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ORIGINAL ARTICLE

Effects of growth hormone on hepatic insulin sensitivity and glucose effectiveness in healthy older adults

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Abstract

Purpose Growth hormone (GH) replacement decreases insulin sensitivity in healthy individuals. However, the effects of GH on organ-specific insulin sensitivity and glucose effectiveness are not well characterized. The purpose of this study was to evaluate the effects of GH administration for 26 weeks on muscle and hepatic insulin sensitivity and glucose effectiveness in healthy older individuals.

Methods This report is from a 26-week randomized, double-blind, placebo-controlled parallel-group trial in healthy, ambulatory, community-dwelling older women and men. We compared surrogate indices of insulin sensitivity [quantitative insulin-sensitivity check index (QUICKI), muscle insulin sensitivity index (MISI), hepatic insulin resistance index (HIRI)] and glucose effectiveness [oral glucose effectiveness index (oGE)] derived from oral glucose tolerance tests (OGTTs) in subjects before and after 26 weeks of administration of GH ($n = 17$) or placebo ($n = 15$) as an exploratory outcome.

Results GH administration for 26 weeks significantly increased fasting insulin concentrations and HIRI but did not significantly change MISI or oGE compared to placebo.

Conclusions GH administration for 26 weeks in healthy older subjects impairs insulin sensitivity in the liver but not skeletal muscle and does not alter glucose effectiveness.

Keywords Growth hormone · Insulin resistance · Glucose effectiveness · Aging

Introduction

Glucose intolerance, insulin resistance, and diabetes mellitus (DM) are frequent clinical manifestations in patients with acromegaly [1, 2]. Increased hepatic glucose production, peripheral insulin resistance, and impaired pancreatic beta cell function contribute to the pathogenesis of glucose intolerance in acromegaly [3–6]. Surgical removal of growth hormone (GH) secreting tumors reverses glucose intolerance and insulin resistance in most patients with acromegaly [3, 7]. Administration of pegvisomant, a specific antagonist for the GH receptor (GHR), improves insulin sensitivity in patients with acromegaly [8]. Genetic ablation of the GH receptor (GHR) in mice and GHR deficiency in humans confers increased insulin sensitivity and protection from diabetes mellitus [9, 10]. These findings suggest an important role for GH in modulating glucose homeostasis. It appears that intact GH signaling and even physiological increases in GH levels antagonizes insulin action [11].

Despite many years of research, the tissue-specific GH effects that alter insulin sensitivity are unclear [12, 13]. Both liver and adipose tissue have been suggested to be major sites of GH-induced alterations in insulin action in rodent models [12, 13]. In humans, acute GH administration stimulates lipolysis and the resulting increase in free fatty acid (FFA) levels contributes to higher hepatic

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gluconeogenesis and lower peripheral glucose disposal [14–16]. In contrast to these studies suggesting a causal role for enhanced lipolysis in mediating the effects of GH, pegvisomant improves hepatic insulin sensitivity with no effects on peripheral insulin sensitivity or lipolysis [17]. Thus, in humans, the effects of GH may be mediated by its actions on the liver and adipose tissue. However, the short duration of these studies is a potential limitation and precludes us from making any definitive conclusions. The effects of long-term GH administration on insulin sensitivity in adults with GH deficiency are variable and appear to be dependent on the dose and duration of GH administration as well as other concomitant hormonal deficiencies [4, 18, 19]. In contrast, in normal healthy adults, chronic GH administration reduces insulin sensitivity [4, 20]. However, the effects of chronic GH administration on tissue-specific insulin sensitivity in healthy individuals are unknown. In this study, we examined the effects of GH administration on indices of muscle and hepatic insulin sensitivity and glucose effectiveness derived from an oral glucose tolerance test (OGTT) in healthy older adults.

Methods

Study design and subjects

Our objective of this exploratory analysis was to study the effects of chronic GH administration on tissue-specific insulin sensitivity in healthy individuals. We previously reported that GH administration to healthy older individuals for six months reduced insulin sensitivity [20]. A detailed description of the original study design, protocol, participants, and hormone interventions has been published [21]. The original study was designed as a randomized, placebo-controlled, double-masked 2×2 factorial, non-crossover trial. Participants received either GH plus placebo, sex steroid (SS) (transdermal estradiol plus oral medroxyprogesterone acetate in women, intramuscular injections of testosterone enanthate in men) plus placebo, GH plus SS, or placebo only. For the GH group, GH (Nutropin; Genentech, Inc., South San Francisco, CA) was administered in a dose of 20 µg/kg body weight and was self-injected subcutaneously three times per week in the evening. For the placebo group, subjects self-injected saline. In the present report, we evaluated surrogate indices of hepatic and muscle insulin sensitivity and glucose effectiveness (exploratory outcomes) before and after treatment only in individuals with normal glucose tolerance who received either GH plus placebo ($n = 17$) or placebo alone ($n = 15$) for 26 weeks.

