# Effects of Growth Hormone on Serum Lipids and Lipoproteins: Possible Significance of Increased Peripheral Conversion of Thyroxine to Triiodothyronine

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**The role of growth hormone (GH) and thyroid hormone in the regulation of lipid and lipoprotein metabolism is not fully established. Furthermore, the possible linkage between the well-known GH-induced increase in peripheral thyroxine ($T_4$) to triiodothyronine ($T_3$) generation and the effects of GH on lipid and lipoprotein metabolism has not been elucidated. In this double-blind placebo-controlled study, we compared the effects of GH and $T_3$ administration alone and in combination on lipid and lipoprotein metabolism in a group of healthy young adults. The dose of $T_3$ was selected to mimic the $T_3$ increase seen during exogenous GH exposure. Eight normal male subjects (aged 21 to 27 years; body mass index, 21.11 to 27.17 kg/m$^2$) were randomly studied during four 10-day treatment periods with (1) daily subcutaneous placebo injections and placebo injections and placebo tablets, (2) daily subcutaneous GH injections (0.1 IU/kg · d) and placebo tablets, (3) daily $T_3$ administration (40 μg on even dates or 20 μg on uneven dates) plus placebo injections, and (4) daily GH injections plus $T_3$ administration. GH administration increased free $T_3$ ($FT_3$) to the same level as during $T_3$ administration. GH caused decreased levels of total cholesterol (TC) and low-density lipoprotein (LDL) cholesterol and increased levels of triglycerides (TG) and lipoprotein(a) (Lp(a)), but no changes in high-density lipoprotein (HDL) cholesterol and apolipoprotein B (apo B). $T_3$ administration caused no alteration in these parameters, except for decreased levels of TC comparable to those seen after GH administration. Combined GH and $T_3$ administration caused changes identical to those seen after GH administration, in addition to decreased apo B levels and a further decrease of TC levels. We conclude that GH and iodothyronines in the physiologic range exert distinct but disparate effects on lipids and lipoproteins, and do not support the hypothesis that the effects observed during GH administration are exclusively secondary to changes in peripheral $T_3$ levels.**


ALTERED SERUM concentrations of lipids and lipoproteins are a known risk factor for the development of cardiovascular disease.[1] Perturbations associated with increased risk include elevated total cholesterol (TC), low-density lipoprotein (LDL) cholesterol, and apolipoprotein B (apo B) and decreased high-density lipoprotein (HDL) cholesterol. Furthermore, attention has been drawn to lipoprotein(a) (Lp(a)) and apo B, both recognized as independent risk factors for atherogenesis.[2-5]

The role of growth hormone (GH) in the regulation of lipid and lipoprotein metabolism is not fully established. Short-term GH administration to normal adults decreased TC and increased triglycerides (TG) in some studies,[6,7] whereas others show only an increase in TG and very–low-density lipoprotein or an isolated decrease in TC.[8,9] Studies with GH substitution in GH-deficient subjects are also ambiguous, but generally report reductions in serum TC, LDL cholesterol, and apo B and no change in HDL cholesterol.[6,10,11] Part of the diversity in findings may be explained by the fact that GH-deficient adults are a heterogenous population with regard to onset of disease and degree of obesity. Reports on Lp(a) are not consistent, inasmuch as one study reported no effects[10] and others reported increased levels of Lp(a).[12,13]

Thyroid hormones also play a distinct role in lipid and lipoprotein metabolism. Increased levels of thyroid hormones have been shown to decrease serum TC, HDL cholesterol, LDL cholesterol, and apo B, with TG being unaffected.[4,14,15] Furthermore, recent studies have suggested that a thyroid hormone excess decreases Lp(a).[16,17]

Several placebo-controlled trials show that GH administration stimulates the peripheral conversion of thyroxine ($T_4$) to triiodothyronine ($T_3$) in both normal and obese adults, as well as GH-deficient adults.[18-22] The question of whether this modest GH-induced increase in circulating $T_3$ contributes to the concomitant changes in lipid and lipoprotein profiles during GH administration has so far not been elucidated. One study demonstrated that the modest hypercholesterolemia seen in GH deficiency can be corrected through thyroid replacement,[23] whereas another study could not confirm these findings.[11]

In this double-blind placebo-controlled study, we compared the effects of GH and $T_3$ administration alone and in combination on lipid and lipoprotein metabolism in a group of healthy young adults. The dose of $T_3$ was selected to mimic the $T_3$ increase seen during exogenous GH exposure.

