Interrelationships of Spontaneous Growth Hormone Axis Activity, Body Fat, and Serum Lipids in Healthy Elderly Women and Men

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Aging is associated with decreased growth hormone (GH) secretion and plasma insulin-like growth factor-I (IGF-I) levels, increased total and abdominal fat, total and low-density lipoprotein (LDL) cholesterol, and triglycerides, and reduced high-density lipoprotein (HDL) cholesterol. Similar changes in lipids and body composition occur in nonelderly GH-deficient adults and are reversed with GH administration. To examine whether GH/IGF-I axis function in the elderly is related to the lipid profile independently of body fat, we evaluated GH secretion, serum IGF-I and IGF binding protein-3 (IGFBP-3) levels, adiposity via the body mass index (BMI), waist to hip ratio (WHR), dual-energy x-ray absorptiometry (DEXA), and magnetic resonance imaging (MRI), and circulating lipids in 101 healthy subjects older than 65 years. Integrated nocturnal GH secretion (log IAUPGH) was inversely related ($P < .005$) to DEXA total and abdominal fat and MRI visceral fat in both genders. Log IAUPGH was inversely related to visceral fat in women ($P < .005$) and men ($P < .0001$), but was not significantly related to total fat in either gender. In women, log IAUPGH was related inversely to total and LDL cholesterol and positively to HDL cholesterol ($P < .008$). In men, log IAUPGH was inversely related to total cholesterol and triglycerides ($P < .005$). In women, HDL cholesterol was inversely related to the WHR ($P < .005$). In men, triglycerides were positively related ($P < .001$) to the WHR and DEXA abdominal and MRI visceral fat. Multivariate regression revealed log IAUPGH, but not DEXA total body fat, to be an independent determinant of total ($P < .001$ for women and $P = .01$ for men) and LDL ($P < .007$ and $P = .05$) cholesterol in both sexes and of HDL cholesterol ($P < .005$) and triglycerides ($P < .03$) in women. Log IAUPGH, but not DEXA abdominal fat, was related to total ($P < .005$ and $P < .03$) and LDL ($P < .03$ and $P = .05$) cholesterol in both genders and to HDL in women ($P < .05$). Log IAUPGH, but not MRI visceral fat, was related to total cholesterol ($P < .03$ and $P = .05$) in women and men. Age, IGF-I, and IGFBP-3 were not significantly related to any body fat or lipid measures, except for a positive correlation of IGF-I with triglycerides in men. Thus, endogenous nocturnal GH secretion predicts total, LDL, and HDL cholesterol levels independently of total or abdominal fat, suggesting that it is an independent cardiometabolic risk factor in healthy elderly people.

CARDIOVASCULAR and cerebrovascular diseases are the major causes of death in persons over age 65 in Western societies. Age-related increases in total and abdominal fat have been implicated as contributing to this augmented cardiovascular risk, at least until 80 years of age.[1] With normal aging, women and men exhibit increasing levels of total and low-density lipoprotein (LDL) cholesterol and decreasing or unchanging levels of high-density lipoprotein (HDL) cholesterol. After the menopause, women tend to have higher levels of LDL and HDL cholesterol than do men.[2,3] Most studies,[4-6] but not all,[7] have associated these lipid changes with adverse cardiovascular risk in the elderly.

Young and middle-aged growth hormone (GH)-deficient adults exhibit some changes similar to those of normal aging, including increased total and abdominal fat,[8] elevated total and LDL cholesterol and triglycerides, and decreased HDL cholesterol.[9-11] Administration of recombinant human GH to patients with adult GH deficiency partly reverses these changes in body fat distribution[8] and the associated lipid abnormalities.[9,12,13] A number of studies have reported substantial reductions in spontaneous and stimulated GH secretion in the elderly and in the obese.[14] GH treatment in healthy elderly persons decreases total fat and LDL cholesterol levels.[15,16] Taken together, these data suggest that the decline in GH secretion with aging contributes to age-related changes in body composition and lipid metabolism.

Because the dynamics of the relationships in elderly persons among GH, body fat, and lipid metabolism are largely unknown, we performed a cross-sectional study of healthy older people to test the hypothesis that circulating lipid levels are more closely related to endogenous GH/insulin-like growth factor-I (IGF-I) axis activity than to adiposity per se. Our findings suggest that total and LDL cholesterol levels are inversely related and HDL levels are directly related to nocturnal GH secretion independently of total or abdominal fat.