All subjects were healthy, ambulatory, US community-dwelling individuals aged 65–88 years. Participants were deemed healthy based on history, physical examination, routine serum chemistries, and urinalysis. Medications that affected the GH/IGF-1 axis or glucose metabolism were not permitted. Written informed consent was obtained from each participant. The Institutional Review Board of the Johns Hopkins Bayview Medical Center approved the study protocol.

Body composition, fat distribution, and cardiovascular endurance

Body mass index (BMI) was calculated as weight (kg)/height (m^2). Total body fat (TBF) and lean body mass (LBM) were measured by DEXA (Lunar model DPX-L; Lunar Radiation, Madison, Wisconsin). Total abdominal fat, abdominal subcutaneous fat (ASF) and abdominal visceral fat (AVF) were measured by abdominal Magnetic Resonance Imaging at the level of L4-L5 as previously described [22]. Cardiovascular endurance (VO_2max) was measured as previously described [21].

OGTT and hormone assays

A 75 g standard OGTT after an overnight fast was performed at baseline and after 26 weeks of intervention. Plasma glucose and insulin levels were measured at 0, 30, 60, 90, 120 min. Impaired glucose tolerance and diabetes mellitus (DM) were defined as per recent ADA guidelines [23]. Plasma insulin and glucose concentrations were measured at the Johns Hopkins Bayview General Clinical Research Center Core Laboratory. Insulin concentrations were determined by RIA (Linco Research Inc., St. Louis, MO). The assay had a sensitivity of 1.2 pmol/l with a linear range from 12 to 1200 pmol/liter. Intra-assay and inter-assay coefficients of variation (CVs) were 2.1 and 2.8%, respectively. Glucose concentrations were measured using an automated glucose-oxidase assay (Beckman Diagnostics, Fullerton, CA) and exhibited intra-assay and inter-assay CVs of 2.8 and 2.1%, respectively. IGFBP-1 levels were measured by immunoradiometric assay (Diagnostic Systems Laboratories, Webster, TX). The intra and inter-assay CVs were 2.5 and 9.4%, respectively [24]. Total serum IGF-1 levels were measured by RIA after acid-ethanol extraction (Endocrine Sciences Laboratories, Calabasas Hills, CA). The intra- and inter-assay coefficients of variation (CVs) were, respectively, 5.9 and 7.3% at 289 µg/L and 4.6 and 6.3% at 591 µg/L [24].

Hepatic insulin resistance index (HIRI), muscle insulin sensitivity index (MISI), and glucose effectiveness (oGE)

Tissue-specific surrogate indices for insulin sensitivity were derived from plasma insulin and glucose levels from oral

glucose tolerance tests [25]. The hepatic insulin resistance index (HIRI) was calculated as {[glucose (mg/dl) $AUC_{0\text{-}30}$] × [insulin (μU/ml) $AUC_{0\text{-}30}$]} where AUC between 0 and 30 min was calculated by the trapezoidal method. The muscle insulin sensitivity index (MISI) was derived by dividing the rate of decline in plasma glucose concentration calculated as the slope of the decrease in plasma glucose concentration (dG/dt) from peak to nadir by the mean plasma insulin concentration and measured as 10^{-2} (mg/dL. min^{-1}/(μU/mL)). We identified study participants in whom glucose levels continued to rise from 60 min to 120 min during the OGTT. Because of the assumption of calculating MISI requires there to be a negative slope from 60 to 120 min, 5 subjects from the placebo group and 3 subjects from the GH treated group were excluded from the analyses. Glucose effectiveness is the ability of glucose to facilitate its own disposal at basal insulin concentrations. oGE was calculated from the OGTT as previously described [26, 27]. oGE was derived from the equation: oGE = {[PPG_without insulin action and GE]−[PPG with GE but without insulin action] × [2hPG/$2hPG_E$]}/120, where PPG = post-loading plasma glucose, GE = glucose effectiveness, 2hPG = 2-h post-glucose PG, and $2hPG_E$ = expected 2hPG. QUICKI, a measure of insulin sensitivity was calculated as defined previously [28]. QUICKI = 1/[log (I_0) + log(G_0)], where I_0 is fasting insulin (μU/ml) and G_0 is fasting glucose (mg/dl). Because QUICKI is the reciprocal of the log-transformed product of fasting glucose and insulin, it is a dimensionless index without units.

