Changes in Serum Apolipoprotein Concentrations After L-Thyroxine Therapy in Infants With Congenital Hypothyroidism

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To further characterize the impact of thyroid hormones on the serum lipid profile, we studied serum apolipoproteins in infants with congenital hypothyroidism before and after L-thyroxine ($L-T_4$) replacement therapy. Serum high-density lipoprotein cholesterol (HDLC) decreased after $L-T_4$ therapy. Total cholesterol (TC) and low-density lipoprotein cholesterol (LDLC) levels did not change significantly after therapy. Two months after $L-T_4$ replacement therapy, serum apolipoprotein A-I (apo A-I), C-III, and E declined and apo B increased significantly. No significant changes were observed for serum concentrations of apo A-II and C-II after $L-T_4$ substitution. We conclude that in infants, thyroid hormone reduces serum levels of apo A-I, the principal protein component of HDLC, and this may contribute to the decline of serum HDLC concentrations after $L-T_4$ replacement therapy.

ALTHOUGH IT IS WELL KNOWN that serum total cholesterol (TC) and low-density lipoprotein cholesterol (LDLC) are elevated in hypothyroidism, serum levels of high-density lipoprotein cholesterol (HDLC) have been variously reported as normal,[1-3] increased,[4-8] or decreased.[9-11] Previous studies on the alterations of the serum lipid profile in the hypothyroid state have implicated a number of factors, including changes in the activity of hepatic lipase[12] or lecithin-cholesterol acyltransferase,[13] HDL catabolism,[14] hepatic cholesterol biosynthesis,[15] biliary cholesterol secretion,[16] and apolipoprotein A-I (apo A-I) genes.[17] Detailed mechanisms for the effect of thyroid hormones on these processes have not been determined. In previous studies, contrasting results concerning the effects of thyroid hormones on HDLC and apo A-I (which is the principal protein component of HDLC and constitutes about 70% to 80% of the HDL protein mass[18]) are reported.

The aim of this study was to clarify the effects of thyroid hormones on serum HDLC and apolipoprotein levels. It is based on our previous study indicating that both serum LDLC and HDLC are elevated in infants with congenital hypothyroidism as compared with normal controls and that L-thyroxine ($L-T_4$) reduces elevated HDLC, but not LDLC.[8]

SUBJECTS AND METHODS

Seventeen infants (seven males and 10 females) identified during neonatal mass screening for congenital hypothyroidism were enrolled in the study. The patients were aged 1 month at the first blood sampling and 3 months at the second blood sampling. These patients had elevated blood thyrotropin (TSH) levels (>97th percentile of the assay) and were referred to our hospital for further evaluation at the age of 1 month. They were later confirmed to have congenital hypothyroidism (fetal thyroid developmental defects, 12 cases; defective synthesis, four cases; and maternal antibody, one case). Eleven of the babies were breast-fed exclusively and the remaining six babies were mainly breast-fed, with occasional substitution with formula feedings.

Blood samples were taken for measurement of serum levels of TSH, triiodothyronine (T_3), thyroxine (T_4), free T_4, TC, HDLC, triglyceride (TG), apolipoproteins, and other chemicals on an autoanalyzer (model 7170; Hitachi, Tokyo, Japan). Serum TC, HDLC, and TG levels were measured by an enzymatic assay, and apo A-I, A-II, B, C-II, C-III, and E levels were measured by an immunoturbidity method on the same autoanalyzer. Serum concentrations of LDLC were calculated using the formula, LDLC = TC − HDLC − (TG/5). Informed consent was obtained from the parents at the first visit to our hospital.

