Basal Growth Hormone Levels in Women Are Positively Correlated With High-Density Lipoprotein Cholesterol and Apolipoprotein A-I Independently of Insulin-Like Growth Factor 1 or Insulin

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Previous studies in growth hormone (GH)-deficient or acromegalic patients yielded contradictory results on the effect of GH on lipoprotein metabolism. In a cross-sectional study, we analyzed the relationships between unstimulated GH, insulin-like growth factor 1 (IGF1), insulin, and lipoprotein metabolism in 44 non-obese young women. On univariate analysis, basal serum levels of GH correlated positively with triglycerides, high-density lipoprotein (HDL) cholesterol, apolipoprotein A-I (apoA-I) and apoA-II and negatively with lipoprotein lipase (LPL) activity. These associations remained significant on multivariate analyses that, in addition to GH, took into account the effects of insulin or C-peptide, as well as the effects of total, protein-bound, or free IGF1. In most cases, the relationships of these lipid parameters with insulin/C-peptide and IGF1 and its free or protein-bound subfractions were opposite of those with GH and not significant. Thus, GH appears to regulate the metabolism of HDL and triglycerides independently of IGF1 and insulin.

SEVERAL IN VITRO EXPERIMENTS and clinical studies of patients with either a deficiency or an excess of growth hormone (GH) have pointed to a regulatory role of GH in lipid metabolism. In vitro, GH stimulates the secretion of free fatty acids from adipose tissue[1] and of triglycerides and very–low-density lipoprotein (VLDL) from liver cells.[2] In the latter, GH also increases expression of the low-density lipoprotein (LDL) receptor.[3,4] In agreement with the modulation of LDL receptor activity by GH, GH-deficient patients have elevated levels of LDL cholesterol, which decrease with substitution therapy.[5] Contradictory results have been reported on the effect of GH on high-density lipoprotein (HDL) metabolism. Substitution therapy of GH deficiency was associated with decreasing levels of HDL cholesterol and apolipoprotein A-I (apoA-I) in some studies,[5,6] but also with significant increases or no change in others.[7-10] Administration of GH to patients with osteoporosis or short children without GH deficiency either did not alter or even decreased HDL cholesterol levels.[11-14] In acromegalic patients, hypophysectomy caused an increase in HDL cholesterol.[15] In agreement with the HDL-raising effects of GH, we found in a previous cross-sectional study of a population without GH-related disorders a positive correlation between basal GH levels and HDL cholesterol.[16]

It is not entirely understood how GH affects HDL metabolism, either at the site of the regulating hormones or at the site of the regulated steps in lipoprotein metabolism. Generally, GH exerts some of its regulatory actions directly via binding to specific GH receptors on peripheral cells. Other effects are mediated indirectly either via insulin-like growth factor 1 (IGF1) or via insulin.[17,18] The interaction of GH and IGF1 is further complicated by the fact that the majority of IGF1 in plasma is bound to various IGF binding proteins (IGFBPs) that prolong the half-life of IGF1 in plasma and interfere with the interaction of the active, free IGF1 with its cellular receptors.[18,19] In the plasma, approximately 20% of IGF1 is associated with a complex of 35 to 45 kd, and approximately 80% with a complex of 150 kd molecular mass. The latter complex contains IGF1, IGFBP-3, and acid-labile substance. Only 1% of IGF1 circulates as a free and active hormone.[18,19]

To obtain more detailed insight into the possible regulation of HDL metabolism by GH under physiological conditions, we performed another cross-sectional population study in young women free of GH-related diseases. In addition to GH, we measured insulin, C-peptide, and total IGF1, as well as its free and protein-bound subfractions. We limited this study to women, since in men GH is secreted in rare pulses of high concentration so that the diurnal time course of GH levels is discontinuous.[20] Moreover, we included only young and non-obese women to avoid the confounding effects of body mass index and age on both lipid metabolism and hormone levels.[16] Finally, we also related the hormones to the activities of plasma enzymes that modify the metabolism of HDL[21-24] to obtain information on the mechanisms regulated by GH. These enzymes include lecithin:cholesterol acyltransferase (LCAT), which esterifies cholesterol, cholesteryl ester transfer protein (CETP), which exchanges cholesteryl esters and triglycerides between HDL and apoB-containing lipoproteins, and the lipolytic enzymes lipoprotein lipase (LPL) and hepatic lipase (HL).[21-24]