## SUBJECTS AND METHODS

### *Subjects*

Eight healthy men (aged 21 to 29 years) with a normal body mass index (22.5 to 27.0 kg/m$^2$) volunteered to participate in the study. All were characterized by an unremarkable medical history; in particular, they were without any evidence of thyroid disease or premature ischemic heart disease. Before participation, the nature, purpose, and potential risks of the study were explained to all subjects, and written informed consent was obtained from each. The protocol was approved by the regional ethics committee.

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*Study Design*

Each subject underwent four different 10-day experiments, receiving (1) saline injections and placebo tablets, (2) GH injections and placebo tablets, (3) saline injections and $T_3$ tablets, and (4) GH injections and $T_3$ tablets. At least 10 days separated each study. GH (Norditropin; Novo Nordisk, Gentofte, Denmark) or saline were administered by subcutaneous self-injection at 8 PM at a dosage of 0.1 IU/kg, with a maximal dosage of 10 IU/d. $T_3$ (20 μg per tablet) or placebo tablets were given in the following pattern: one tablet on uneven days in the evening and two tablets on even days, one in the morning and one in the evening. The $T_3$ dose schedule was selected, following a pilot study in three healthy adults, to yield approximately a 10% increase in morning $T_3$ levels to mimic the expected GH-induced increment in $T_3$ concentrations, as observed in a previous study.[18] The different experiments were performed in random order.

*Blood Sampling*

Blood was sampled for determination of thyroid hormones, lipids, lipoproteins, GH, and insulin-like growth factor-I (IGF-I) before each study period and in the morning after an overnight fast following the final day of treatment. Samples were immediately frozen after centrifugation at −20°C until assayed.

*Assays*

Serum GH and IGF-I levels were measured using an immunofluorometric assay (DELFIA; Wallac, Turku, Finland). Total $T_4$ ($TT_4$), free $T_4$ ($FT_4$), $TT_3$, $FT_3$, and $rT_3$ levels were measured by radioimmunoassay as previously described.[24] TG, TC, and HDL cholesterol were determined by standard enzymatic assays (Boehringer, Mannheim, Germany). LDL cholesterol level was calculated using the Friedewald formula (LDL cholesterol = TC − 0.45 TG − HDL cholesterol (mmol/L).[25] Apo B and Lp(a) levels were measured by commercially available radioimmunoassays (Pharmacia, Uppsala, Sweden).

*Statistical Analysis*

The data are presented as the mean ± SEM. For each of four studies, changes in the measured variables before (baseline) and after (day 10) treatment were evaluated by a paired *t* test or Wilcoxon's test, where appropriate. To compare treatment effects between the four studies, repeated-measures ANOVAs were performed on delta values (baseline − day 10). In case of significant differences, the Student-Neuman-Keuls method for pairwise multiple comparison was included. *P* values less than .05 were considered significant.

## RESULTS

*Lipid and Lipoprotein Profiles*

Lipid and lipoprotein profiles are shown in Table 1 and Fig 1. For all parameters, baseline values were comparable and within the normal range (Table 1). Serum TG (mmol/L = 0.01129 × mg/dL) were significantly elevated during GH and GH + $T_3$ administration compared with the placebo experiment, whereas $T_3$ administration alone resulted in unaltered serum levels of TG. Serum TC (mmol/L = 0.02586 × mg/dL) was significantly decreased following both GH and $T_3$ administration as compared with the placebo experiment, and concomitant GH + $T_3$ administration caused an additional reduction in TC. GH administration decreased LDL cholesterol significantly from placebo levels, whereas GH + $T_3$ tended to reduce LDL cholesterol even further. $T_3$ administration tended to decrease LDL cholesterol, although not significantly. No significant differences in HDL cholesterol were observed, although GH + $T_3$ administration tended to decrease HDL cholesterol. Lp(a) was significantly increased during GH administration as compared with the placebo experiment, whereas $T_3$ treatment had no effect on Lp(a) levels. Finally, GH + $T_3$ decreased apo B levels significantly, whereas apo B levels during placebo, GH, and $T_3$ experiments were similar.