Statistical analysis

The distributions of variables were examined by Q-Q plot, stem-leaf plots, box plots and the D'Agostino and Pearson tests. Variables with normal distributions are expressed as mean ± standard deviation (SD). Variables with a non-normal distribution are expressed as median (IQR). The comparison of baseline characteristics between groups (placebo vs. GH group) was assessed by independent *t*-test or The Wilcoxon-Mann-Whitney test. Relationships of surrogate indexes of insulin sensitivity / resistance and oGE with body composition and metabolic profiles were assessed by Spearman correlation. Relationships were assessed in women and men together when slopes of regressions in each sex showed no significant differences. The effects of 26-week treatment (placebo or GH) on MISI and HIRI were assessed by the analysis of covariance (ANCOVA). The dependent variables in the ANCOVAs were the changes (post-pre) in values of the outcome variable being studied. Independent variables included the subject's age, the initial value of the outcome variable, and treatment group (GH or placebo). A simple contrast method was used for post-hoc, between-group analyses in ANCOVA. A p-value less than 0.05 was considered to be statistically significant in all analyses. Data were analyzed with JMP version 7.0 (SAS Institute, Cary, NC) and GraphPad Prism 7 (GraphPad Software Inc, La Jolla, CA).

Results

Subject characteristics and baseline metabolic profiles

Baseline characteristics and metabolic parameters of the study participants are depicted in Table 1. Baseline characteristics were similar between the placebo and GH groups (Table 2). Our cohort was comprised of lean (31%) and overweight (68%) individuals. In the overall group (GH and placebo combined) there were no differences in age-adjusted QUICKI ($p = 0.31$), MISI ($p = 0.36$), and HIRI ($p = 0.81$) between women and men at baseline, whereas oGE was higher in women (adjusted mean ± SEM; 3.52 ± 0.13 vs. 2.46 ± 0.13 mg/dL/min, $p < 0.0001$) (Table 1). IGF-1 binding protein 1 (IGFBP-1), a marker of hepatic insulin sensitivity [29], was higher in women (73 ± 7 vs. 36 ± 6 ng/mL, $p < 0.001$) (Table 1).

Women had higher age-adjusted TBF (42.1 ± 0.9 vs. 29.3 ± 0.9 %, $p < 0.0001$) and ASF (77.9 ± 2.2 vs. 60.1 ± 2.0 %, $p < 0.0001$), but lower AVF (22.0 ± 2.2 vs. 39.8 ± 2.0 %, $p < 0.0001$), LBM (35.2 ± 1.0 vs. 55.0 ± 0.9 kg, $p < 0.0001$), and maximal oxygen capacity, VO_2max (23.1 ± 0.9 vs. 28.1 ± 0.8 ml/kg/min, $p < 0.001$) compared with men (Table 1). At baseline in the combined cohort (GH and placebo), oGE was directly related to TBF, ASF, IGFBP-1 and inversely related to BMI, AVF, HIRI, and plasma concentrations of IGF-1, fasting glucose, and fasting insulin (Table 3). HIRI was positively associated with AVF, fasting glucose and insulin levels, and negatively associated with ASF, and oGE. MISI was directly related to VO_2max and inversely related to fasting insulin concentrations (Table 3). Circulating IGFBP-1 levels were directly related to oGE, and negatively correlated to HIRI, albeit non-significantly ($p = 0.07$) (Table 3). There was no sexual dimorphism in these relationships.

Effects of GH versus placebo administration on insulin sensitivity and glucose effectiveness

When compared with placebo, GH administration increased IGF-1 levels [110 μg/L (95% CI: 59–160), $p < 0.001$], LBM [1.81 kg (95% CI: 1.01–2.60), $p < 0.001$], and VO_2max [1.92 ml/kg/min (95% CI: 0.55–3.28), $p = 0.008$], and decreased TBF [−3.1% (95% CI: −5.0 to −1.2), $p < 0.001$] (Table 4) but did not significantly affect AVF or ASF. GH decreased total and LDL cholesterol levels but increased

