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Articles

Magnetic Resonance Imaging–Assessed Adipose Tissue and Serum Lipid and Insulin Concentrations in Growth Hormone–Deficient Adults

Effect of Growth Hormone Replacement

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Abstract

Abstract The visceral and subcutaneous abdominal adipose tissue (AT) areas and the subcutaneous hip AT area were assessed by magnetic resonance imaging (MRI) in relation to serum lipid and plasma insulin levels in 12 growth hormone–deficient (GHD) adults before and after 6 months of replacement therapy with recombinant human growth hormone (rhGH) and in 12 healthy control subjects. Compared with control subjects, GHD patients had a significantly increased amount of visceral AT, which was inversely related with plasma HDL cholesterol and positively correlated with plasma triglyceride levels. Visceral AT was not associated with plasma total and LDL cholesterol or plasma insulin concentrations. GHD patients also had elevated serum total cholesterol, LDL cholesterol, and triglyceride levels compared with control subjects. After 6 months of rhGH replacement therapy the mean visceral, subcutaneous abdominal, and subcutaneous hip AT areas and serum concentration of total cholesterol decreased significantly, whereas serum HDL cholesterol concentration increased significantly. No significant correlations were found between changes in the amount of AT and changes in serum lipid and plasma insulin levels.

Top
Abstract
Introduction
Methods
Results
Discussion
References

Key Words: adipose tissue • serum lipids • plasma insulin • magnetic resonance imaging • growth hormone–deficient adults

Introduction

Recent data show that GHD in adults is associated with increased mortality due to cardiovascular causes despite adequate replacement therapy with glucocorticoids, thyroxine, and sex hormones.[1] GHD is associated with an increased BF mass and a decreased fat-free mass.[2] [3] [4] [5] [6] Moreover, the increased amount of BF is located mainly in the abdominal region, and the amount of visceral fat appears to decrease during replacement therapy with rhGH.[3] GHD patients have high triglyceride and total serum cholesterol levels due to increased

Top
Abstract
Introduction
Methods
Results
Discussion
References

LDL-C[7] [8] [9] [10] [11] [12] and low HDL-C,[10] [11] and insulin sensitivity is reduced.[13] [14] The mechanisms underlying these lipid profiles and insulin resistance in GHD patients are not well understood.[15] To our knowledge, no study has investigated the association between visceral AT and plasma lipid and insulin concentrations in GHD adults before and after rhGH replacement therapy.

The aim of the study was to assess the relation between the visceral abdominal, subcutaneous abdominal, and subcutaneous hip AT areas as assessed by MRI and serum lipid and plasma insulin levels in healthy control subjects and GHD adults before and after 6 months of rhGH replacement therapy.

Methods

Top
Abstract
Introduction
Methods
Results
Discussion
References

Subjects

Seven men and five women (25 to 60 years of age) known to have GHD for at least 2 years (mean, 11.3 years; range, 3 to 20 years) were included in the study. Hypopituitarism was treated according to general standards. Secondary hypothyroidism (11 patients) was treated with levothyroxine 75 to 200 μg daily (average dose, 134 μg) to obtain free thyroxine plasma levels in the upper part of the normal range. Secondary hypogonadism in 6 men was treated with testosterone undecanoate 80 mg BID PO or testosterone esters 250 mg IM every 3 weeks, and 3 women were treated with cyclic estrogen (30 μg ethinylestradiol) and progesterone (150 μg levonorgestrel) therapy. Secondary adrenal insufficiency was present in all patients and was treated with cortisone acetate 10 to 37.5 mg daily (average dose, 28.3 mg). During rhGH treatment no adjustment in any replacement dose of any patient was made. GHD was defined as a peak plasma growth hormone concentration ≤5 μg/L to arginine infusion. After arginine infusion, GH was not detectable in 10 patients; in the other 2 patients peak plasma GH concentrations were ≤1.0 and ≤2.9 μg/L.

The control group consisted of 12 healthy adult volunteers (7 men and 5 women) matched for age, body height, weight, and BMI (Table 1).