SUBJECTS AND METHODS

Subjects

One hundred one community-dwelling individuals (45 women and 56 men) aged 65 to 82 years were recruited by mailed advertisement. Subjects were selected to be moderately active by self-report and performed regular household activities. Persons engaged in regular strenuous or athletic exercise training were excluded. All subjects were healthy by screening history and physical examination, routine blood studies, urinalysis, and graded-treadmill electrocardiogram. None of the women used estrogen or progestogen for at least 6 months prior to study. The body mass index (BMI) was 19.7 to 32.5 kg/m^2, and none of the subjects had diabetes mellitus, coronary artery disease, or untreated

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thyroid disease. Study participants were nonsmokers, consumed less than 2 oz alcohol per day, and used no medications known to interfere with the GH/IGF-I axis or any other outcome measure. The study was approved by the combined Institutional Review Board of the Johns Hopkins Bayview Medical Center/Gerontology Research Center. Written informed consent was obtained from all subjects.

Study Protocol

All subjects were admitted to the General Clinical Research Center (GCRC) at Johns Hopkins Bayview Medical Center at 8:00 AM on day 1. Anthropometric measures of body composition were recorded, and dual-energy x-ray absorptiometry (DEXA) and abdominal magnetic resonance imaging (MRI) scans were performed to assess total and regional fat distribution. At 7:00 PM, an intravenous catheter was inserted into a forearm vein and kept patent with heparinized (1,000 U/L) 0.9% sodium chloride. From 8:00 PM to 8:00 AM, blood samples (1 mL) were collected at 20-minute intervals, and the sera were saved at −70°C for subsequent GH determinations. At 8:00 AM on day 2 after an overnight fast, blood was collected for measurement of IGF-I, IGF binding protein-3 (IGFBP-3), total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides.

Laboratory Assays

Serum GH levels were measured in duplicate in the Endocrinology Research Laboratory at the Gerontology Research Center using a two-site radioimmunometric method (Nichols Institute, San Juan Capistrano, CA). The sensitivity of the assay was 0.05 ng/mL, and the intraassay and interassay coefficients of variation (CVs) were 1.6% and 5.1%, respectively.

Total serum IGF-I was determined by radioimmunoassay (RIA) after acid-ethanol extraction, and IGFBP-3 was measured by RIA using a specific high-affinity polyclonal antibody directed against the binding subunit (Endocrine Sciences Laboratories, Calabasas Hills, CA). The sensitivity of the IGF-I assay was 30 ng/mL, and intraassay and interassay CVs were 5.4% and 7.3%, respectively. The sensitivity of the IGFBP-3 assay was 0.3 ng/mL, with intraassay and interassay CVs of 2.7% and 7.5%, respectively.

Lipid assays were performed at the Johns Hopkins Hospital Lipoprotein Analytical Laboratory using Centers for Disease Control (CDC) standards. Plasma levels of total cholesterol and triglycerides were analyzed enzymatically on a Hitachi 704 analyzer (Boehringer-Mannheim, Indianapolis, IN) using reagents supplied by the manufacturer. The intrassay and interassay CVs were less than 1.4% for cholesterol and less than 2.5% for triglycerides. The HDL cholesterol level was measured using a variation of the heparin-$MnCl_2$ method,[17] with intraassay and interassay CVs both less than 3.6%. LDL cholesterol levels were calculated from the other lipid measures using the equation of Friedewald.[18]

Measurements of Body Composition

The BMI (kg/m^2) was used as a measure of total adiposity. The waist to hip ratio (WHR), defined as the minimum circumference of the waist divided by the maximum circumference of the buttocks, was used as an index of central adiposity.

MRI assessment of abdominal fat was performed on a Resonex RX 5000 0.38T clinical imaging system (Resonex, Sunnyvale, CA) using an inversion-recovery spin-echo pulse sequence set to minimize the aqueous signal from adjacent tissue (inversion time, 350 milliseconds; repetition time, 550 milliseconds; echo time, 15 milliseconds; acquisition number, 4). A 1-cm thickness axial image of the minimum field of view necessary to include the entire cross-section of the subject's abdomen was acquired at the level of the L4-L5 junction, prescribed graphically from a sagittal scout image. Data analysis was performed by a single observer on a Macintosh computer (Apple Computer, Cupertino, CA) using the public-domain NIH Image program (developed at the US National Institutes of Health and available on the Internet at http://rsb.info.nih.gov/nih-image/). After correction for the cross-sectional area of the scan, the total abdominal fat and subcutaneous, visceral, and retroperitoneal fat compartments were quantified with a CV of 4.7%.