Table 1 Baseline clinical and metabolic characteristics: Women vs. Men

	All ($n = 32$)	Women ($n = 15$)	Men ($n = 17$)	*P*-value
Age, yr	71 ± 5	71 ± 5	71 ± 5	0.97
Systolic blood pressure, mmHg	130 ± 15	131 ± 18	129 ± 13	0.72
Diastolic blood pressure, mmHg	79 ± 8	78 ± 9	79 ± 6	0.79
BMI, kg/m²	25.8 ± 2.6	24.7 ± 2.8	26.7 ± 2.2	0.04
Lean body mass (LBM, kg)	45.7 ± 11.0	35.3 ± 3.1	55.0 ± 5.6	<0.0001
Total body fat, %	34 (29–42)	42 (38–46)	29 (26–33)	<0.0001
Abdominal visceral fat, % of total	31 (21–40)	22 (18–28)	39 (33–48)	<0.0001
Abdominal subcutaneous fat, % of total	69 (60–79)	78 (72–82)	61 (52–68)	<0.0001
Maximal oxygen capacity, VO_2max (ml/kg/min)	26 ± 5	23 ± 4	28 ± 5	<0.001
Total cholesterol, mg/dL	188 ± 30	203 ± 30	174 ± 23	0.002
HDL cholesterol, mg/dL	49 ± 13	57 ± 12	42 ± 10	<0.001
LDL cholesterol, mg/dL	119 ± 30	129±34	109 ± 22	0.04
Triglycerides, mg/dL	106 ± 38	98 ± 34	112 ± 41	0.29
Fasting glucose, mg/dL	94 ± 7.6	93 ± 7	95 ± 8	0.44
Fasting insulin, µU/mL	9.1 (7.4–10.6)	9.0 (7.0–11.3)	9.1 (8.1–10.6)	0.36
2-h plasma glucose, OGTT, mg/dL	114 ± 18	110 ± 15	118 ± 20	0.18
QUICKI	0.342 ± 0.014	0.345 ± 0.015	0.340 ± 0.014	0.31
Hepatic insulin resistance index (HIRI)	2.81 (2.21–3.66)	2.68 (2.26–2.85)	3.19 (1.82–4.28)	0.81
Muscle insulin sensitivity index (MISI)	0.011 (0.006–0.019)	0.009 (0.007–0.019)	0.014 (0.007–0.019)	0.36
Oral glucose effectiveness index, oGE, mg/dL/min	2.95 (2.51–3.43)	3.44 (3.31–3.75)	2.54 (2.37–2.88)	<0.0001
Insulin-like growth factor 1 (IGF-1), µg/mL	114 (81–162)	84 (59–114)	155 (107–207)	<0.001
IGF binding protein-1, ng/mL	57 (26–73)	69 (58–91)	26 (17–61)	<0.001

Data are presented as unadjusted arithmetic mean ± SD or as median (IQR); *P*-values indicate significance for comparisons between groups at baseline

n no. of subjects, *IGF-1* insulin like growth factor-1, *IGFBP-1* IGF binding protein-1

Table 2 Baseline clinical and metabolic characteristics: Placebo vs. GH treatment arms

	Placebo ($n = 15$)	GH ($n = 17$)	*P*-value
Age, yr	73 ± 5	70 ± 4	0.89
Number of women/men	8/7	7/10	
Systolic blood pressure, mmHg	131 ± 17	129 ± 14	0.63
Diastolic blood pressure, mmHg	79 ± 9	78 ± 6	0.66
BMI, kg/m²	25.7 ± 2.1	25.8 ± 3.1	0.84
Lean body mass (LBM, kg)	44.9 ± 11.1	46.5 ± 11.1	0.57
Total body fat, %	37 (31–45)	32 (26–42)	0.17
Abdominal visceral fat, % of total	31 (21–40)	32 (20–41)	0.89
Abdominal subcutaneous fat, % of total	69 (59–79)	68 (59–79)	0.97
Maximal oxygen capacity, VO_2max (ml/kg/min)	24 ± 5	28 ± 5	0.03
Total cholesterol, mg/dL	188 ± 29	187 ± 31	0.88
HDL cholesterol, mg/dL	49 ± 15	48 ± 12	0.84
LDL cholesterol, mg/dL	118 ± 32	119 ± 26	0.95
Triglycerides, mg/dL	114 ± 46	98 ± 29	0.24
Fasting glucose, mg/dL	95 ± 8	93 ± 8	0.38
Fasting insulin, µU/mL	9.2 (7.7–11.4)	8.9 (7.1–10.6)	0.33
2-h plasma glucose, OGTT, mg/dL	117 ± 19	111 ± 17	0.33
QUICKI	0.339 ± 0.014	0.346 ± 0.015	0.16
Hepatic insulin resistance index (HIRI)	3.03 (2.21–4.08)	2.52 (2.13–3.11)	0.17
Muscle insulin sensitivity index (MISI)	0.009 (0.003–0.015)	0.014 (0.009–0.024)	0.05
Oral glucose effectiveness index,oGE, mg/dL/min	2.88 (2.51–3.44)	2.97 (2.55–3.54)	0.65
Insulin-like growth factor 1 (IGF-1), µg/mL	108 (80–155)	140 (82–173)	0.47
IGF binding protein-1, ng/mL	45 (20–89)	65 (31–73)	0.55

Data are presented as unadjusted arithmetic mean ± SD or as median (IQR); *P*-values indicate significance for comparisons between intervention groups at baseline

n no. of subjects, *IGF-1* insulin like growth factor-1, *IGFBP-1* IGF binding protein-1

Table 3 Relationships between tissue-specific insulin resistance indices, oral glucose effectiveness, and clinical parameters in the entire cohort at baseline