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Table 1. Characteristics of Patients and Control Subjects

Design

The study had a randomized double-blind design in which rhGH (Pharmacia AB, Peptide Hormones) or placebo was administered for 6 months. Thereafter, all GHD patients were treated with daily subcutaneous injections of rhGH for 6 months. The first month's dose was 0.125 IU · kg^{-1} · wk^{-1}, followed by 0.25 IU · kg^{-1} · wk^{-1} for 5 months. MRI assessments were performed at 6 and 12 months, and in this study we describe the subjects who received placebo during the first half-year and rhGH for the second half-year. The patients were studied as outpatients at the Department of Endocrinology. The aims and methods of the study were explained to the patients and control subjects, and an informed consent was obtained. The study was approved by the ethics committee of the University Hospital of Utrecht.

Body Composition

Body height was measured to the nearest millimeter by using a wall-mounted stadiometer, and body weight was measured to the nearest 0.05 kg. BMI was calculated as weight in kilograms divided by height in meters squared.

BF was assessed by bioelectrical impedance analysis (tetrapolar BIA-101 analyzer, RJL Systems) based on resistance and reactance measurements. Resistance and reactance were measured in ohms after application of an alternating current of 800 μA at 50 kHz with the electrodes placed as described by Lukaski et al.[16]

AT area at the abdominal and hip level was assessed by using MRI scanning. MRI was performed with a 1.5-T whole-body scanner (Gyroscan S15, Philips Medical Systems) by using a multislice inversion recovery sequence with a 300-msec inversion time, 820-msec repetition time, and 20-msec echo time. This sequence highlights the AT while effectively suppressing all other tissues.[17] A transverse scan at the abdominal level consisting of three 10-mm-thick slices with a gap of 2 mm was taken halfway between the lower rib margin and the iliac crest. Similarly, at the hip level a scan was taken at the level of the great trochanter. We used a 179x256 acquisition matrix

and a 500-mm field of view with four averages at the abdominal level and two averages at the hip level. Increasing the number of signal averages suppresses motion artifacts. The acquisition time of one experiment was 15 minutes (10 minutes for the abdominal area and 5 for the hip area).

Analysis of the 12-bit images was performed on a Sparc-2 workstation (Sun) by using software developed at the Department of Biomedical Engineering at the Free University Hospital, Amsterdam. In this program, partial volume effects are taken into account as described by Fowler et al.[18] The average of the three slices per examination level was used in the statistical analysis. A seed-growing method was used for calculating AT areas. At the abdominal level the area of visceral AT was first distinguished from the area of subcutaneous AT by tracing a line. After a seed-point was positioned in a part of the AT depot with typical signal intensity, the boundaries of the defined region were grown toward interactively set threshold intensities. All measurements were performed by the same observer and repeated in a second session. The observer was blinded with regard to the treatment group. The intraobserver differences, which were expressed as coefficients of variation,[19] were 2.9% for the visceral AT area in healthy control subjects and 2.0% and 3.7% before and after rhGH replacement in GHD adults, respectively; respective values for the subcutaneous abdominal AT area were 0.9%, 0.9%, and 1.7%, and for the subcutaneous hip AT area they were 0.8%, 0.9%, and 1.4%. The visceral/subcutaneous AT ratio was calculated as the visceral AT area divided by the subcutaneous AT area at the abdominal level.

Biochemical Analysis

Blood samples were drawn in the morning after an overnight fast. Plasma GH concentration was determined by using the radioimmunoassay of the Oris Industry Co, which has a lower detection limit of 0.50±0.04 mIU/L (1 µg/L=1 ng/mL=2 mIU/L); the intra- and interassay coefficients of variation were 7.7% and 11%, respectively. Cholesterol and triglyceride levels were measured by using a fully automated Hitachi 717 analyzer; reagents for the enzymatic applications were obtained from Boehringer Mannheim. The phosphotungstic acid–magnesium chloride precipitation method was used to measure HDL-C. LDL-C was calculated by the Friedewald formula (in millimoles per liter, LDL-C=total cholesterol-0.45xtriglyceride-HDL-C).[20] Insulin concentration was measured by radioimmunoassay.

Statistical Analyses

Statistical analyses were performed with the SPSS PC program (version 4.0.1) (SPSS). All values are expressed as mean±SEM. The nonparametric Mann-Whitney *U* test was used to test for differences between patients and control subjects and between men and women. Wilcoxon's signed-rank test was used to test for the effects of rhGH replacement. Spearman's rank correlation test was used to assess the relationships among the variables. Differences were considered significant if the probability value was <.05.