SUBJECTS AND METHODS

Probands and Samples

We investigated the relationships between basal GH, IGF1, insulin, and lipid metabolism in 44 healthy female students age 21 to 34 years. Table 1 summarizes the anthropometric, metabolic, and endocrinologic data from these volunteers.

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Table 1. Anthropometric, Metabolic, and Endocrinologic Data for the 44 Women

Parameter	Mean	Range
Age (yr)	24.3	21-34
BMI (kg/m^2)	20.2	18.1-25.8
Triglycerides (mg/dL)	94	46-210
Cholesterol (mg/dL)	190	121-251
HDL cholesterol (mg/dL)	67	36-90
LDL cholesterol (mg/dL)	104	64-170
ApoA-I (mg/dL)	163	102-228
ApoA-II (mg/dL)	41	27-57
ApoB (mg/dL)	67	42-103
LCAT (nmol/mL/h)	18.0	11.4-24.6
LPL (nmol/mL/h)	18	10-46
HTGL (nmol/mL/h)	26	10-94
CETP (nmol/mL/h)	72	22-165
Insulin (ng/mL)	0.59	0.25-1.39
C-peptide (ng/mL)	1.6	1.1-2.4
GH (ng/mL)	1.58	0.09-9.05
Total IGF-I (ng/mL)	145	28-361
Free IGF1 (ng/mL)	1.8	0.8-5.8
40-kd IGF1 (ng/mL)	31.4	15.8-106.0
150-kd IGF1 (ng/mL)	152	87-228

NOTE. The arithmetic mean value and range are shown, except for triglycerides, CETP, LPL, HL, insulin, GH, total IGF1, free IGF1, and 40-kd IGF1, which are the geometric mean and range.

Venous blood samples without additives were drawn after at least 12 hours of fasting between 8:00 AM and 9:30 AM. Venipuncture was performed after the probands had been seated for at least 15 minutes. Serum blood was taken for measurement of lipids, lipoproteins, apolipoproteins, basal GH, insulin, and C-peptide levels. EDTA-blood was taken for quantification of IGF1 and its subfractions, as well as for determination of the activities of LCAT, CETP, HL, and LPL. EDTA-blood samples were placed on ice until centrifugation. Samples for determination of LPL and HL activities were collected 15 minutes after intravenous injection of 70 IU heparin (Roche, Basel, Switzerland) per kilogram body weight. Serum and plasma samples were obtained by centrifugation at 800 × *g* for 15 minutes at 4°C. Aliquots were stored at −70°C until analyzed.

Determination of Lipids, Lipoproteins, and Apolipoproteins

Serum concentrations of triglycerides and cholesterol were quantified enzymatically with an autoanalyzer (Hitachi/Boehringer, Mannheim, Germany). The HDL cholesterol level was measured after precipitation of apoB-containing lipoproteins with phosphotungstic acid/$MgCl_2$ (Boehringer Mannheim). LDL cholesterol was calculated using the Friedewald formula.[25] Concentrations of apoA-I, apoA-II, and apoB were determined with modified commercially available immunoturbidimetric assays (Boehringer Mannheim).