	HIRI		MISI		oGE	
	r-value	*p*-value	*r*-value	*p*-value	*r*-value	*p*-value
Age, yr	−0.08	0.64	−0.32	0.07	0.27	0.13
Body mass index, kg/m^2	0.09	0.58	−0.12	0.52	−0.64	<0.0001
Total body fat (TBF), %	0.03	0.87	−0.26	0.14	0.51	<0.001
Abdominal visceral fat (AVF), % of total	0.38	0.03	0.23	0.62	−0.47	0.005
Abdominal subcutaneous fat (ASF), % of total	−0.38	0.03	−0.23	0.62	0.47	0.005
Cardiovascular endurance (VO_2max), ml/kg/min	0.08	0.65	0.42	0.01	−0.31	0.08
Total cholesterol, mg/dL	−0.09	0.59	0.17	0.35	0.23	0.19
Triglycerides, mg/dL	0.21	0.25	0.08	0.63	−0.23	0.21
LDL cholesterol, mg/dL	−0.05	0.78	0.22	0.23	0.14	0.43
HDL cholesterol, mg/dL	−0.11	0.49	−0.27	0.15	0.41	0.01
Fasting glucose, mg/dL	0.38	0.04	0.16	0.40	−0.40	0.02
Fasting insulin, μU/mL	0.50	<0.001	−0.42	0.01	−0.41	0.02
2-h plasma glucose, mg/dL	0.07	0.68	−0.13	0.48	0.05	0.75
Insulin-like growth factor 1 (IGF-1), μg/mL	0.04	0.78	0.16	0.40	−0.54	<0.0001
IGF binding protein-1, ng/mL	−0.32	0.07	0.14	0.43	0.55	<0.001
HIRI	—		−0.05	0.76	–0.38	0.03
MISI	−0.05	0.76	—		−0.11	0.54
oGE	−0.38	0.03	−0.11	0.54	—	

Correlation analyses of the relationships between tissue-specific insulin resistance indexes, oral glucose effectiveness index, and clinical parameters

HIRI hepatic insulin resistance index, *MISI* muscle insulin sensitivity index, *oGE* oral glucose effectiveness index

plasma triglyceride concentrations (Table 4). The effects of GH and placebo administration on fasting plasma glucose and insulin levels, 2 h glucose levels during an OGTT, insulin sensitivity/resistance indices, and glucose effectiveness are summarized in Table 5. GH treatment elicited significant increases in fasting insulin levels and HIRI ($p < 0.001$), reduced QUICKI, but did not significantly change MISI or OGE (Fig. 1 and Table 5). Levels of IGFBP-1, a marker for hepatic insulin sensitivity were also lower after GH versus placebo [−11.1 (95% CI: −19.3 to −2.8) ng/mL, $p = 0.01$] (Table 5).

Discussion

Short-term GH administration in healthy older adults increases circulating IGF-1 levels and lean body mass and correspondingly decreases total body fat and abdominal visceral fat mass. These salutary changes would be expected to favorably impact insulin sensitivity, yet GH administration worsens glucose tolerance and insulin sensitivity. In the present study, we found that GH administration decreased hepatic insulin sensitivity but exerted no significant effect on muscle insulin sensitivity or glucose effectiveness. In addition, we observed novel relationships among glucose effectiveness, hepatic insulin sensitivity, and the IGF-1/IGFBP-1 axis.

Clinical characteristics of participants

In this study of healthy, non-obese, ambulatory, community-dwelling individuals, observed sex differences in BMI and TBF were consistent with previous studies; [30–33] women exhibited a lower BMI and AVF, but higher TBF, compared with men. Glucose per se regulates blood glucose levels by decreasing hepatic glucose production and augmenting peripheral glucose disposal, thereby lowering plasma glucose levels at basal insulin concentrations, a process referred to as glucose effectiveness. Postprandial glucose effectiveness, as determined by the oral glucose minimal model, was higher in women than in men, independent of age [33]. Similarly, in a Danish population-based study of 380 young healthy Caucasians, glucose effectiveness (measured by frequently sampled IV glucose tolerance test, FSIVGTT) was 15% higher in women versus men [34]. These studies support our finding of lower glucose effectiveness in men compared with women. We observed that oGE was inversely related to BMI, AVF, IGF-1, HIRI, and fasting insulin and glucose levels. The relationship with body composition is expected,

Table 4 Effects of placebo and GH administration for 26 weeks on body composition and IGF-1 and plasma cholesterol concentrations