Results

Top
Abstract
Introduction
Methods
Results
Discussion
References

Total BF, AT Areas, and Serum Lipid and Plasma Insulin Levels in GHD Patients and Healthy Control Subjects

Compared with control subjects, GHD patients had a significantly greater amount of total BF as assessed by bioelectrical impedance analysis. Visceral AT area (*P*=.003) and subcutaneous abdominal AT area (*P*=.013) were significantly larger in the patients, whereas no difference was found in subcutaneous hip AT area (*P*=.299). The patients had a significantly higher visceral/subcutaneous AT ratio than did the control subjects (*P*=.033) (Table 2). GHD patients had higher concentrations of total cholesterol (*P*=.024), LDL-C (*P*=.049), and triglycerides (*P*=.035) than did healthy control subjects. The concentrations of HDL-C (*P*=.505) and plasma insulin (*P*=.614) did not differ between GHD patients and control subjects (Table 2).

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Table 2. Initial Amounts of Total BF and AT and Serum Lipid and Plasma Insulin Levels in GHD Patients and Healthy Control Subjects

Changes in Body Composition, AT Areas, and Serum Lipid and Plasma Insulin Levels After 6 Months of rhGH Replacement Therapy

Table 3 shows the changes in body composition, AT areas, and serum lipid and plasma insulin levels after 6 months of replacement therapy with rhGH. Body weight (*P*=.239) and BMI (*P*=.308) were not changed, but after 6 months of rhGH replacement therapy, total BF (*P*=.004), visceral AT area (*P*=.002), and subcutaneous abdominal AT area (*P*=.019) decreased. There was also a significant

reduction in subcutaneous hip AT area (*P*=.006) and the visceral/subcutaneous AT ratio (*P*=.004). The relative decreases in AT areas, denoted as a percentage of their baseline level, were 38.2% for visceral abdominal AT (men, 42.6%; women, 31.9%), 15.6% for subcutaneous abdominal AT (men, 15.3%; women, 16.2%), and 12.4% for subcutaneous hip AT (men, 14.0%; women, 9.7%). No significant differences were found in visceral AT area, subcutaneous abdominal AT area, and subcutaneous hip AT area between the healthy control subjects and the GHD patients treated for 6 months with rhGH. The serum concentration of total cholesterol decreased significantly (*P*=.049), whereas HDL-C increased significantly (*P*=.019). No significant change was found in serum LDL-C (*P*=.131) and serum triglyceride (*P*=.638) concentrations. After the 6-month replacement therapy with rhGH, no significant differences were found in serum concentrations of total cholesterol, HDL-C, and LDL-C between patients and control subjects. Compared with control subjects, serum triglyceride levels were still significantly higher in GHD patients after 6 months of replacement therapy with rhGH. Fasting plasma insulin concentrations increased significantly after 6 months of rhGH replacement therapy (*P*=.018) (Table 3).

View this table: [in this window] [in a new window]	**Table 3.** Changes From Baseline in Body Composition Variables and Serum Lipid and Plasma Insulin Levels After rhGH Replacement Therapy

Relations Between AT Areas and Serum Lipid and Plasma Insulin Levels

The visceral AT area was positively correlated with serum triglyceride (*r*=.560, *P*<.05) and inversely correlated with HDL-C (*r*=-.761, *P*<.01) levels in healthy control subjects and GHD patients before (*r*=.664, *P*<.01; *r*=-.554, *P*<.05, respectively) and after (*r*=.601, *P*<.05; *r*=-.518, *P*<.05, respectively) rhGH replacement therapy. Serum HDL-C level was inversely correlated with the amount of subcutaneous abdominal AT in control subjects (*r*=-.578, *P*<.05). In control subjects, serum concentrations of triglycerides (*r*=.546, *P*<.05) and HDL-C (*r*=-.655, *P*<.05) correlated with the visceral/subcutaneous AT ratio. In GHD patients at 6 months, serum concentrations of triglycerides correlated with the amount of subcutaneous abdominal AT area (*r*=.692, *P*<.05). A significant inverse relationship between serum LDL-C and visceral AT was found in GHD patients at baseline (*r*=-.578, *P*<.05), whereas these parameters were not correlated in control subjects or GHD patients after 6 months of rhGH replacement therapy. No significant correlations were found between AT areas and plasma insulin concentrations (Table 4).