Total body fat mass was estimated by DEXA scanning using a three-compartment model of body composition (model DPX-L; Lunar Radiation, Madison, WI).[19] To estimate the amount of abdominal fat by DEXA, we performed a manual analysis to define an abdominal region of interest between the top of the greater trochanters and a line midway between the clavicles and trochanters. Reproducibility of DEXA measurements was confirmed by performing two total-body scans on a separate group of 12 elderly men (>65 years) at 6-week intervals. The scans were analyzed by two observers, with intraobserver and interobserver CVs of about 4%.

Statistical Analysis

All data are expressed as mean values ± SD. Because the genders differed substantially with respect to most baseline measurements (Table 1), all analyses were performed in women and men separately. Results of the GH assays were reduced using a curve-fitting program, and serum GH concentrations were estimated using the derived constants. GH secretion was assessed using the Pulsar program[20] and characterized as the integrated area under the spontaneous nocturnal GH peak (IAUPGH), mean GH, GH peak frequency, and GH peak amplitude. Peaks were identified as elevations above the smoothed curve of at least 2.5, 2.0, 1.75, 1.5, and 1.2 times the assay variance at that hormone level for one-, two-, three-, four-, and five-point elevations, respectively, to yield an expected false-positive rate of less than 1%.

Most data were normally distributed as assessed by the Kolmogorov-Smirnov test. However, the distribution of values for BMI, WHR, MRI visceral fat, IAUPGH, mean GH, GH peak amplitude, and plasma triglycerides was skewed to the right. Logarithmic transformations resulted in a normal distribution of these data and were used for all subsequent analyses. Gender differences for variables were compared by *t* tests or the Mann-Whitney *U* test as appropriate.

Relationships between continuous variables were analyzed using simple linear regression analyses and expressed as correlation coefficients (r), with a P level less than .05 considered significant. All regression plots were inspected for appropriateness of fit of the linear model. For all regressions, no higher-order polynomial equations improved the goodness-of-fit versus the linear model, as determined by an F test of residual variances.

Multiple regression analysis was used to examine the interrelationships of IAUPGH and body fat as independent variables with the dependent lipid variable of interest. As IAUPGH was itself significantly inversely related to body fat, the magnitude of such collinearity was determined by calculating variance inflation factors[21] for every combination of IAUPGH and a body fat measure in men and women considered separately. The maximum value of any such factor was 1.69, indicating that collinearity did not interfere with the model. Moreover, an interaction term for IAUPGH and body fat was entered in the model and found not to be significant in any analysis. Consequently, the interaction term was removed by backward elimination. Forward stepwise regression analysis was used to compare the relative variance of IAUPGH explained by total, abdominal, and visceral fat measures. The F statistic to enter a variable in such a model was set at 4 and the F to remove at 3.996. Our sample size was sufficient to detect an intercorrelation among two or more variables with an r greater than .217. Gender differences in regression analyses were investigated by analysis of covariance.

Table 1. Characteristics of the Study Population

Characteristic	Men (n = 56)		Women (n = 45)		P*
	Mean ± SD	Range	Mean ± SD	Range	
Age (yr)	71.4 ± 4.6	65.8-82.6	71.1 ± 4.2	65.1-80.1	NS
Weight (kg)	81.9 ± 9.8	58.8-103.0	64.8 ± 8.5	49.4-88.5	<.0001
BMI (kg/m²)	26.9 ± 2.8	20.2-32.2	25.5 ± 2.8	19.7-32.5	<.01
WHR	0.97 ± 0.06	0.83-1.19	0.82 ± 0.07	0.62-0.95	<.0001
DEXA total fat (kg)	24.1 ± 6.3	8.7-38.8	25.9 ± 6.2	15.1-40.7	NS
DEXA abdominal fat (kg)	7 ± 2.2	2.0-13.4	6.5 ± 1.9	2.4-11.1	NS
MRI visceral fat (cm²)	130 ± 63	38-385	99 ± 57	23-285	<.005
Total cholesterol (mg/dL)	179 ± 28	124-276	206 ± 26	162-292	<.0001
HDL cholesterol (mg/dL)	39 ± 9	22-58	51 ± 12	29-76	<.0001
LDL cholesterol (mg/dL)	114 ± 26	55-203	131 ± 28	82-225	<.001
Triglycerides (mg/dL)	130 ± 62	49-334	120 ± 45	46-238	NS
IGF-I (μg/L)	138 ± 44	43-254	120 ± 46	55-244	<.05
IGFBP-3 (μg/L)	2.3 ± 0.7	0.8-4.3	2.6 ± 0.6	1.5-4.0	<.05
IAUPGH (μg · min/L)	517 ± 429	0.0-2,183	668 ± 565	0.0-2,396	NS
Mean GH (ng/mL)	0.8 ± 0.67	0.03-3.24	1.03 ± 0.89	0.04-4.19	NS
GH peak frequency (peaks/12 h)	3.96 ± 1.37	2.9-10.0	4.54 ± 1.51	1.4-11.4	NS
GH peak amplitude (ng/mL)	1.78 ± 1.1	0.53-5.59	2.1 ± 1.4	0.19-6.31	NS

Abbreviation: NS, not significant.
*Men *v* women.