	Placebo ($n = 15$)	GH ($n = 17$)	*P*-value
BMI, kg/m²			
Baseline	25.7 ± 2.1	25.8 ± 3.1	
26 weeks	25.8 ± 2.1	25.7 ± 3.0	
Change (Δ)	0.1 ± 0.6	−0.1 ± 1.3	
Between-group difference in Δ	−0.2 (−0.9 to −0.6)		0.62
Total body fat, %			
Baseline	37 (31–45)	32 (26–42)	
26 weeks	37 (31–45)	29 (24–36)	
Change (Δ)	−0.7 (−2 to 0.2)	−3.0 (−5 to −2)	
Between-group difference in Δ	−3.1 (−5.0 to −1.2)		0.002
Lean body mass (LBM, kg)			
Baseline	44.9 ± 11.1	46.5 ± 11.1	
26 weeks	43.1 ± 10.3	49.4 ± 11.3	
Change (Δ)	0.6 ± 0.9	2.3 ± 1.1	
Between-group difference in Δ	1.8 (1.0–2.6)		<0.0001
Insulin-like growth factor 1 (IGF-1), µg/mL			
Baseline	108 (80–155)	140 (82–173)	
26 weeks	87 (75–136)	218 (139–325)	
Change (Δ)	−16 (−27 to 6)	59 (31–203)	
Between-group difference in Δ	109 (59–160)		0.0001
Total cholesterol, mg/dL			
Baseline	188 ± 29	187 ± 31	
26 weeks	196 ± 33	180 ± 27	
Change (Δ)	8 ± 25	−6 ± 16	
Between-group difference in Δ	−16 (−31 to 1)		0.04
LDL cholesterol, mg/dL			
Baseline	118 ± 32	119 ± 26	
26 weeks	126 ± 34	104 ± 21	
Change (Δ)	8 ± 26	−14 ± 16	
Between-group difference in Δ	−23 (−38 to −9)		0.002
HDL cholesterol, mg/dL			
Baseline	49 ± 15	48 ± 12	
26 weeks	48 ± 13	48 ± 12	
Change (Δ)	−2 ± 8	0 ± 8	
Between-group difference in Δ	1 (−4 to 7)		0.62
Triglycerides, mg/dL			
Baseline	114 ± 46	98 ± 29	
26 Weeks	112 ± 34	137 ± 71	
Change (Δ)	−2 ± 33	40 ± 59	
Between-group difference in Δ	37 (−0.2 to 75)		0.05

Baseline and week 26 data are unadjusted values expressed as arithmetic mean (SD) or median (IQR); Δ, difference in post- and pre-treatment values. Differences in mean Δ between the treatment groups are adjusted for age, baseline value, and treatment group and is expressed as adjusted means (95% CI); *P*-values indicate significance for comparisons between the GH and placebo-treated groups

n number of subjects

Table 5 Effects of placebo and GH administration for 26 weeks on glucose metabolism and insulin sensitivity

	Placebo ($n = 15$)	GH ($n = 17$	*P* -Value
Fasting glucose, mg/dL			
Baseline	95 ± 8	93 ± 8	
26 Weeks	99 ± 21	100 ± 9	
Change (Δ)	3 ± 20	7 ± 9	
Between-group Difference in Δ	3.7 (−8.0 to 15.4)		0.52
Fasting insulin, µU/mL			
Baseline	9.2 (7.7–11.4)	8.9 (7.1–10.6)	
26 Weeks	11.3 (6.6–14.6)	13.3 (10.1–15.8)	
Change (Δ)	−0.3 (−1.5 to 5.1)	4.6 (1.9–7.9)	
Between-group Difference in Δ	6.7 (−0.5 to 13.7)		0.01
2-hour Plasma glucose, OGTT, mg/dL			
Baseline	117 ± 19	111 ± 17	
26 Weeks	139 ± 29	138 ± 30	
Change (Δ)	22 ± 27	27 ± 26	
Between-group Difference in Δ	7 (−13 to 26)		0.50
IGF binding protein-1, ng/mL			
Baseline	45 (20–89)	65 (31–73)	
26 Weeks	42 (24–62)	34 (23–54)	
Change (Δ)	−3 (−27 to 12)	−22 (−34 to −12)	
Between-group Difference in Δ	−11 (−19 to −3)		0.01
QUICKI			
Baseline	0.339 ± 0.014	0.346 ± 0.015	
26 Weeks	0.335 ± 0.023	0.318 ± 0.021	
Change (Δ)	−0.003 ± 0.017	−0.028 ± 0.022	
Between-group Difference in Δ	−0.025 (−0.040 to −0.009)		0.003
Hepatic insulin resistance index (HIRI)			
Baseline	3.03 (2.21–4.08)	2.52 (2.13–3.11)	
26 Weeks	2.57 (1.72–4.66)	4.43 (2.79–7.19)	
Change (Δ)	0.03 (−1.28 to 0.98)	1.80 (−0.10 to 34.46)	
Between-group Difference in Δ	1.89 (0.27–3.51)		0.005
Muscle insulin sensitivity index (MISI)			
Baseline	0.009 (0.003–0.015)	0.014 (0.009–0.024)	
26 Weeks	0.013 (0.007–0.035)	0.011 (0.005–0.020)	
Change (Δ)	0.008 (−0.001–0.019)	−0.002 (−0.010–0.007)	
Between-group Difference in Δ	−0.007 (−0.037 to 0.022)		0.13
Oral Glucose effectiveness (oGE)			
Baseline	2.88 (2.51–3.44)	2.97 (2.55–3.54)	
26 Weeks	3.20 (2.69–3.52)	3.06 (2.66–3.41)	
Change (Δ)	0.17 (−0.15 to 0.43)	0.07 (−0.26 to 0.33)	
Between-group Difference in Δ	−0.13 (−0.42 to 0.16)		0.37