View this table: [in this window] [in a new window]	**Table 4.** Spearman's Correlation Coefficients Between AT and Serum Lipid and Plasma Insulin Levels in GHD Patients and Healthy Control Subjects

No significant correlations were found between changes in AT areas and serum lipid or plasma insulin levels with the exception of a significant negative correlation between the changes in visceral AT area and serum total cholesterol concentration (*r*=-.507, *P*<.05) (Table 5).

View this table: [in this window] [in a new window]	**Table 5.** Spearman's Correlation Coefficients Between Changes From Baseline in AT and Changes in Serum Lipid and Plasma Insulin Levels After rhGH Replacement Therapy

Discussion

To our knowledge, this is the first study in which the AT deposition in different parts of the body is compared with plasma lipid and insulin concentrations in GHD adults. We found that GHD patients had a significantly increased visceral AT area that was inversely related with plasma HDL-C levels and positively correlated with plasma triglyceride levels, features known to be associated with increased risk of arteriosclerosis. After 6 months of rhGH replacement therapy the amount of visceral AT decreased markedly and was not significantly different from that of healthy control subjects. Notwithstanding the significant decrease of visceral AT, we still found an

Top
Abstract
Introduction
Methods
Results
Discussion
References

inverse association of visceral AT with HDL-C and a positive correlation of visceral AT with triglyceride levels. In contrast, visceral AT was not associated with the levels of plasma total cholesterol, LDL-C, or plasma insulin. GHD patients compared with control subjects had elevated serum total cholesterol, LDL-C, and triglyceride levels. After 6 months of rhGH replacement therapy, serum concentration of total cholesterol decreased significantly, whereas serum HDL-C concentration increased significantly; the triglyceride concentration remained unchanged.

Other investigators report that during rhGH replacement therapy serum concentrations of total cholesterol decrease[5 21 22 23] or remain unaltered,[6 24 25 26] that plasma triglyceride concentrations do not change significantly,[5 6 23 24 25] and that HDL-C concentrations increase[23 24] or remain unchanged.[22 26] The mechanisms responsible for the changes in plasma lipid concentrations are not well established. Two recent studies[23 27] show an increase in LDL receptor expression after rhGH replacement therapy, which may improve the clearance of VLDL and LDL from the circulation, thus accounting for the decrease in LDL-C. Furthermore, GH may stimulate the peripheral uptake of lipids into muscle, which is mediated by lipoprotein lipase. In addition, the effects of GH on plasma lipids may be regulated partly via insulin.[23]

The amount of visceral AT could also contribute to the altered lipid metabolism. Our study shows that adult GHD patients have an increased visceral and subcutaneous abdominal AT area compared with healthy control subjects. Six months of rhGH replacement therapy reduced the visceral, subcutaneous abdominal, and subcutaneous hip AT areas of the GHD patients. The most pronounced reduction was in the visceral AT area. Bengtsson et al[3] report similar findings after using computerized tomography to assess changes in visceral AT in GHD patients during rhGH replacement therapy. The more pronounced reduction in the visceral AT area compared with the other AT areas during rhGH replacement therapy might be due to a higher rate of lipolysis in the visceral fat cells and a GH-induced reduction of the antilipolytic effect of insulin on these fat cells.[28] Both in healthy control subjects and GHD patients at baseline and after 6 months of rhGH replacement therapy we found a significant negative correlation between HDL-C levels and visceral AT and a significant positive correlation between plasma triglyceride levels and visceral AT. The association between serum triglycerides and visceral AT is in agreement with the high lipolytic activity of intra-abdominal AT, which, by exposing the liver to high free fatty acid concentrations, stimulates triglyceride synthesis.[29]

The mechanism responsible for the association between visceral AT and HDL-C level is not well established. Després et al[29] suggest that the influence of visceral AT on HDL-C concentrations is mediated by hepatic triglyceride lipase, resulting in reduced HDL levels. In agreement with studies in obese subjects,[30 31 32] we found no significant correlations between the visceral, subcutaneous abdominal, and subcutaneous hip AT areas and total cholesterol and LDL-C levels in either healthy control subjects or GHD patients after 6 months of rhGH replacement therapy. This could be due to the particle size and composition of LDL-C.[32 33] Our finding that visceral AT was inversely related with LDL-C concentrations in GHD patients at baseline is difficult to explain and could partly be due to the above-mentioned composition of LDL-C.

