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GH administration decreases subcutaneous abdominal adipocyte size in men with abdominal obesity

Miriam A. Bredella, MD[1], **Kalypso Karastergiou, PhD**[2], **Stijn A. Bos, BS**[1], **Anu V. Gerweck, NP**[3], **Martin Torriani, MD**[1], **Susan K. Fried, PhD**[2,*], and **Karen K. Miller, MD**[3,*]

[1]Department of Radiology, Massachusetts General Hospital and Harvard Medical School, Boston, MA

[3]Neuroendocrine Unit, Massachusetts General Hospital and Harvard Medical School, Boston, MA

[2]Department of Medicine, Section of Endocrinology, Diabetes and Nutrition, Boston University School of Medicine, 650 Albany St., EBRC 810, Boston, MA 02118

Abstract

Objective—To investigate the effects of short-term GH administration on abdominal subcutaneous adipocyte size and CT attenuation in men with abdominal obesity.

Design—6-week, randomized, double-blind, placebo-controlled study of GH (starting dose 2 μg/kg/d) vs placebo of 15 abdominally obese men (mean age: 34±6 years; mean BMI: 37.7±6.1 kg/m, mean IGF-1 SDS: −1.9±0.5) who underwent abdominal subcutaneous adipose tissue (SAT) aspirations to determine adipocyte size, CTs for body composition and measures of glucose tolerance at baseline and 6 weeks. GH dosing was titrated to target IGF-1 levels in the upper normal age-appropriate range.

Results—GH administration decreased subcutaneous abdominal adipocyte size compared to placebo. Adipocyte size was positively associated with 120-min glucose and HOMA-IR and inversely associated with peak-stimulated GH and CT attenuation. CT attenuation of SAT was inversely associated with 120-min glucose and HOMA-IR and increased following GH administration.

Conclusion—In men with abdominal obesity, subcutaneous abdominal adipocyte size is positively associated with measures of impaired glucose tolerance and administration of GH at

Corresponding author: Miriam A. Bredella, MD, Massachusetts General Hospital, Yawkey 6E, 55 Fruit Street, Boston, MA 02114, Phone:617-726-7717, Fax: 617-726-5282, mbredella@mgh.harvard.edu.

*Dr. Susan K. Fried and Dr. Karen K. Miller have contributed equally as senior authors.

Current address: Diabetes, Obesity & Metabolism Institute, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, New York, NY 10029

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doses that raise IGF-1 levels within the normal range, decreases abdominal subcutaneous adipocyte size, suggesting that GH administration improves the health of adipose tissue.

Keywords

growth hormone; obesity; adipocytes; adipose tissue; adiposity; computed tomography

INTRODUCTION

Abdominal obesity is a strong risk factor for cardiometabolic disease, and an important indicator of adipose tissue (AT) health is adipocyte size [1, 2]. Large adipocytes are dysfunctional, with abnormal adipokine secretory patterns and metabolic activity and are associated with increased cardiometabolic risk [1, 2].

Abdominal obesity is also associated with relatively low endogenous growth hormone (GH) secretion [3]. GH is a regulator of body composition and fat distribution, and GH administration to individuals with abdominal obesity decreases abdominal AT and improves cardiometabolic risk markers [4, 5]. However, no studies have assessed the effects of GH administration, at doses designed to raise IGF-1 levels within the normal range, on abdominal subcutaneous adipocyte size in healthy adults with abdominal obesity.

Although abdominal fat depots can be accurately quantified using computed tomography (CT), less is known about whether CT can quantitate fat quality. A recent study in elderly women across the weight spectrum showed that AT with lower CT attenuation (more negative values) corresponds to larger adipocytes, while AT with higher CT attenuation (more positive values) corresponds to smaller adipocytes [6]. However, no such studies have been performed in men with abdominal obesity.

Here we present novel data on the effects of short-term GH administration on subcutaneous abdominal adipocyte size in men with abdominal obesity from a double-blind, placebo-controlled trial. We hypothesized that short-term GH administration would decrease subcutaneous abdominal adipocyte size. In addition, we aimed to assess the use of CT attenuation as a marker of adipocyte quality and hypothesized that larger adipocytes would be associated with lower CT attenuation and that GH would increase CT attenuation of abdominal AT.