Isolation of Lipoproteins and ApoA-I

LDL ($1.006 < d < 1.063$ g/mL), required for the determination of CETP activity, and HDL ($1.063 < d < 1.21$ g/mL), required for the preparation of apoA-I, were isolated from plasma by sequential ultracentrifugation.[26] ApoA-I, needed for determination of LCAT and CETP activities, was isolated from delipidated HDL by reversed-phase high-performance liquid chromatography.[27]

Determination of LCAT Activity

The plasma activity to esterify radiolabeled cholesterol was determined using apoA-I–containing lipoproteins as substrate donors.[28,29] This assay was previously shown to correlate with LCAT mass.[30] Ten micrograms of apo A-I was incorporated into liposomes that were prepared by the method of Batzri and Korn[31] and contained 1 μCi ^{3}H-cholesterol (New England Nuclear, Boston, MA), 93 μg egg yolk lecithin, and 11 μg unesterified cholesterol (molar ratio, 4:1) in 140 μL assay buffer with 10 mmol/L Tris HCl, pH 7.4, 5 mmol/L EDTA, and 150 mmol/L NaCl. After 30 minutes' preincubation at 37°C, 50 μL assay buffer with 80 g/L bovine serum albumin and 10 μL mercaptoethanol was added. Esterification of ^{3}H-cholesterol was started by addition of 15 μL plasma and finished after 30 minutes by addition of 4 mL chloroform:methanol 2:1 (vol/vol). Phases were separated by addition of 1.5 mL 150-mmol/L NaCl and subsequent centrifugation for 10 minutes at 2,000 × *g*. Unesterified cholesterol and cholesteryl esters in the lower phase were separated by thin-layer chromatography and counted for radioactivity. LCAT activity was calculated by multiplying the percentage of radiolabeled cholesterol esters produced per time unit by the concentration of unesterified cholesterol in the substrate.

Determination of CETP Activity

CETP activity was determined also as described previously.[28,32,33] In this assay, apoA-I–containing proteoliposomes were used as donors and LDLs as acceptors of radiolabeled cholesterol esters. Proteoliposomes containing 3 mg apoA-I, 7 mg egg yolk lecithin, 1.16 mg unesterified cholesterol, 77.5 μg cholesteryl oleate, and 10 μCi ^{3}H-cholesteryl oleate (New England Nuclear) (molar ratio of phosphatidylcholine:unesterified cholesterol:cholesteryl esters, 75:25:1) were prepared by the cholate dialysis method.[34] Aliquots with 25 μg apoA-I were mixed at a final volume of 300 μL with 100 μg LDL in a buffer with 39 mmol/L sodium phosphate, pH 7.4, 60 mmol/L NaCl, 5 mmol/L EDTA, and 1.4 mmol/L dithiobisnitrobenzoic acid as a LCAT inhibitor. The assay was started by addition of 5 μL plasma and finished after 20 minutes' incubation at 37°C by placing the sample on ice. LDL was then precipitated with 5 mmol/L $MgCl_2$ and dextran sulfate (weight ratio to LDL protein, 0.01). Radioactivity in the supernatant and infranatant was counted separately. CETP activity was calculated as the transferred cholesteryl oleate per time unit according to the percentage of the transferred label.

Determination of Lipolytic Plasma Activities

Plasma activities of HL and LPL were determined according to the method of Baginsky[35] with some modifications. For measurement of LPL activity, postheparin plasma was mixed with 100 mmol/L sodium dodecyl sulfate (SDS) solution (1:1 vol/vol). For measurement of HL activity, plasma was diluted with 0.2 mol/L Tris HCl, pH 8.8 (1:1 vol/vol). The substrate for both enzymes was prepared by mixing 200 mg trioleylglycerol with 25 μCi tri-[^{14}C]-oleylglycerol per 1 mL toluene. For determination of LPL activity, 1 mL was removed from this stock solution, dried under nitrogen, mixed with 6.8 mL LPL emulsifying agent (15% arabic gum in 0.2 mol/L Tris, pH 8.2), sonicated, and then mixed 3:4 with a solution containing 0.35 mol/L Tris HCl, pH 8.2, 0.16 mol/L NaCl, and 125 mg/mL bovine serum albumin. Heat-inactivated serum as a source of apoC-II was then added, and the mixture was incubated for 80 minutes at 37°C. For determination of HL activity, dried trioleylglycerol was mixed with HL emulsifying agent (15% arabic gum in 0.2 mol/L Tris, pH 8.8), sonicated, and mixed 1:2 with a solution containing 0.23 mol/L Tris HCl, pH 8.8, 1.25 mol/L NaCl, and 83 mg/mL BSA. The mixture was then incubated for 80 minutes at 37°C. The assay was performed by adding 10 μL postheparin plasma to the appropriate substrate and incubating for 60 minutes at 37°C. The reaction was terminated by addition of isopropanol/sulfuric acid (1:9 vol/vol). Subsequently, the lipids were extracted with chloroform:methanol (2:1 vol/vol), and radioactivity was measured by liquid scintillation counting.