**Table 1. Lipid and Lipoprotein Status Before Each 10-Day Treatment Period**

| Variable | Control | GH | $T_3$ | GH + $T_3$ |
|---|---|---|---|---|
| TG (mmol/L) | 1.40 ± 0.2 | 1.46 ± 0.2 | 1.31 ± 0.2 | 1.31 ± 0.1 |
| TC (mmol/L) | 5.3 ± 0.6 | 5.5 ± 0.5 | 5.3 ± 0.5 | 5.3 ± 0.5 |
| HDL C (mmol/L) | 1.2 ± 0.1 | 1.2 ± 0.1 | 1.2 ± 0.1 | 1.2 ± 0.1 |
| LDL C (mmol/L) | 3.5 ± 0.6 | 3.6 ± 0.4 | 3.5 ± 0.5 | 3.5 ± 0.5 |
| Apo B (g/L) | 0.96 ± 0.1 | 0.96 ± 0.1 | 0.99 ± 0.1 | 0.94 ± 0.1 |
| Lp(a) (mg/dL) | 44.0 ± 22 | 45.7 ± 21 | 47.0 ± 22 | 45.3 ± 21 |

NOTE. All basal values were not significantly different.
Abbreviation: C, cholesterol.

*Hormones*

The data on thyroid hormones will be reported elsewhere.[24] In brief, all baseline parameters were comparable and within the normal range. $FT_3$ and $TT_3$ concentrations during GH, $T_3$, and GH + $T_3$ treatments were significantly higher as compared with the placebo experiment. Administration of GH and $T_3$, respectively, resulted in comparable levels of $FT_3$ and $TT_3$, and concomitant GH and $T_3$ administration caused an additional and significant increase in $FT_3$ and $TT_3$ ($FT_3$, 6.2 ± 0.3 (placebo), 7.3 ± 0.5 (GH), 7.7 ± 0.5 ($T_3$), and 10.5 ± 1.1 (GH + $T_3$)). $T_4$ levels after GH, $T_3$, and GH + $T_3$ were significantly lower as compared with the control experiment, and tended to be further decreased when $T_3$ and GH + $T_3$ were administered versus GH administration alone. The same pattern was found in $rT_3$ concentrations. The $FT_3/FT_4$ ratio after institution of GH administration was significantly higher as compared with the placebo experiment, and the ratio was further increased during $T_3$ and GH + $T_3$ administration. Thyrotropin decreased significantly after $T_3$ administration as compared with both the control and GH experiment.

Serum GH and IGF-I levels (micrograms per liter) were similar before therapy in all experiments. Both serum GH and IGF-I were significantly elevated following GH administration (GH, 0.06 ± 0.02 (control) *v* 3.65 ± 0.92 (GH) *v* 4.40 ± 1.45 (GH + $T_3$), $P < .01$; IGF-I, 165.1 ± 0.9 (control) *v* 492.0 ± 5.1 (GH) *v* 531.7 ± 4.6 (GH + $T_3$), $P < .01$). $T_3$ administration alone did not alter serum GH (0.2 ± 0.13, $P = .79$) or IGF-I (186.0 ± 1.6, $P = .49$).

## DISCUSSION

This study was undertaken to examine the effects of GH and $T_3$ administration on lipid and lipoprotein metabolism, and to test whether the modest GH-induced increase in circulating $T_3$ contributes to the concomitant changes in