Baseline and week 26 data are unadjusted values expressed as arithmetic mean (SD) or median (IQR); Δ, difference in post- and pre-treatment values. Differences in mean Δ between the treatment groups are adjusted for age, baseline value, and treatment group and is expressed as adjusted means (95% CI); n, number of subjects; P values indicate significance for comparisons between the GH and placebo treated groups

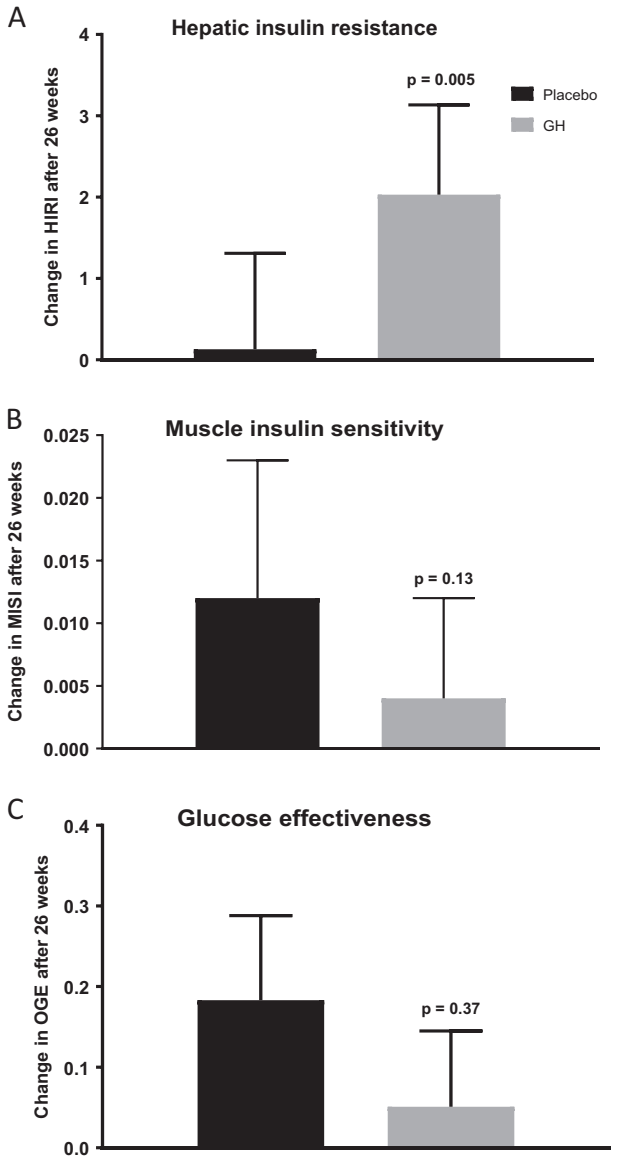

Fig. 1 Effects of GH ($n = 17$) or placebo ($n = 15$) administration on **a** hepatic insulin resistance (HIRI), **b** muscle insulin sensitivity index (MISI), and **c** glucose effectiveness (oGE). GH or placebo was administered to healthy older men and women for 26 weeks. Oral glucose tolerance tests (OGTT) were performed at baseline and after 26 weeks. Changes (post-treatment-baseline) in HIRI, MISI, and oGE were calculated from the OGTTs. Differences in mean change between the treatment groups are adjusted for age, baseline value, and treatment group and is expressed as adjusted means ± SEM

as adiposity is directly related to glucose intolerance and diabetes. Yet, no previous studies have reported an association between glucose effectiveness and serum concentrations of IGF-1. IGF-1 is an anabolic hormone that is synthesized by hepatocytes in response to GH. Like insulin, IGF-1 promotes peripheral glucose uptake and oxidation and suppresses hepatic glucose production [35, 36]. Low plasma IGF-1 concentrations predict impaired insulin-mediated glucose uptake in older individuals [37]. Thus, the increase in glucose effectiveness at lower IGF-1 levels could be a compensatory response to diminished peripheral glucose uptake [38]. Our finding of a negative relationship between OGE and HIRI is consistent with the observation that impaired glucose effectiveness is associated with enhanced hepatic glucose production [39]. The expansion of AVF is hypothesized to contribute to increases in portal FFA and glycerol concentrations, inducing hepatic fatty acid esterification, hepatic steatosis, and hepatic insulin resistance [40, 41]. HIRI was directly related to AVF but inversely related to ASF, suggesting a protective effect of ASF [42]. Finally, circulating IGFBP-1 has been proposed as a liver-specific surrogate marker of hepatic insulin sensitivity [29]. Consistent with this observation, in the current study, serum IGFBP-1 levels were inversely related to hepatic insulin resistance and directly related to glucose effectiveness.