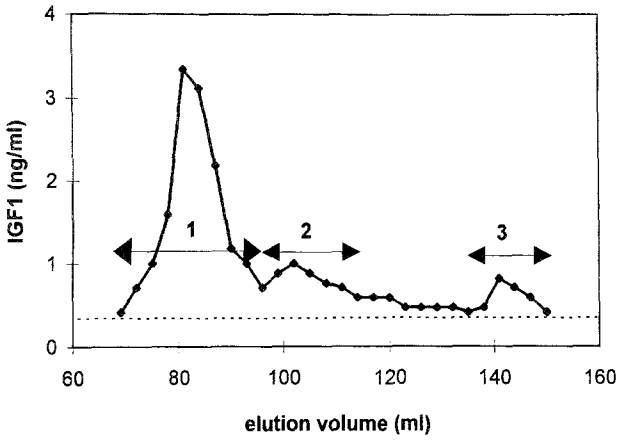

Fig 1. Size distribution of IGF1 in plasma. Plasma (500 μL) was separated by gel filtration using the FPLC system, a Pharmacia 16/100 column with 180 mL Sephacryl S-200 HR (Pharmacia) as the stable phase, and a 0.15-mol/L Tris HCl buffer (pH 7.4) as the mobile phase. The eluted volume was collected in fractions of 3 mL. IGF1 was quantified in these fractions by radioimmunometric assay. The profile shows mean values obtained by gel filtration and subsequent IGF1 quantification of 3 different plasmas. For quantification of protein-bound 150-kd IGF1 and 40-kd IGF1, as well as free IGF1, the following gel filtration fractions were pooled: 69 to 93 mL (no. 1, 150-kd IGF1), 93 to 114 mL (no. 2, 40-kd IGF1), and 132 to 153 mL (no. 3, free IGF1). Compared with the concentration of total IGF1 in plasma, IGF1 recovery in these 3 fractions was 85% ± 3%. The dashed line gives the lower detection limit of the IGF1 assay.

All radiometric assays for determination of lipid-transfer or lipolytic activities were performed as duplicates in series of a maximal 10 samples. The intraassay and interassay CVs were less than 8% and 15%, respectively.

Determination of Hormone Concentrations

Serum levels of insulin and C-peptide were measured by radioimmunoassays purchased from DPC/Biermann (Bad Nauheim, Germany). Serum concentrations of basal GH and plasma concentrations of IGF1 were determined by radioimmunometric assays from Medgenix (Fleurus, Belgium) and Nichols (San Juan Capistrano, CA), respectively. All hormone measurements were performed in single series and as duplicates. Results were only accepted if they differed by less than 10%.

IGF1 levels were measured either in total plasma after extraction of binding proteins according to the method described by Daughaday et al,[36] or in fractions obtained by gel filtration of 500 μL plasma. Gel filtration was performed at 4°C with a flow rate of 1 mL/min by use of the FPLC system (Pharmacia, Bromma, Sweden), a Pharmacia 16/100 column with 180 mL Sephacryl S-200 HR (Pharmacia) as the stable phase, and a 0.15-mol/L Tris HCl buffer (pH 7.4) as the mobile phase. The system was calibrated using a gel filtration calibration kit from Pharmacia. In initial experiments, three different plasma samples were fractionated for determination of IGF1 concentrations. The eluted volume was collected in fractions of 3 mL. IGF1 was quantified in these fractions. IGF1 immunoreactivity peaked in three proportions whose maxima were eluted from the column with an apparent molecular mass of about 150, 40, and 7.6 kd (Fig 1). For quantification of IGF1, fractions containing protein-bound IGF1 (40-kd IGF1 and 150-kd IGF1) and free IGF1 (7.6 kd) were pooled in three proportions as indicated in Fig 1, lyophilized, and resolved in 1 mL distilled water for quantification of IGF1 by radioimmunometric assay. Compared with the concentration of total IGF1 in plasma, the recovery of IGF1 in these three fractions was 85% ± 3%.