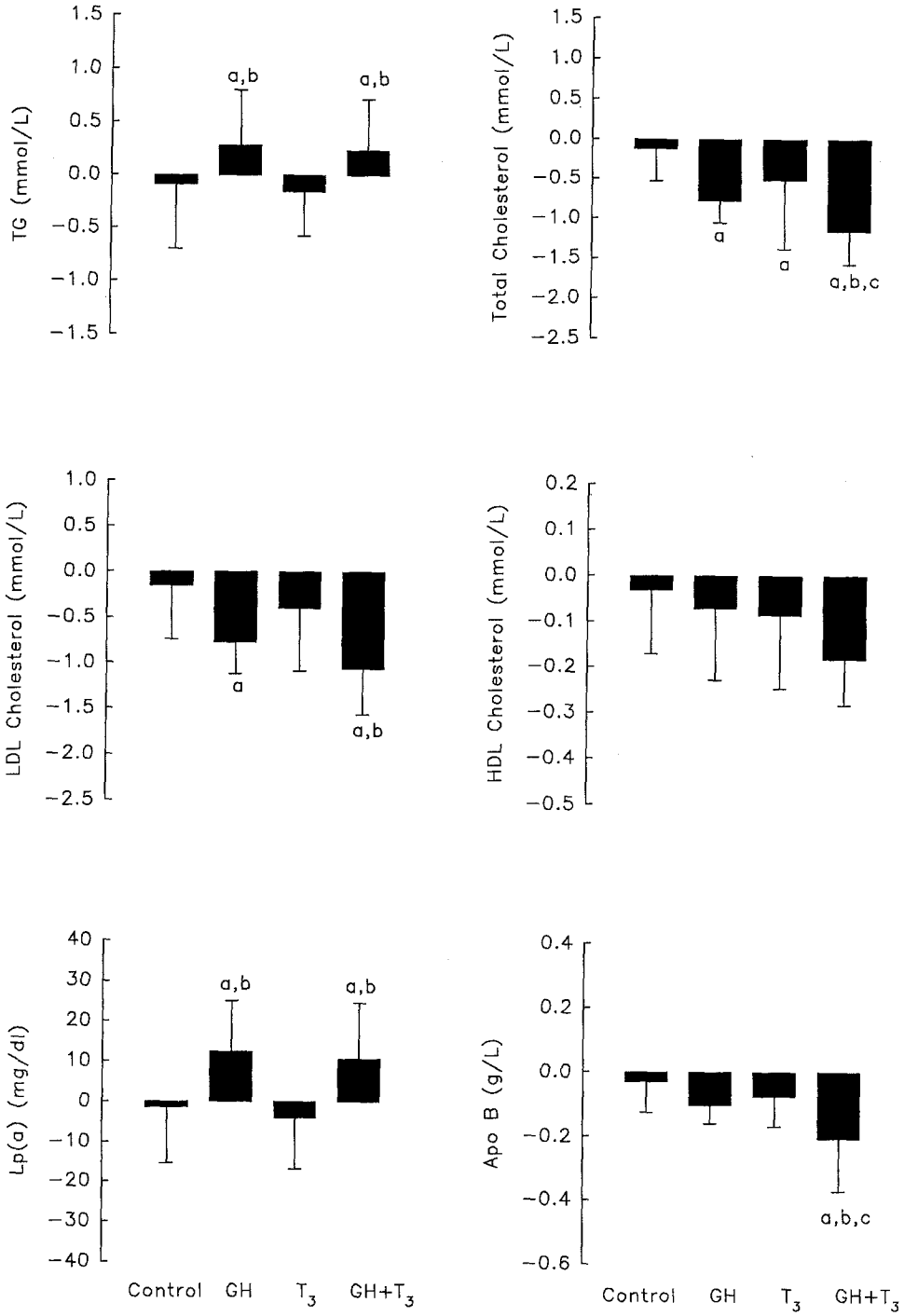


**Fig 1. Change in lipid and lipoprotein status after commencement of 10-day therapy. From left to right, the first bar in each graph represents controls, the second GH, the third $T_3$, and the fourth GH + $T_3$. [a]$P < .05$, control *v* GH, $T_3$, and GH + $T_3$; [b]$P < .05$, $T_3$ *v* GH and GH + $T_3$; [c]$P < .05$, GH *v* GH + $T_3$.**

lipid and lipoprotein profiles during GH administration. The study confirms the ability of GH administration to stimulate extrathyroidal conversion of $T_4$ to $T_3$, as judged by the alterations in $FT_3$, $T_3/T_4$, and $rT_3$. Furthermore, GH administration decreased TC and LDL cholesterol and increased TG and Lp(a), but had no impact on HDL cholesterol and apo B. Administration of $T_3$ alone was not associated with detectable excursions in lipoproteins, apart from a decrease in TC. Finally, GH + $T_3$ administration imposed changes comparable to those seen after GH administration, in addition to decreasing apo B levels, and a more pronounced decrement in TC levels.