MATERIALS AND METHODS

Subjects

The study was IRB-approved, and written informed consent was obtained. Inclusion criteria included male sex, 18 to 45 years, BMI ≥ 25 kg/m, waist circumference >102 cm [7], and IGF-1 level below normal mean for age. Exclusion criteria included smoking, diabetes mellitus, chronic illnesses, and use of glucocorticoids, statins, antihypertensives or aspirin. No exclusion based on GH level (mean peak stimulated GH level at baseline 4.8 ± 7.5 ng/mL). Clinical characteristics have been previously reported [4]; however, no data on adipocyte samples or CT attenuation measurements have been described.

Protocol

Data reported here are from the baseline (pre-treatment) and 6-week visits of a subset of 15 consecutive participants (mean age: 34±6 years; mean BMI: 37.7±6.1 kg/m, mean IGF-1 standard deviations core (SDS): −1.9±0.5) in a double-blind, randomized, placebo-controlled trial of GH vs placebo [4]. Subjects were randomized to daily subcutaneous recombinant human GH (Genentech, Inc) (starting dose 2 μg/kg/d) (n= 6) or placebo (n=9). Participants in the placebo group were sham dose-adjusted to maintain blinding to randomization assignment. A glucagon GH stimulation test was performed pre-treatment, and IGF-1 levels were measured at baseline, 3 and 6 weeks; GH doses were adjusted based on IGF-1 levels as previously described [4]. Serum fasting glucose and insulin were measured and an oral glucose tolerance test was performed at baseline and 6 weeks.

Fat aspirations

Aspirations of abdominal subcutaneous AT (SAT) were performed in all 15 subjects under local lidocaine anesthesia using a blunt-ended needle designed for liposuction (2.5-mm Spirotri cannulas; Unitech Instruments, Fountain Valley, CA), from the mid-abdomen approximately 5–8 cm lateral to the umbilicus by a single blinded investigator (MAB). Samples were washed with saline at bedside, and tissue samples (100 mg) were fixed in Z-fix for 24h and stored in PBS at +4C. Sections (5 micrometers thick) were stained with eosin and hematoxylin. Cell size (internal perimeter) was estimated with Cell Profiler (Broad Institute) by a single blinded investigator (KK). Between 700–1100 cells in at least four 10X fields were sized using a published pipeline [8] updated and modified to allow manual correction of outlines. Frequency histograms were generated (with 10 micrometer bins), and weighted volumes were calculated as $\sum(\frac{4}{3}\pi r_i^3 p_i)$ where r_i is the mean radius and p_i the relative frequency of each bin [9]. Three samples were inadequate for analysis.

Body composition

Fourteen subjects underwent single-slice axial abdominal CT at the 4th lumbar vertebra (LightSpeedPro, General Electric, Waukesha, WI) at baseline and 6 weeks with a calibration phantom (Mindways Software, Inc., Austin, TX) (parameters: 80kV, 70 mA, 144 mm table height, 1 cm slice thickness and 48 cm field of view). Thresholding methods were applied to identify AT (threshold set −50 to −250 Hounsfield units (HU)). Total and superficial SAT (deep to the fascia superficialis) [10] cross-sectional areas (CSA) (cm^2) were quantified. SAT mean attenuation (HU) was assessed in a circular region of interest avoiding areas of prior fat aspiration. Osirix software version 3.2.1 (www.osirix-viewer.com/index.html) was used for analyses.

Statistical Analysis

Statistical analysis was performed using JMP software (version 11, SAS Institute, Cary, NC). Baseline means and mean 6-week changes (6-week value minus baseline value) between the GH and placebo groups were compared using analysis of variance (ANOVA). As AT attenuation can be affected by extremes of BMI, associations were adjusted for BMI as previously described [11, 12]. Univariate regression analysis was performed to determine

predictors of adipocyte size and CT attenuation, and partial correlation coefficients are reported after controlling for covariates. A priori power calculations were not performed for this exploratory study.

RESULTS

At baseline (pretreatment), subcutaneous abdominal adipocyte size correlated positively with 120-minute glucose (r=0.64, p=0.02) and HOMA-IR (r=0.62, p=0.03) and inversely with peak stimulated GH levels (r= −0.74, p=0.006).

CT attenuation of abdominal SAT was inversely associated with subcutaneous adipocyte size (r= −0.55, p=0.07), 120-minute glucose (r= −0.67, p=0.02), and HOMA-IR (r= −0.47, p=0.097), independent of BMI.

Baseline subject characteristics of the GH and placebo groups are compared in Table 1. Both groups were of comparable mean age, body composition, peak-stimulated GH and IGF-1 levels, and measures of glucose homeostasis. The mean GH dose for the GH-treatment group at 6 weeks was 0.49±0.07 mg/d, which resulted in a significant increase in mean IGF-1 levels compared to placebo (p<0.0001) (Table 1).