Regardless of the influence of visceral AT on plasma lipid levels, the well-established association of visceral AT with insulin resistance must be taken into account.[34] In GHD adults insulin sensitivity is decreased.[35] Furthermore, O'Neal et al[36] report that 1 week after the initiation of rhGH replacement therapy in GHD patients mild glucose intolerance, hyperinsulinemia, and insulin resistance occurred that returned to baseline values except for a persistent modest elevation of fasting insulin levels. In accordance with other studies,[5 23] we found significantly increased fasting insulin concentrations after 6 months of rhGH replacement therapy. No significant correlations between plasma insulin and visceral AT area were observed in our study.

No significant correlations between changes in the visceral, subcutaneous abdominal, and subcutaneous hip AT areas and changes in serum lipid levels were found with the exception of a negative correlation between the decreases in the visceral AT area and total serum cholesterol concentration. This could be partly explained by the relatively large within-person variations in the variables[37 38] ; similar variations are also reported by Leenen et al[30] in a study of obese subjects after weight loss. This may also be due to the fact that we determined only a given AT area in the abdominal and hip region.

In summary, our study shows that GHD patients compared with healthy control subjects have markedly increased visceral AT and dyslipoproteinemia characteristics, both of which are associated with an increased risk of arteriosclerosis. After 6 months of rhGH replacement therapy, the amount of visceral AT and the plasma lipid profile, except the serum triglyceride level, were not significantly different from those of healthy control subjects. It appears that in GHD adults visceral AT is a major determining factor for the increase in atherogenic plasma lipids.

Selected Abbreviations and Acronyms

AT	= adipose tissue
BF	= body fat
BMI	= body mass index
GH	= growth hormone
GHD	= growth hormone–deficient
HDL-C	= HDL cholesterol
LDL-C	= LDL cholesterol
MRI	= magnetic resonance imaging
rhGH	= recombinant human growth hormone