RESULTS

Characteristics of the Study Population

The mean age of the study group was 71.3 ± 4.4 years (range, 65.1 to 82.6). The mean age of men and women did not differ significantly. Values for weight, BMI, WHR, MRI visceral fat, and IGF-I were greater in men, whereas total, LDL, and HDL cholesterol and IGFBP-3 levels were greater in women (Table 1).

Bivariate Regressions of IAUPGH With Body Fat Measures

There were significant inverse relationships between IAUPGH and each of the measured indices of total and abdominal fat in both men and women (Table 2). To compare the relative strength of the relationship of IAUPGH with total versus visceral fat, we performed a forward stepwise regression analysis with IAUPGH as the dependent measure and DEXA total fat and MRI visceral fat as the independent variables. IAUPGH was inversely related to visceral fat, and not to total fat, in both women ($F = 10.63$, $P < .005$) and men ($F = 22.46$, $P < .0001$). Similar results were obtained when DEXA abdominal fat was substituted for MRI visceral fat in the regression model.

Table 2. Bivariate Regressions of Fat Measures With IAUPGH

Dependent Variable	Gender	r	P
BMI	Women	−.47	.0011
	Men	−.51	.0001
WHR	Women	−.62	.0001
	Men	−.32	.02
DEXA total fat	Women	−.49	.0006
	Men	−.49	.0001
DEXA abdominal fat	Women	−.64	.0001
	Men	−.57	.0001
MRI visceral fat	Women	−.49	.0026
	Men	−.59	.0001

Bivariate Regressions of IAUPGH With Lipid Variables

In women and men considered separately, IAUPGH ($.05 < P < .005$) was significantly inversely related to the concentration of total and LDL cholesterol and triglycerides (Table 3 and Fig 1). In women but not in men, IAUPGH was significantly positively related to HDL cholesterol ($P < .01$). However, there were no significant gender differences in the relationship of IAUPGH with any lipid variable, as assessed by comparison of the intercept and slope values between the sexes.

Bivariate Regressions of Lipid Variables and Body Fat

We next examined the relationship of the lipid variables with each of the measured indices of body fat (Table 4). In women, LDL cholesterol ($r = .28$, $P = .05$) and triglycerides ($r = .33$, $P < .02$) were positively related to the WHR, whereas HDL cholesterol was inversely related to the WHR ($r = -.41$, $P < .005$), DEXA abdominal fat ($r = -.33$, $P < .03$), and MRI visceral fat ($r = -.37$, $P < .05$). In men, triglycerides were positively related to every fat measure ($.02 < P < .0005$), while HDL cholesterol was inversely related to MRI visceral fat ($r = -.31$, $P < .05$). No significant relationships of total cholesterol were observed with indices of body fat in either gender.

Table 3. Bivariate Regressions of Plasma Lipids With IAUPGH

Dependent Variable	Gender	r	P
Total cholesterol	Women	−.44	.0026
	Men	−.38	.0042
LDL cholesterol	Women	−.39	.0074
	Men	−.30	.0263
HDL cholesterol	Women	.40	.0072
	Men	.24	.0773
Triglycerides	Women	−.31	.0355
	Men	−.38	.004