GH administration for 6 weeks decreased subcutaneous abdominal adipocyte size compared to placebo. Superficial abdominal SAT CSA decreased and SAT CT attenuation increased in the GH group compared to placebo (Table 1 and Figure 1). There was no detectable effect of GH vs. placebo on 120-min glucose or HOMA-IR.

DISCUSSION

We observed a positive association between subcutaneous abdominal adipocyte size and measures of impaired glucose tolerance (120-minute glucose and HOMA-IR). Furthermore, adipocyte size was inversely associated with peak GH levels, and GH administration reduced subcutaneous abdominal adipocyte size and superficial SAT. This suggests that endogenous GH secretion may be an important determinant of abdominal subcutaneous adipocyte size, and provides evidence that GH may improve fat quality in the short term.

GH is an important regulator of lipolysis and fat distribution, and patients with GH deficiency have increased abdominal AT [13, 14]. Fat aspirations in hypopituitary adults with GH deficiency have found larger subcutaneous abdominal adipocytes compared to controls, associated with elevated serum and AT inflammatory markers [14]. One uncontrolled study demonstrated that long-term GH replacement (5 years) in hypopituitary adults with GH deficiency decreased adipocyte size without affecting AT mass [15], while a 3-month study in hypopituitary patients showed no change in adipocyte size with GH replacement at a dose one-half of the lowest dose administered in our study [16].

No studies have examined the effects of physiologic GH administration on subcutaneous abdominal adipocyte size in healthy individuals with obesity-related relative GH deficiency [3]. We have previously demonstrated decreased abdominal AT following 6 months of GH administration in individuals with abdominal obesity associated with improvements in

cardiometabolic risk markers [4, 5]. Here we show that GH administration for 6 weeks, at a dose that increased IGF-1 levels within the normal age-appropriate range, decreased subcutaneous abdominal adipocyte size and superficial SAT CSA – the depot we were able to sample. We found no increase in 120-min glucose or HOMA-IR in the GH group, which may have been due to the small sample size. GH causes lipolysis and results in increased plasma free fatty acids which has been implicated in GH-induced insulin resistance, despite a decrease in AT [17]. Our data support an effect of GH to improve the health of abdominal SAT and may be evidence that GH exerts positive effects on AT depot health in general, though it should be noted that different fat depots, even within SAT, are associated with differential cardiometabolic effects.

Recent studies have suggested that CT attenuation of abdominal AT may represent a non-invasive technique to assess cardiometabolic risk [12, 18, 19], but only one human study has investigated CT attenuation as a reflection of fat cell size or quality. This recent study in elderly women across the weight spectrum who underwent elective gynecological surgery demonstrated inverse associations between adipocyte volume and CT attenuation associated with measures of cardiometabolic risk [6]. Our results are the first to show in men with abdominal obesity that subcutaneous abdominal adipocyte volume is inversely associated with CT attenuation and positively associated with markers of impaired glucose tolerance, independent of BMI.

We also observed an increase in SAT CT attenuation following GH administration, likely reflecting a decrease in adipocyte size. It is plausible that an increase in fibrosis or edema could contribute to an increase in CT attenuation of AT [20]. However, we did not observe evidence of pericellular or tissue fibrosis or edema in our biopsy samples.

Conclusion

In conclusion, we show that subcutaneous abdominal adipocyte size is positively associated with measures of impaired glucose tolerance and that administration of GH at doses that raised IGF-1 levels within the normal, age-appropriate range, in otherwise healthy men with abdominal obesity decreases abdominal subcutaneous adipocyte size, suggesting that GH administration improves the health of abdominal SAT. Moreover, SAT attenuation by CT is inversely associated with subcutaneous abdominal adipocyte size and measures of impaired glucose tolerance, suggesting that CT attenuation values may reflect adipose tissue quality.

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HIGHLIGHTS

- Abdominal obesity is associated with relatively low endogenous GH secretion.
- Abdominal subcutaneous adipocyte size is positively associated with measures of impaired glucose tolerance and lower peak GH.
- Subcutaneous adipocyte size decreases following short-term GH administration in men with overweight/obesity, a state of relative GH deficiency.
- Abdominal subcutaneous adipocyte size and CT attenuation of adipose tissue are inversely associated, suggesting that CT may reflect adipose tissue quality.