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References

Top
Abstract
Introduction
Methods
Results
Discussion
References

1. Rosén T, Bengtsson B-Å. Premature mortality due to cardiovascular disease in hypopituitarism. *Lancet.* 1990;336:285-288. [Medline] [Order article via Infotrieve]
2. Bengtsson B-Å, Brummer R-JM, Rosén T. Effects of growth hormone on body composition in growth hormone deficient adults. In: Laron Z, Butenandt O, eds. *Growth Hormone Replacement Therapy in Adults: Pros and Cons*. London, England: Freund Publishing House Ltd; 1993:73-85.
3. Bengtsson B-Å, Edén S, Lönn L, Kvist H, Stokland A, Lindstedt G, Bosaeus I, Tölli J, Sjöström L, Isaksson OGP. Treatment of adults with growth hormone (GH) deficiency with recombinant human GH. *J Clin Endocrinol Metab.* 1993;76:309-317. [Abstract]
4. Jörgensen JOL, Pedersen SA, Thuesen L, Jörgensen J, Ingemann-Hansen T, Skakkebaek NE, Christiansen JS. Beneficial effects of growth hormone treatment in GH-deficient adults. *Lancet.* 1989;1:1221-1225. [Medline] [Order article via Infotrieve]
5. Salomon F, Cuneo RC, Hesp R, Sönksen PH. The effects of treatment with recombinant human growth hormone on body composition and metabolism in adults with growth hormone deficiency. *N Engl J Med.* 1989;321:1797-1803. [Abstract]
6. Whitehead HM, Boreham C, McIlrath EM, Sheridan B, Kennedy L, Atkinson AB, Hadden DR. Growth hormone treatment of adults with growth hormone deficiency: results of a 13-month placebo controlled cross-over study. *Clin Endocrinol.* 1992;36:45-52. [Medline] [Order article via Infotrieve]
7. Merimee TJ, Hollander W, Fineberg SE. Studies of hyperlipidemia in the HGH-deficient state. *Metabolism.* 1972;21:1053-1061. [Medline] [Order article via Infotrieve]
8. Merimee TJ, Pulkkinen A. Familial combined hyperlipoproteinaemia: evidence for a role of growth hormone deficiency in effecting its manifestation. *J Clin Invest.* 1980;65:829-835. [Medline] [Order article via Infotrieve]
9. Libber SM, Plotnick LP, Johanson AJ, Blizzard RM, Kwiterovich PO, Migeon CJ. Long-term follow-up of hypopituitary patients treated with human growth hormone. *Medicine.* 1990;69:46-55. [Medline] [Order article via Infotrieve]
10. Cuneo RC, Salomon F, Watts GF, Hesp R, Sönksen PH. Growth hormone treatment improves serum lipids and lipoproteins in adults with growth hormone deficiency. *Metabolism.* 1993;42:1519-1523. [Medline] [Order article via Infotrieve]
11. Rosén T, Edén S, Larsson G, Wilhelmsen L, Bengtsson B-Å. Cardiovascular risk factors in adult patients with growth hormone deficiency. *Acta Endocrinol.* 1993;129:195-200. [Medline] [Order article via Infotrieve]
12. De Boer H, Blok GJ, Voerman HJ, Phillips M, Schouten JA. Serum lipid levels in growth hormone-deficient men. *Metab Clin Exp.* 1994;43:199-203. [Medline] [Order article via Infotrieve]
13. Salomon F, Cuneo RC, Sönksen PH. Glucose metabolism in adults with growth hormone deficiency. *Acta Pediatr Scand.* 1991;377(suppl):64-68.
14. Karnieli E, Laron Z, Richer N, Singer P, Wasserman M, Meyerovitch Y, Harel C, Svirsky B. Insulin resistance in GH-deficient adult patients treated with human growth hormone: evidence for a postbinding defect in vivo. In: Laron Z, Butenandt O, eds.

Growth Hormone Replacement Therapy in Adults: Pros And Cons. London, England: Freund Publishing House Ltd; 1993:41-49.

