± 4.4	0.32	0.72 ± .73**	0.48 ± .47***	0.04
HCY (µmol/L)	9.9 ± 2.3	9.4 ± 2.9	0.26	9.6 ± 3.4	8.6 ± 6.4*	0.004
Leptin (ng/ml)	10 ± 7.6	19 ± 11	0.002	7.1 ± 5.7*	14 ± 11.9*	0.01
BMI (kg/m ²)	31.3 ± 4.6	28.6 ± 5.0	0.04	30 ± 5.7	27.6 ± 5.6	0.04
Waist circumference (cm)	105 ± 18	90 ± 22	<0.01	101 ± 12	86 ± 12	<.0001
Total Body Fat mass (kg)	32.7 ± 11.5	31 ± 11.8	0.59	23.4 ± 11.5**	23.9 ± 12.6*	0.97
Total Body Lean mass(kg)	65 ± 7.9	43 ± 6.8	<.0001	72 ± 9.1***	48 ± 7.1*	<.0001
Total Body % Fat	33 ± 6.3	40 ± 8.3	<.001	23 ± 8.9***	31.5 ± 10.7**	0.004
Trunk Fat mass(kg)	19.2 ± 5.1	16.5 ± 6.4	0.09	13.6 ± 6.8***	11.9 ± 6.8*	0.25
Trunk Lean mass (kg)	30.3 ± 4.3	21.3 ± 3.2	<.0001	35 ± 5.4***	23 ± 3.5*	<.0001

	Remission Group		M vs. F	Active Group		M vs. F
	Males (n=32)	Females (n=29)	p-value	Males(n = 45)	Females (n=32)	p-value
Trunk % Fat	38 ± 5.1	42 ± 8.9	0.036	27 ± 9.9***	32 ± 12**	0.12
IMAT free SM (kg)	32 ± 4.9	19 ± 5.5	0.0043	36 ± 5.6**	23 ± 4.3*	<.0001

∫ Glucose Intolerance defined as fasting plasma glucose 100–125 mg/dL. Compared to male gender remission groups;

* p-value 0.01 and 0.05;
** p-value < 0.01 and > 0.001;
*** p-value 0.001.

Table 3

Spearman Correlation of Endocrine, CV risk and Body Composition Parameters.

	% ULN IGF-1	OGTT * Nadir GH	HOMA	ComplSI	CRP	HCY	Leptin	Total body Fat *	Total Body % Fat *
Total Body Fat	r-value	-0.351	0.257	-0.2356	0.491	0.088	0.788		
	p value	0.0001	<.00001	0.006	<.00001	0.36	<.00001		
Total Body % Fat	female r-value	-0.515	0.106	-0.402	0.524	0.077			
	female p-value	0.0003	<.00001	0.45	0.78	0.0001	0.7		
	male r-value	-0.519	0.109	-0.168	0.506	0.279			
	male p-value	<.00001	<.00001	0.38	0.17	<.00001	0.03		
Lean Tissue	female r-value	0.4038	0.3315	0.4589	-0.4217	0.092	-0.087	0.091	0.18
	female p-value	0.004	0.022	0.001	0.0044	0.54	0.56	0.56	0.22
	male r-value	0.527	0.527	0.3932	-0.3268	-0.271	-0.394	-0.0264	0.0004
	male p-value	<.0001	<.0001	0.0011	0.0074	0.029	0.0014	0.85	0.996
SM^E	female r-value	0.4	0.366	0.412	-0.364	-0.034	-0.178	-0.006	0.199
	female p-value	0.005	0.01	0.004	0.015	0.82	0.24	0.97	0.17
	male r-value	0.507	0.532	0.419	-0.305	-0.288	-0.391	-0.088	-0.089
	male p-value	<.00001	<.00001	0.005	0.013	0.02	0.002	0.48	0.47
Waist Circ.	female r-value	-0.276	-0.371	0.1548	0.215	0.634	0.131	0.212	0.789
	female p-value	0.04	0.006	0.25	0.12	<.00001	0.38	0.13	<.00001
	male r-value	-0.163	-0.309	0.2973	-0.358	0.499	0.147	0.676	0.827
	male p-value	0.18	0.01	0.012	0.002	<.00001	0.27	<.00001	<.00001
Leptin	female r-value	-0.231	-0.304	0.3229	-0.261	0.239	0.128	0.244	0.214
	female p-value	0.08	0.02	0.0162	0.062	0.09	0.39	0.11	0.08
	male r-value	-0.22	-0.424	0.3158	-0.378	0.438	0.273	0.797	0.77
	Male p-value	0.06	0.0002	0.007	0.0013	0.0001	0.02	<.00001	<.00001