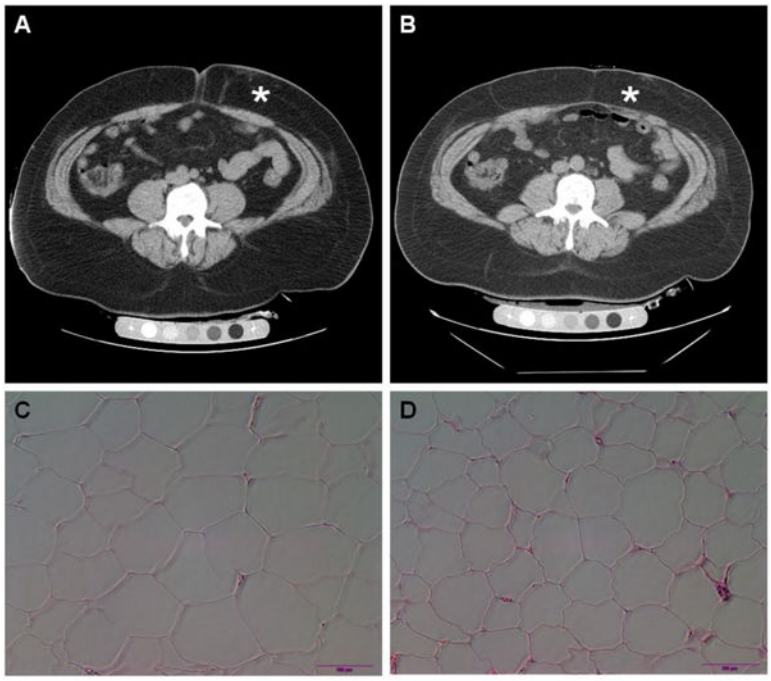

Figure 1.

Abdominal CT of a 43-year-old man with obesity (BMI: 46 kg/m^2) before (A) and after (B) 6 weeks of GH administration, at doses which raised IGF-1 levels within the normal, age-appropriate range, resulting in increased CT attenuation of abdominal subcutaneous adipose tissues (asterisks). Images are presented using the same window and level. Bright-field images of H&E-stained paraffin-sectioned abdominal subcutaneous adipose tissue of the same subject before (C) and after (D) GH administration demonstrate a decrease in adipocyte cell size (20X magnification, bar represents 100μm).

Table 1

Clinical characteristics, body composition and adiposity size in 15 young men with obesity treated for 6 weeks with GH or placebo.

Variable	Treatment	Baseline	6 weeks	6-week change	*p* between groups (baseline)	*p* between groups (0–6 weeks)*
Age (years)	GH	33±7			0.7	
	Placebo	35±6				
BMI (kg/m^2)	GH	38.4±5.9	39.0±6.0	0.5±0.8	0.7	0.1
	Placebo	37.1±6.6	36.8±6.8	−0.3±0.9		
Peak stimulated GH (ng/mL)	GH	2.9±2.3			0.4	
	Placebo	6.1±9.6				
IGF-1 (ng/mL)	GH	100±28	264±75	164±74	0.2	<0.0001
	Placebo	127±49	122±37	−5±15		
IGF-1 SDS	GH	−2.2±0.2	−0.4±0.9	1.8±0.8	0.09	<0.0001
	Placebo	−1.7±0.6	−1.8±0.4	−0.07±0.2		
120-min glucose (mg/dL)	GH	120±20	127±36	8±29	0.2	0.3
	Placebo	100±29	93±25	−6±17		
HOMA-IR	GH	2.46±1.01	6.11±3.97	3.6±0.8	0.8	0.1
	Placebo	2.74±2.21	4.44±3.06	1.7±0.8		
Total SAT (cm^2)	GH	462.4±152.6	451.0±131.4	−11.4±40.9	0.8	0.7
	Placebo	438.4±156.1	429.7±143.6	−8.7±18.3		
Superficial SAT (cm^2)	GH	191.8±60.7	176.6±58.6	−15.2±5.8	0.3	0.006
	Placebo	143.0±16.3	145.7±29.0	2.7±17.4		
SAT attenuation (HU)	GH	−127.7±12.5	−124.1±12.6	3.6±2.0	0.4	0.03
	Placebo	−121.4±15.2	−121.5±12.8	−0.1±3.8		
SAT adipocyte volume/cell (pL)	GH	538.0±46.3	433.8±50.1	−104.3±26.5	0.1	0.02
	Placebo	444.9±105.3	477.6±132.6	32.8±127.7		

Data presented as mean±SD. BMI: body mass index, GH: growth hormone, IGF-1: insulin-like growth factor 1, SDS: standard deviation score, SAT: abdominal subcutaneous adipose tissue, HU: Hounsfield Units

*Analyses were controlled for age and BMI