Apart from observing the direct effects of GH and $T_3$ administration alone and in combination on lipid and lipoprotein metabolism, the aim of the present study was to obtain comparable $T_3$ levels through administration of GH and $T_3$, respectively. Comparable values of $FT_3$ were indeed obtained, but the reported thyroid hormone levels are

morning values, which do not imply identical levels on a circadian basis. All participants presented with mild subclinical hyperthyroid symptoms in terms of elevated heart rate and resting metabolic rate when given GH, $T_3$, and GH + $T_3$.[24]

The changes in lipid and lipoprotein metabolism following GH administration are in agreement with most studies, and differences among other studies probably relate mainly to differences in dosage and duration of administration, and possibly to variation between normal subjects and GH-deficient patients. The latter are characterized by normal or slightly increased TC, normal or decreased HDL cholesterol, increased LDL cholesterol, and increased TG concentrations before GH administration.[26] It is noteworthy that GH-deficient patients are a heterogenous group with wide variations in chronological age, concomitant pituitary disease, and body composition, all of which may impact lipoprotein levels and the response to GH therapy. A difference in the duration of administration is also of potential importance, since recent studies in GH-deficient adults with 6 months of GH administration showed increments in HDL cholesterol,[13,27] as compared with reductions in TC and LDL cholesterol following GH administration on a more short-term basis.[6,10,11]

The results are noteworthy with regard to the increased levels of Lp(a), which is also known to be elevated in patients with coronary heart disease and stroke. GH administration is generally associated with an improved lipid and lipoprotein profile and a decreased risk of cardiovascular disease.[10,11] Although this holds true with most lipids and lipoproteins, our results and other studies[12,13] suggest that this is not the case with Lp(a). Since some GH-deficient patients may receive replacement therapy for decades, increased Lp(a) levels could represent a potential risk that merits long-term monitoring.

Mild hyperthyroidism evoked by $T_3$ administration caused a significant reduction in TC and tended to decrease LDL cholesterol, albeit insignificantly, both of which are in agreement with another study in subclinically hyperthyroid adults.[28] The reduction in TC following both GH and $T_3$ administration is notable, inasmuch as the reductions are similar in magnitude to those reported in primary prevention studies of drug intervention in hyperlipidemia.[29,30]

Other studies in hyperthyroidism have reported significant decrements in HDL cholesterol, LDL cholesterol, apo B, and Lp(a),[4,16,17] which we could not detect in our study. Those studies were conducted in overtly hyperthyroid patients in whom iodothyronines were elevated approximately four times over the levels in our study. This is of particular interest with regard to Lp(a) levels, which apparently remain unaltered in the subclinically hyperthyroid but become significantly decreased in the overtly hyperthyroid. One previous study[31] did not show a relationship between Lp(a) and thyroid hormone concentrations during treatment of hypothyroid subjects with L-$T_4$ substitution, supporting the concept that changes in thyroid hormones within the low-normal range do not seem to influence Lp(a).

Winter and Green[23] have suggested that thyroid hormones mediate the cholesterol-lowering effect of GH through enhanced peripheral conversion of $T_4$ to $T_3$. Other studies have failed to confirm this theory.[11,32] The present study suggests that thyroid hormone at a level comparable to that observed after GH administration is only capable of mimicking the TC-lowering effect of GH. The disparate effects of GH and $T_3$ on LDL cholesterol and Lp(a) and the notion of more pronounced reductions in TC following GH + $T_3$ suggest separate modes of action of the two hormones.

Coadministration of GH and $T_3$ decreased apo B concentrations, whereas GH or $T_3$ alone did not alter apo B significantly. Both GH and thyroid hormone have been reported to decrease apo B levels,[4,10,11,16] and also tended to decrease apo B in the present study, even though treatment was given over a short period and, in the case of $T_3$, in small amounts. It may be that GH and $T_3$ exert synergistic effects on apo B levels.

To summarize, GH administration caused decreased levels of TC and LDL cholesterol and increased levels of TG and Lp(a), but no changes in HDL cholesterol and apo B. $T_3$ administration, yielding serum $T_3$ levels comparable to those observed during GH therapy, caused no alterations apart from decreased levels of TC. GH + $T_3$ administration caused changes identical to those seen after GH administration, in addition to decreased apo B levels and a further decrease of TC levels.

These data emphasize that GH and iodothyronines in the physiologic range exert distinct but disparate effects on lipids and lipoproteins, and do not support the hypothesis that the effects observed during GH administration are exclusively secondary to changes in peripheral $T_3$ levels. Such information may help to clarify the complex and seemingly paradoxical effects of GH on lipoprotein metabolism.

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