Statistical Analysis

Statistical regression analyses were performed by use of the statistical package for the Social Sciences (SPSS).[37] Univariate regression analysis was performed by Pearson's test. Multivariate analysis was performed directly on all indicated parameters. Values for triglycerides, CETP, LPL, HL, GH, insulin, total IGF1, free IGF1, and 40-kd IGF1 did not exhibit gaussian frequency distribution and were therefore analyzed statistically after Ig_e transformation.

RESULTS

Within the small age and body mass index (BMI) intervals of the women analyzed, age correlated significantly with IGF1 (−.37), LDL cholesterol (.36), and apoB (.35; all $P < .05$). The BMI had no significant correlation with any hormone or lipid parameter.

Table 2 summarizes the results of bivariate regression analysis of the relationships between hormones and parameters of lipoprotein metabolism. GH correlated positively with triglycerides, HDL cholesterol, apoA-I, and apoA-II and negatively with LPL. Insulin, C-peptide, total IGF1, and free IGF1 did not correlate significantly with any lipid parameter. The 40-kd IGF1 had significant negative correlations with total cholesterol and HDL cholesterol. The 150-kd IGF1 correlated significantly and negatively with apoB.

GH correlated negatively with total IGF1 ($P < .05$) and with its protein-bound and free subfractions (not significant). Significant positive correlations were found between total IGF1 and

Table 2. Bivariate Correlations Between Hormones and Parameters of Lipoprotein Metabolism

Parameter	Ig_e Insulin	C-Peptide	Ig_e GH	Ig_e Total IGF1	Ig_e Free IGF1	Ig_e 40-kd IGF1	150-kd IGF1
Ig_e triglycerides	.14	.29	.40†	−.04	.01	−.23	−.25
Total cholesterol	.14	−.08	.26	−.15	−.13	−.32*	−.20
HDL cholesterol	.03	−.22	.39†	−.20	−.29	−.34*	.22
LDL cholesterol	.08	−.01	.00	−.06	−.25	−.24	−.25
ApoA-I	.10	.04	.40†	−.19	−.23	−.26	−.12
ApoA-II	.14	.27	.43†	−.17	−.17	−.20	−.11
ApoB	.19	.13	.28	−.14	−.08	−.21	−.52†
LCAT	−.24	−.20	.03	.05	−.21	−.02	−.07
Ig_e CETP	−.13	−.02	−.15	−.08	−.07	.11	−.15
Ig_e LPL	−.07	−.04	−.31*	−.03	−.02	−.02	−.05
Ig_e HL	−.16	−.08	−.09	.02	−.04	−.13	−.09

*$P < .05$.
†$P < .01$.

free IGF1 and 150-kd IGF1. Insulin and C-peptide correlated with one another, but not with GH or IGF1.

Because the age and BMI did not correlate significantly with any lipid parameter that had a significant association with an endocrinologic parameter, we limited the multivariate analysis to relationships between insulin/C-peptide, IGF1, and GH (Table 3). The positive correlations of basal GH with HDL cholesterol, apoA-I, and apoA-II, as well as the negative association with LPL, remained significant and were independent also on multivariate analysis that took into account C-peptide (or insulin; not shown) and total IGF1, free IGF1, or 150-kd IGF1 (Table 3). In all three models, GH, C-peptide, and IGF1 explained approximately 20% of the interindividual variation of HDL cholesterol and apoA-I, as well as approximately 30% of the interindividual variation in apoA-II. In this multivariate analysis, triglycerides correlated significantly with both C-peptide and basal GH, which, together with IGF1, explained approximately 30% of the interindividual variation in triglycerides. Finally, in our multivariate model, the correlation of apoB with 150-kd IGF1 remained significant and was independent of C-peptide and GH (Table 3).