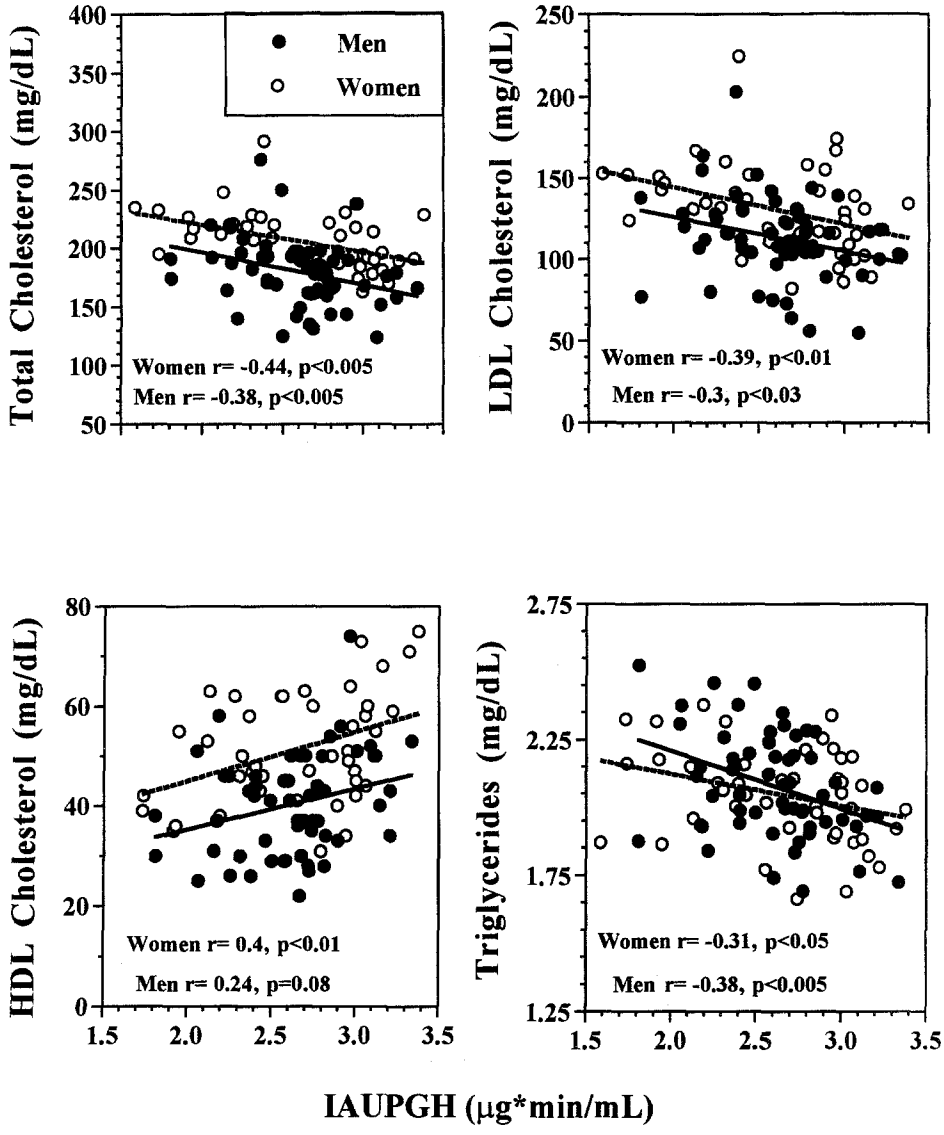

Fig 1. Bivariate relationships of nocturnal GH secretion with plasma lipids in healthy elderly women and men. Total and LDL cholesterol and triglycerides were related inversely and HDL cholesterol was related positively to log IAUPGH.

Relationships Among Body Composition Measures

We assessed the strength of interrelationships among the measured indices of total and abdominal fat. In women and men, respectively, the BMI was positively related ($P < .0001$) to DEXA total fat ($r = .82$ and .79), DEXA abdominal fat ($r = .77$ and .73), and MRI visceral fat ($r = .61$ and .56) and less strongly related (ie, $.01 < P < .001$) to the WHR. The WHR was positively related ($P < .0001$) to DEXA abdominal fat ($r = .53$ and .58 in women and men, respectively) and to MRI visceral fat in men ($r = .67$) and women ($r = .58$, $P < .001$). The WHR was less strongly related to the measures of total body fat ($.01 < P < .001$). DEXA total fat was positively related ($P < .0001$) to DEXA abdominal fat ($r = .92$ and .94 in women and men, respectively) and MRI visceral fat ($r = .61$ and .74). DEXA abdominal and MRI visceral fat measures were highly intercorrelated ($P < .0001$) in women ($r = .71$) and men ($r = .81$).

Multivariate Regressions of Lipid Variables Versus IAUPGH and Body Fat

In view of the numerous significant interrelationships among the lipid variables, IAUPGH, and indices of body fat, we used multivariate regression analysis to evaluate the extent to which the relationships between lipid variables and IAUPGH might be independent of body fat (Table 5). IAUPGH, but not DEXA total body fat, was independently and inversely related to total cholesterol in women ($P < .001$) and men ($P < .02$) and LDL cholesterol in women ($P < .01$) and men ($P = .05$). IAUPGH was also independently associated with HDL cholesterol ($P < .005$) and triglycerides ($P < .03$), but only in women.