15. Sacca L, Cittadini A, Fazio S. Growth hormone and the heart. *Endocr Rev.* 1994;15:555-573. [Abstract]
16. Lukaski HC, Johnson PE, Bolonchuk WW, Lykken GI. Assessment of fat-free mass using bioelectrical impedance measurements of the human body. *Am J Clin Nutr.* 1985;41:810-817. [Abstract]
17. Abate N, Burns D, Peshock RM, Garg A, Grundy SM. Estimation of adipose tissue mass by magnetic resonance imaging: validation against dissection in human cadavers. *J Lipid Res.* 1994;35:1490-1496. [Abstract]
18. Fowler PA, Fuller MF, Glasbey CA, Cameron GG, Foster MA. Validation of the in vivo measurement of adipose tissue by magnetic resonance imaging of lean and obese pigs. *Am J Clin Nutr.* 1992;56:7-13. [Abstract]
19. Armitage P, Berry G. *Statistical Methods in Medical Research*. 2nd ed. Oxford, England: Blackwell Scientific Publications; 1988.
20. Friedewald WT, Levy RI, Friedricksen DS. Estimation of plasma low density lipoprotein cholesterol concentration without use of preparative ultracentrifugation. *Clin Chem.* 1972;18:499-512. [Abstract/Free Full Text]
21. Binnerts A, Swart GR, Wilsson JHP, Hoogerbrugge N, Pols HAP, Birkenhäger JC, Lambents SWJ. The effects of growth hormone administration in growth hormone deficient adults on bone, protein, carbohydrate and lipid homeostasis, as well as on body composition. *Clin Endocrinol (Oxf).* 1992;37:79-87. [Medline] [Order article via Infotrieve]
22. Stiegler C, Leb G. One year of replacement therapy with growth hormone deficiency. *Endocrinol Metab Clin North Am.* 1994;1 (suppl A):37-42.
23. Russell-Jones DL, Watts GF, Weissberger A, Naoumova R, Myers J, Thompson GR, Sönksen PH. The effect of growth hormone replacement on serum lipids, lipoproteins, apolipoproteins and cholesterol precursors in adult growth hormone deficient patients. *Clin Endocrinol (Oxf).* 1994;41:345-350. [Medline] [Order article via Infotrieve]
24. Edén S, Wiklund O, Oscarsson J, Rosén T, Bengtsson B-Å. Growth hormone treatment of growth hormone–deficient adults results in a marked increase in Lp(a) and HDL cholesterol concentrations. *Arterioscler Thromb.* 1993;13:296-301. [Abstract]
25. Degerblad M, Elgindy N, Hall K, Sjöberg H-E, Thorén M. Potent effect of recombinant human growth hormone on bone mineral density and body composition in adults with panhypopituitarism. *Acta Endocrinol.* 1992;126:387-393. [Medline] [Order article via Infotrieve]
26. Modigliani E, Kerchouni R, Uzzan B, Valensi P, Chanson P, Caron J. Modification of blood lipids and lipoproteins after human growth hormone treatment in adults with growth hormone deficiency: a preliminary report. *Endocrinol Metab Clin North Am.* 1994;1(suppl A):31-35.
27. Rudling M, Norstedt G, Olivecrona H, Reihnér E, Gustafsson J-Å, Angelin B. Importance of growth hormone for the induction of hepatic low density lipoprotein receptors. *Proc Natl Acad Sci U S A.* 1992;89:6983-6987. [Abstract/Free Full Text]
28. Rosenbaum M, Gertner JM, Leibel R. Effects of systemic growth hormone (GH) administration on regional adipose tissue distribution and metabolism in GH-deficient children. *J Clin Endocrinol Metab.* 1989;69:1274-1281. [Abstract]
29. Després J-P, Moorjani S, Lupien PJ, Tremblay A, Nadeau A, Bouchard C. Regional distribution of body fat, plasma lipoproteins, and cardiovascular disease. *Arteriosclerosis.* 1990;10:497-511. [Abstract]
30. Leenen R, van der Kooy, Seidell JC, Deurenberg P. Visceral fat accumulation measured by magnetic resonance imaging in relation to serum lipids in obese men and women. *Atherosclerosis.* 1992;94:171-181. [Medline] [Order article via Infotrieve]
31. Després J-P, Moorjani S, Ferland M, Tremblay A, Lupien PJ, Nadeau A, Pinault S, Thériault G. Adipose tissue distribution and plasma lipoprotein levels in obese women: importance of intra-abdominal fat. *Arteriosclerosis.* 1989;9:203-210. [Abstract]
32. Terry RB, Stefanick ML, Haskell WL, Wood PD. Contributions of regional adipose tissue depots to plasma lipoprotein concentrations in overweight men and women: possible protective effects of thigh fat. *Metabolism.* 1991;40:733-740. [Medline] [Order article via Infotrieve]
33. Després J-P. Obesity and lipid metabolism: relevance of body fat distribution. *Curr Opin Lipidol.* 1991;2:5-15.
34. Björntorp P. Regional fat distribution: implications for type II diabetes. *Int J Obes*. 1992;16(suppl 4):S19-S27.
35. Alford E, Hew FL, Koschmann M, Christopher M, Rantzau C, Ward G. Defects of glucose metabolism in growth hormone deficient (GHD) adults. *Endocrinol Metab*. 1994;1(suppl B):27. Abstract.
36. O'Neal DN, Kalfas A, Dunning PL, Christopher MJ, Sawyer SD, Ward GM. The effect of 3 months of recombinant human growth hormone (GH) therapy on insulin and glucose-mediated glucose disposal and insulin secretion in GH-deficient adults: a minimal model analysis. *J Clin Endocrinol Metab.* 1994;79:975-983. [Abstract]
37. Seidell JC, Bakker CJG, van der Kooy K. Imaging techniques for measuring adipose-tissue distribution: a comparison between computed tomography and 1.5-T magnetic resonance. *Am J Clin Nutr.* 1990;51:953-957. [Abstract]
38. Brown SA, Boerwinkle E, Kashanian FK, Swanson J, Patsch W. Variation in concentrations of lipids, lipoprotein lipids, and apolipoproteins A-I and B in plasma from healthy women. *Clin Chem.* 1990;36:207-210.[Abstract/Free Full Text]