Table 3. Multivariate Correlations Between C-Peptide, Free IGF1, and GH and Parameters of Lipoprotein Metabolism

Model	Model	(a) Ig_e Total IGF1 (b) Ig_e Free IGF1 (c) 150-kd IGF1	C-Peptide	Ig_e GH	R^2
Total cholesterol	a	.09	.04	.23	.07
	b	−.09	−.05	.23	.08
	c	−.17	−.05	.23	.09
Ig_e triglycerides	a	−.01	.37†	.39†	.29
	b	.09	.35*	.45†	.28
	c	−.20	.34*	.41†	.31
HDL cholesterol	a	−.09	−.07	.36	.16
	b	−.24	−.18	.32*	.23
	c	.28	−.17	.40†	.25
LDL cholesterol	a	−.07	.02	−.02	0
	b	−.26	−.03	−.05	.07
	c	−.25	−.01	−.04	.06
ApoA-I	a	−.10	.22	.36†	.22
	b	−.16	.08	.38†	.19
	c	−.06	.09	.40†	.17
ApoA-II	a	−.09	.37†	.40†	.33
	b	−.08	.32*	.46†	.30
	c	−.05	.32*	.46†	.29
ApoB	a	−.09	.22	.25	.13
	b	−.02	.16	.30	.11
	c	.49†	.17	.24	.35
LCAT	a	.10	−.26	.06	.07
	b	−.22	−.21	−.03	.08
	c	−.07	−.19	0	.04
Ig_e CETP	a	−.12	−.09	−.18	.05
	b	−.10	−.04	−.17	.03
	c	−.17	−.04	−.17	.05
Ig_e LPL	a	−.13	0	−.34*	.11
	b	−.08	−.08	−.33*	.11
	c	0	−.08	−.31	.10
Ig_e HL	a	−.04	.01	−.20	.04
	b	−.06	−.10	−.12	.02
	c	−.12	−.02	−.20	.05

NOTE. a, b, and c denote the 3 models tested, ie, total IGF1, C-peptide, and basal GH (a), free IGF1, C-peptide, and basal GH (b), or IGF1 in the 150-kd complex, C-peptide, and basal GH (c).

*$P < .05$.

†$P < .01$.

Table 4. Bivariate Correlation Coefficients Between Lipids, Apolipoproteins, and Enzyme Activities in the Students

Parameter	LCAT	Ig_e CETP	Ig_e LPL	Ig_e HTGL
Total cholesterol	.01	−.20	.25	−.21
Ig_e triglycerides	−.14	−.19	−.03	−.06
HDL cholesterol	.03	−.09	−.12	−.31*
LDL cholesterol	.09	−.05	.35*	.10
ApoA-I	.16	−.18	−.16	−.33*
ApoA-II	−.10	.13	−.27	−.19
ApoB	.10	−.25	.24	−.15
LCAT	—	.08	−.27	.13
Ig_e CETP		—	−.36*	.29*
Ig_e LPL			—	.05
Ig_e HL				—

*$P < .05$.

Table 4 presents correlations for the plasma activities of lipid-transfer proteins and lipolytic enzymes with other parameters of lipid metabolism. HTGL correlated negatively with HDL cholesterol and apoA-I and positively with CETP. LPL correlated positively with LDL and negatively with CETP. Except for the negative correlation between GH and LPL, no enzyme had significant correlations with any hormone (Tables 2 and 3).