When DEXA abdominal fat was substituted in the model, IAUPGH, but not abdominal fat, remained the independent determinant in women and men for total ($P < .005$ and $P < .02$) and LDL ($P < .03$ and $P = .05$) cholesterol. For HDL cholesterol, IAUPGH, but not abdominal fat, was the significant

Table 4. Bivariate Regressions of Plasma Lipids Versus Body Fat

Dependent Variable	Women			Men		
	Independent Variable	*r*	*P*	Independent Variable	*r*	*P*
Total cholesterol	BMI	.003	.9900	BMI	.029	.8300
	WHR	.244	.0882	WHR	.077	.5632
	DEXA total fat	.064	.6592	DEXA total fat	.181	.1665
	DEXA abdominal fat	.157	.2762	DEXA abdominal fat	.224	.0850
	MRI visceral fat	.128	.4642	MRI visceral fat	.162	.2705
LDL cholesterol	BMI	.082	.5716	BMI	.101	.4423
	WHR	.277	.0514	WHR	.165	.2153
	DEXA total fat	.145	.3156	DEXA total fat	.144	.2728
	DEXA abdominal fat	.226	.1138	DEXA abdominal fat	.136	.2989
	MRI visceral fat	.189	.2771	MRI visceral fat	.093	.5294
HDL cholesterol	BMI	−.186	.2010	BMI	−.190	.1478
	WHR	−.410	.0034	WHR	−.231	.0809
	DEXA total fat	−.170	.2426	DEXA total fat	−.208	.1108
	DEXA abdominal fat	−.328	.0215	DEXA abdominal fat	−.246	.0579
	MRI visceral fat	−.370	.0314	MRI visceral fat	−.308	.0335
Triglycerides	BMI	.018	.9034	BMI	.305	.0177
	WHR	.332	.0184	WHR	.421	.0010
	DEXA total fat	.045	.7585	DEXA total fat	.311	.0154
	DEXA abdominal fat	.232	.1047	DEXA abdominal fat	.449	.0003
	MRI visceral fat	.225	.1938	MRI visceral fat	.483	.0005

independent determinant in women only ($P < .05$). There were no significant independent relationships of IAUPGH with triglyceride levels.

With MRI visceral fat in the model, there were persistent weakly significant independent relationships of total cholesterol with IAUPGH in both genders ($P < .03$ and $P = .05$), but visceral fat itself did not appear as a significant determinant. For LDL cholesterol, the corresponding relationships were stronger with IAUPGH than with visceral fat but were nonsignificant. Similar findings were obtained by stepwise regression analysis. There were no significant independent relationships of IAUPGH with HDL cholesterol or triglycerides in this model.

Similarly, when BMI and WHR were substituted as fat measures in the multivariate model, significant independent relationships of IAUPGH with total, LDL, and HDL cholesterol persisted in women and men (data not shown). In contrast to the bivariate analyses, multivariate analyses revealed significant direct relationships in men ($P < .03$) for the BMI with total and LDL cholesterol and for the WHR with LDL cholesterol. Once again, there were no consistent independent relationships between IAUPGH and triglycerides.

We examined the relationships of other indices of spontaneous GH secretion with lipid variables and body fat. Compared with IAUPGH, the values for mean GH and GH peak amplitude demonstrated similar but slightly less consistent relationships with lipid variables and body fat (data not shown). GH peak frequency was not consistently related to any lipid variable. In men, GH peak frequency was inversely related to the BMI ($r = -.33$, $P = .01$), DEXA total fat ($r = -.33$, $P = .01$), DEXA abdominal fat ($r = -.36$, $P = .005$), and MRI visceral