GH administration affects hepatic but not skeletal muscle insulin sensitivity or glucose effectiveness

Our results demonstrate that short-term GH administration affects insulin resistance in the liver but not skeletal muscle in healthy adults. Acutely, GH administration in healthy individuals elicits higher hepatic glucose production and lower peripheral glucose disposal [14–16]. Simultaneous administration of acipimox, which lowers FFA levels by inhibition of the hormone-sensitive lipase, with GH abolished the negative effects of GH on hepatic insulin sensitivity [14–16, 43, 44]. Based on these and other studies in GH-deficient adults [44–46], the lipolytic effects of GH have been postulated to mediate GH induced insulin resistance. The magnitude and the effects of lipolytic actions of GH after continued GH administration in healthy individuals are unknown. However, in patients with acromegaly, acute administration of pegvisomant, a human GH receptor antagonist, reduced FFA levels and hepatic glucose production but did not alter peripheral glucose disposal [8]. Consistent with the latter finding, GH blockade during fasting also reduced endogenous glucose production and FFA levels in obese individuals [47]. These studies suggest that GH-induced insulin resistance may be primarily confined to the liver. The mechanism by which long-term GH administration induces hepatic but not skeletal muscle insulin resistance is unclear. In one recent study, adipocyte-specific deletion of *Janus Kinase 2* (*Jak2*), an important transducer and activator of the STAT pathway, prevented GH-mediated hepatic insulin resistance in mice [12]. In an elegant set of experiments, Corbit et al. demonstrated that GH-mediated inhibition of insulin-induced suppression of lipolysis (via JAK2) was the proximate cause of hepatic insulin resistance. These recent findings in mice and aforementioned studies in humans suggest that the

diabetogenic action of GH may be primarily mediated by enhanced lipolysis which leads to increases in hepatic acetyl CoA and accentuated hepatic gluconeogenesis [48]. Moreover, in our study, another marker of hepatic insulin sensitivity IGFBP-1 was also lower after GH treatment. Insulin inhibits hepatic IGFBP-1 synthesis, and thus compensatory hyperinsulinemia following GH administration may explicate the lower circulating IGFBP-1 levels [49].

In this study, GH administration did not negatively affect peripheral insulin sensitivity. Several possible mechanisms may explain the differential tissue-specific effects of GH. Favorable body composition changes caused by long-term GH administration, such as increased LBM and decreased fat mass, might exert beneficial effects on peripheral insulin sensitivity [21]. In our study, GH increased maximum exercise capacity when compared with placebo. Improved or high levels of exercise tolerance may promote glucose disposal in skeletal muscle by increasing expression and translocation of the glucose transporter isoform 4 (GLUT-4) [50, 51]. Finally, GH-administration may improve peripheral insulin sensitivity by increasing circulating IGF-1 levels, which directly acts on skeletal muscle and facilitates peripheral glucose uptake. The effects of GH on glucose effectiveness in healthy individuals has not been previously examined. However, similar to our findings, six months of GH administration in patients with GH deficiency did not alter glucose effectiveness [52].

Our study had several limitations. First, we used surrogate markers of insulin sensitivity/resistance and glucose effectiveness derived from an OGTT [25–27]. The gold-standard method to evaluate hepatic and peripheral (muscle) insulin sensitivity is a hyperinsulinemic euglycemic clamp with isotope- or radio-labeled glucose tracers [28]. Similarly, somatostatin pancreatic-glucose clamp and minimal model analysis of frequently sampled intravenous glucose tolerance test (FSIVGTT) are standard procedures used to assess glucose effectiveness. However, these methods are labor-intensive, technically demanding, and not feasible for large studies. The surrogate indexes used in the current study have been widely used in other studies and correspond closely to indexes derived from the reference glucose clamp procedure (HIRI: $r = 0.58$–0.64; MISI: $r = 0.49$–0.78; and oGE: $r = 0.32$–0.35) [25–27, 53, 54]. Second, we consider the changes we observed in tissue-specific insulin sensitivity indexes following GH administration to be exploratory. Thus, the results of our study need to be confirmed in studies where these outcomes are pre-specified as primary outcomes and measured using reference techniques (e.g., glucose clamp). Third, the duration of our study was relatively short (6 months) and whether similar effects occur after longer-term GH administration remains to be determined. Fourth, we did not measure FFA levels and thus cannot address the role of FFA in mediating reduced hepatic insulin sensitivity. Finally, no objective measures of diet intake and physical activity were taken during the trial, and participants were simply advised to follow their normal diet and exercise regimen.

In conclusion, GH administration to healthy older women and men for 6 months decreased hepatic insulin sensitivity but did not significantly affect muscle insulin sensitivity or glucose effectiveness. These observations are consistent with recent findings in rodents and inform our understanding of alterations in glucose metabolism in states of GH excess such as acromegaly, GH deficiency (congenital or acquired), or GH insensitivity/resistance as observed in Laron Syndrome.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of The Institutional Review Board of the Johns Hopkins Bayview Medical Center and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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