DISCUSSION

This study of healthy students extends our previous observation[16] that basal GH levels in women are positively correlated with HDL cholesterol and apoA-I (Tables 2 and 3). We have previously found that this relationship is independent of hormonal contraception and menopause, which are both associated with changes in HDL cholesterol and GH levels.[16] In this study, we have demonstrated that correlations between basal GH and HDL are independent of insulin/C-peptide, as well as IGF1 and its subfractions (Table 3). Thus, GH appears to influence HDL metabolism directly rather than indirectly via those mediators.

One may argue that basal GH levels are not representative, since unstimulated GH levels oscillate with time and the stress of venipuncture and blood sampling can even induce secretion of GH.[20] However, we limited this cross-sectional study to women, in whom the 24-hour concentration profile of GH is more continuous.[38,39] Moreover, blood samples were obtained in the morning, when secretion peaks are less likely,[40] and the probands rested for at least 15 minutes before venipuncture to avoid at least physical stress. Finally, the positive association between GH and HDL in this study reproduces a finding of another study in an independent cohort.[16] A positive correlation between GH and HDL cholesterol is in agreement with HDL cholesterol levels being lower in GH-deficient children versus BMI-matched controls.[41] Likewise, in most[7-9,42] but not all[6,13,14] clinical studies, treatment of GH-deficient patients with GH increased HDL cholesterol.

GH exerts many of its effects on metabolism indirectly via IGF1.[17,18] Therefore, and since IGF1 levels are more stable intraindividually than unstimulated GH levels,[17,18] we also tested by regression analysis whether total, free, or protein-

bound IGF1 is correlated with HDL cholesterol. Interestingly, these correlations were insignificant and negative (Tables 3 and 4). This lack of association is in agreement with the results of a clinical study wherein treatment of osteoporosis with IGF1 did not alter HDL cholesterol levels.[43] However, the negative correlation is in contrast to another study wherein administration of IGF1 to patients with non–insulin-dependent diabetes mellitus increased HDL cholesterol.[44] However, this treatment achieved unphysiologically high plasma concentrations of IGF1. Interestingly, GH also exerts other effects on lipoprotein metabolism independently of IGF1. For example, lipoprotein(a) was increased by GH but decreased by IGF1.[43] Moreover, GH but not IGF1 stimulates expression of LDL receptors in cultured hepatocytes.

In addition to IGF1, we excluded insulin as a hormone by which GH exerts its regulatory effects on HDL metabolism (Tables 2 and 3). It thus appears that GH regulates HDL directly rather than through its indirect mediators.

We also used regression analysis to identify the mechanism by which GH increases HDL levels. Several investigators reported that LCAT, CETP, LPL, and HL are important factors that determine interindividual variation in HDL cholesterol levels.[21-24] In our study, only LPL had a significant association with GH. On multivariate regression analysis, GH explained about 30% of the intraindividual variation in LPL activity. The negative correlation between GH and LPL is in agreement with previous clinical observations in both acromegalic and GH-deficient patients.[45,46] LPL activity was low in acromegalic patients and increased after extirpation of the adenoma.[45] Replacement of GH-deficient patients led to decreases in LPL plasma activity.[46] More recent studies found that GH inhibits secretion of LPL from adipose tissue at a posttranscriptional step.[6,47,48] However, the negative association between GH and LPL activity is unlikely to explain the positive association between GH and HDL, since LPL does not correlate significantly with HDL and since low LPL activity is associated with low HDL cholesterol levels.[22-24,49]

Several investigators have also observed an inhibitory effect of GH on HL activity.[6,45,46] Since in our study and several other[22-24] HL activity was negatively correlated with HDL cholesterol, we expected that GH exerts its HDL-raising effect through inactivation of HL. However, the negative correlation between GH and HL activity observed in our study was not significant (Tables 2 and 3).

GH mobilizes lipids from adipose tissue not only by inhibition of LPL but also by activation of hormone-sensitive lipase.[50] Unfortunately, we had no biopsies available to investigate the associations between basal GH levels and the activity of hormone-sensitive lipase.

In conclusion, our study further confirms our previous notion that GH is an important positive determinant of HDL cholesterol levels. Moreover, GH appears to influence HDL metabolism indirectly of IGF1 or insulin.

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