Table 5. Multiple Regressions of Plasma Lipids Versus IAUPGH and Body Fat

Dependent Variable	Gender	Relationship of DEXA Total Fat			Relationship of DEXA Abdominal Fat			Relationship of MRI Visceral Fat		
		Independent Variable	Model *r*	*P*	Independent Variable	Model *r*	*P*	Independent Variable	Model *r*	*P*
Total cholesterol	Women (n = 45)	IAUPGH	.48	.0010	IAUPGH	.45	.0044	IAUPGH	.40	.0241
		Total fat		.1555	Abdominal fat		.3806	Visceral fat		.6339
	Men (n = 56)	IAUPGH	.38	.0134	IAUPGH	.38	.0245	IAUPGH	.37	.0554
		Total fat		.9771	Abdominal fat		.8241	Visceral fat		.8433
LDL cholesterol	Women (n = 45)	IAUPGH	.41	.0065	IAUPGH	.40	.0215	IAUPGH	.34	.1031
		Total fat		.3985	Abdominal fat		.6989	Visceral fat		.8746
	Men (n = 56)	IAUPGH	.30	.0525	IAUPGH	.30	.0504	IAUPGH	.27	.1249
		Total fat		.9738	Abdominal fat		.8121	Visceral fat		.8535
HDL cholesterol	Women (n = 45)	IAUPGH	.43	.0044	IAUPGH	.40	.0427	IAUPGH	.41	.2916
		Total fat		.2513	Abdominal fat		.9437	Visceral fat		.1499
	Men (n = 56)	IAUPGH	.30	.2432	IAUPGH	.27	.3601	IAUPGH	.29	.4931
		Total fat		.4470	Abdominal fat		.3256	Visceral fat		.2753
Triglycerides	Women (n = 45)	IAUPGH	.34	.0229	IAUPGH	.32	.1674	IAUPGH	.27	.3759
		Total fat		.3413	Abdominal fat		.7031	Visceral fat		.4847
	Men (n = 56)	IAUPGH	.41	.1866	IAUPGH	.48	.2393	IAUPGH	.51	.2553
		Total fat		.0536	Abdominal fat		.0160	Visceral fat		.0221

NOTE. *r* values are adjusted for degrees of freedom.

fat ($r = -.44$, $P < .005$). Using forward stepwise regression analysis, the influence of DEXA abdominal fat ($F = 8.26$, $P < .005$) on GH peak frequency was found to be stronger than that of DEXA total fat ($F = 0.118$). In women, in a bivariate regression analysis, GH peak frequency was inversely related to DEXA abdominal fat ($r = -.32$, $P < .05$) and not significantly related to MRI visceral fat. When the effects of DEXA total and abdominal fat were compared by forward stepwise regression analysis, GH peak frequency was not significantly related to total fat ($F = 0.81$) after adjusting for the effect of abdominal fat ($F = 4.75$, $P < .03$).

Serum IGF-I was positively related to GH peak frequency ($r = .38$, $P < .01$) but not to IAUPGH ($r = .30$, $P = .05$) in women. IGF-I was directly related to IGFBP-3 in women ($r = .36$, $P < .01$) and men ($r = .59$, $P < .0001$). Simple regression analyses revealed no significant relationships for either IGF-I or IGFBP-3 with any of the body fat or lipid measures, except for a significant positive correlation ($P = .01$) of IGF-I with triglycerides in men. This relationship remained significant ($P < .02$) even after adjustment for the effects of total body or abdominal fat.

Within the narrow age range of the subjects studied, there were no significant relationships of age with any of the other measured outcome variables. Consequently, age was not entered in any multivariate model.

DISCUSSION

In this study of healthy, generally non-obese, community-dwelling elderly women and men, we, like others,[14] found strong inverse relationships between various measures of body fat and indices of spontaneous GH secretion. We found that integrated GH secretion, GH peak amplitude, and GH peak frequency were all more strongly related to abdominal fat than to total fat. In this regard, our findings in this elderly population are similar to those in a recent study in an obese population in which adiposity explained some but not all of the effects of age on GH secretion.[22] In the latter investigation, the predominant relationship of adiposity was with GH pulse amplitude and its correlate, GH burst mass (assessed by deconvolution analysis), but not with GH pulse frequency.

In our healthy ambulatory predominantly non-obese subjects, the relationships between the various lipid measures and body fat tended to be weak. In prior studies in severely obese patients, total cholesterol levels were positively related to the amount of abdominal visceral fat,[1] whereas in less obese populations, there were no significant relationships of total or LDL cholesterol with visceral fat.[23] In addition, in a large population-based survey, a weaker relationship of total and LDL cholesterol was observed with total fat as assessed by the BMI in older versus younger individuals,[24] and in a comparison study, total and LDL cholesterol levels were higher in middle-aged versus young men even after adjustment for total and visceral fat.[25] Taken together, these and the current data suggest that with aging, the strength of the relationship of total and LDL cholesterol with total and abdominal body fat is attenuated.

Because GH secretion was inversely associated with measures of body fat, any apparent relationship of GH with lipid measures still may have been a function of the relationships of GH and/or lipid variables with body fat. In this study, we found independent relationships of total and LDL cholesterol in women and men with spontaneous nocturnal GH secretion, but not with total or abdominal fat. It must be emphasized that our study subjects were non-obese and free of clinically overt or silent coronary heart disease as assessed by maximal exercise testing. Our findings may not be generalizable to obese patients and patients with coronary disease.