* Fasting GH(not shown) was very similar to OGTT nadir GH. Total trunk fat, % trunk fat (not shown) were similar to total body measures.

Multivariable Regression Analysis. Multivariable regression models were built to examine outcome variables (left column) with predictors (top row) that were significant at 0.1 level in univariable linear regression models.

Table 4

Outcome Variable	Age	Male	Eugonadal	% ULN IGF-1	GH Fasting	GH Nadir	Total Body Fat Mass	% Total Body Fat	Trunk Fat Mass	% Trunk Fat	SM ^E
HOMA	Estimate (SE)	−.05(.016)		.011(.002)	.006(.032)	−.004(.05)	.04(.05)		.073(.10)		0.013(.02)
	p-value	0.003		<.0001	0.85	0.925	0.451		0.465		0.589
QUICKI	Estimate (SE)	.0005(.0003)		−.0002(.00004)	.0001(.0006)	−.0004(0.0009)	−.0006(0.001)		−.0016(.002)		−0.0004(.0005)
	p-value	0.151		< .0001	0.908	0.71	0.553		0.414		0.395
Comp ISI	Estimate (SE)			−.024(.006)	−.036(.091)	.022(.136)	−.078(0.14)		−.150(.262)		−0.050(.06)
	p-value			<.0001	0.695	0.872	0.577		0.567		0.404
CRP	Estimate (SE)		−.420(.431)	−.005(.002)			.167(0.12)	−.013(.15)	−.152(.22)	.003(.15)	
	p-value		0.332	0.029			0.164	0.935	0.484	0.986	
Leptin	Estimate (SE)	−6.788(2.01)			−.036(.10)	.054(.15)	1.02(.35)	−.313(.51)	−.934(.61)	0.377(.43)	
	p-value	0.001			0.717	0.71	0.004	0.538	0.13	0.388	
Total Body Fat Mass	Estimate (SE)		−5.507(2.243)	−.031(0.013)	−.021(0.2)	−.096(.29)					
	p-value		0.016	0.019	0.916	0.743					
% Total Body Fat	Estimate (SE)	−8.889(1.72)	−3.148(1.73)	−.041(0.01)	0.008(0.15)	−.107(.22)					
	p-value	< .0001	0.072	< .0001	0.955	0.63					
Trunk Fat Mass	Estimate (SE)			−.020(.007)	−0.055(0.11)	.013(.16)					
	p-value			0.005	0.616	0.937					
% Trunk Fat	Estimate (SE)	−6.215(1.87)	−2.659(1.89)	−.048(.011)	−0.010(0.16)	−.082(.24)					
	p-value	0.001	0.161	< .0001	0.95	0.732					
Waist Circ.	Estimate (SE)	14.64(2.87)			−0.009(0.27)	−.118(.40))					
	p-value	< .0001			0.973	0.766					
Total Body Lean Mass	Estimate (SE)	−0.124(0.057)	23.65(1.46)	.037(.008)							
	p-value	0.034	< .0001	< .0001							

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Outcome Variable	Age	Male	Eugonadal	% ULN IGF-1	GH Fasting	GH Nadir	Total Body Fat Mass	% Total Body Fat	Trunk Fat Mass	% Trunk Fat	SM ^E
SM ^E	Estimate (SE)	13.8(1)	-1.014(0.949)	.022(.005)							
	p-value	< .0001	0.917	< .0001							