The evidence suggests that GH exerts important effects on cholesterol metabolism and cardiovascular disease. GH-deficient young and middle-aged adults exhibit increased levels of total and LDL cholesterol, reduced levels of HDL cholesterol,[9-11] and increased morbidity and mortality due to cardiovascular disease.[11,26] GH replacement therapy reduces the level of total and LDL cholesterol[9,27,28] and increases HDL cholesterol,[12] although the effects on clinical cardiovascular outcomes are currently unknown. One possible explanation is that GH administration increases the expression of hepatic LDL receptor mRNA and the receptor number, thus reducing serum levels of total cholesterol.[29]

We found that triglyceride levels were independently and directly associated with the amount of abdominal fat but not with endogenous GH secretion in men. Prior studies have shown that triglyceride levels are related to the amount of total and/or abdominal visceral fat independently of age, gender, or obesity.[23-25,30,31]

Studies of GH administration in the adult GH-deficient population have shown less consistent effects on triglyceride levels versus cholesterol levels. Triglyceride levels may remain unchanged[9,28] or may decrease with GH treatment, particularly if the initial levels are elevated.[13] Consequently, we propose that GH exerts direct effects to reduce circulating levels of total and LDL cholesterol and indirect effects, probably via changes in body fat, on circulating triglyceride levels. However, it is possible that the closer association we observed between cholesterol levels and GH secretion than between cholesterol and body fat results from a common influence of adiposity on both GH secretion and cholesterol metabolism via some yet undefined metabolic intermediate.

We detected no significant relationships of IGF-I with any of the body fat or lipid measures in elderly individuals, except that IGF-I was positively related to triglyceride levels in men independently of body fat. In a small study of physically fit young GH-deficient adults,[32] baseline levels of total cholesterol were inversely related to circulating levels of IGF-I, but in a much larger study of healthy elderly men and women, there was no significant independent relationship of total cholesterol with IGF-I levels after adjustment for confounds such as the BMI,[33] consistent with the present findings.

IGFBP-3 levels were significantly higher in women than in men, but there were no relationships of IGFBP-3 with any body fat or lipid measures in either sex. In contrast, Ceda et al[33] have recently reported a significant positive relationship between IGFBP-3 and HDL levels in a pooled group of healthy elderly women and men independently of age and BMI.

The current data are thus consistent with the concept that in the elderly, lipid indices of cardiometabolic risk are more closely related to measures of spontaneous nocturnal GH secretion than to circulating levels of IGF-I or IGFBP-3. GH exerts its lipolytic effect on adipocytes directly, whereas IGF-I

appears to act indirectly via a reduction in insulin levels.[34] GH administration in humans reduces LDL levels, whereas IGF-I administration does not.[35] Similarly, in rats, IGF-I administration does not increase LDL receptor mRNA and LDL receptor number or reduce LDL and IDL cholesterol.[36] Thus, the stimulatory effect of GH on the hepatic LDL receptor is not reproduced by substitution with IGF-I. Finally, in healthy men, triglyceride levels are increased by administration of GH and reduced by treatment with IGF-I.[37]

It is possible that in our subjects, the sleep quantity and quality may have been disturbed in an unfamiliar environment in a manner that would diminish nocturnal GH secretion. However, the effect of such an underestimation would likely be to diminish rather than to augment any associations of GH secretion with body fat and lipids. We therefore conclude that any effect of sleep disturbance on nocturnal GH secretion does not invalidate our observations.

A single-slice axial view of the abdomen, whether by MRI or CT scanning, may not be as valid as a volumetric method, such as multislice MRI scanning, in quantifying total abdominal fat[38] and establishing its relationships with metabolic indices.[39] Consequently, we included a measure of axial (MRI) and total abdominal (DEXA) fat and an anthropometric measure (WHR). The current observations appear valid because these measures were highly intercorrelated and the relationships of GH secretion with the metabolic variables were similar regardless of the abdominal fat measure used.

In summary, in healthy elderly non-obese men and women, endogenous nocturnal GH secretion is predictive of total and LDL cholesterol levels independently of total or abdominal fat, and thus may serve as a separate cardiometabolic risk factor in this population. Whether GH supplementation will exert a beneficial effect on cardiovascular risk, morbidity, and mortality in the somatopausal elderly remains to be determined.

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