At the age of 1 month, the first blood samples were taken and L-thyroxine ($L-T_4$) substitution therapy was started. Each patient received an oral dose of $L-T_4$ of approximately 10 μg/kg body weight once per day in the morning. Two months after $L-T_4$ substitution, at the age of 3 months, the second blood samples were taken. Per Wiseman et al,[6] we analyzed the effects of $L-T_4$ on the serum lipid profile with respect to changes in the serum TSH concentration. The height and weight of the 17 infants were within the normal range, distributed between −1.2 standard deviation (SD) and +1.9 SD (normal SD range, −2 to +2), before and 2 months after $L-T_4$ substitution. Since changes in the infants' lipids, lipoproteins, and apolipoproteins may reflect not only the direct effects of $L-T_4$ substitution but also changes in the weight, height, and body mass index (body weight in kilograms divided by height in meters squared), we analyzed the obtained significant data using covariance analysis.

Serum lipid values examined by the Kolmogorov-Smirnov test were not normally distributed. The significance of differences in serum lipids before and after $L-T_4$ therapy was determined by Wilcoxon's signed-rank sum test. Data are presented as the mean ± SD. A P value less than .05 was considered significant.

RESULTS

Changes in Serum TSH Concentration

Serum TSH levels in these patients before $L-T_4$ therapy were 224.0 ± 464.5 μU/mL. In all 17 patients at 2 months after $L-T_4$ therapy at the age of 3 months, serum TSH decreased to 1.8 ± 2.3 μU/mL.

Changes in Serum TC, HDLC, and TG Concentrations

At the age of 3 months at 2 months after replacement therapy with $L-T_4$, serum HDLC decreased significantly. There were no statistically significant changes in serum concentrations of TC, TG, and LDLC after replacement therapy (Table 1).

Changes in Serum Apolipoprotein Concentrations

Variable changes were observed for the serum concentration of the six apolipoproteins after $L-T_4$ replacement. Serum levels

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of apo A-I, C-II, and E decreased significantly after L-T_4 therapy. The decline in serum apo A-I was still statistically significant after adjusting for changes in the body weight, height, and body mass index. Conversely, serum apo B concentrations showed a statistically significant increase after L-T_4 therapy. For apo A-II and C-II, no significant changes in the serum level were observed before and after therapy (Table 1).

DISCUSSION

In this study, serum HDLC levels were confirmed to decrease with L-T_4 replacement therapy in infants with congenital hypothyroidism. Serum levels of apo A-I (the principal protein component of HDLC) were demonstrated to decrease with L-T_4 substitution, and the decline in apo A-I was still statistically significant after adjusting for changes in the body weight, height, and body mass index. Since normal control infants without medication, including L-T_4, did not show any significant change in serum HDLC levels from 1 to 3 months of age in a previous study,[8] we did not enroll normal infants as controls in the present study.

The effects of thyroid hormones on apo A-I have been demonstrated in numerous studies. Plasma apo A-I concentrations in women are increased in hyperthyroidism[19,20] and decreased in hypothyroidism.[21] Administration of thyroid hormone (T_3 or T_4) increases plasma apo A-I in rats.[22] In contrast to the findings in humans,[19-21] plasma apo A-I concentrations in hypothyroid rats are generally reported as unchanged.[23] However, more recent studies have shown different results. Using a rat model, Fong et al[24] observed a significant increase in both LDLC and HDLC in hypothyroid animals and demonstrated that thyroid hormone affects the expression of the HDL binding site in liver cells, which may contribute to the reduced HDL clearance in the hypothyroid animal. Daily injection of T_3 led to an increase in the hepatic mRNA level for apo A-I and an increase in the serum apo A-I level.[25] In contrast, long-term administration of T_3 increased apo A-I gene expression in rat liver by enhancing mRNA maturation but reduced apo A-I mRNA synthesis to 50% of the control level.[26] The results of these studies imply that apo A-I synthesis and apo A-I mRNA levels increase with T_4/T_3 treatment but the serum levels may not always reflect this. In our study using hypothyroid infants as subjects, a reduction of serum HDLC and apo A-I levels with L-T_4 substitution was clearly shown.

Table 1. Changes in Serum Lipid and Apolipoprotein Concentrations in Infants With Congenital Hypothyroidism Before and After L-T_4 Therapy

Parameter	Age 1 Month (before L-T_4)	Age 3 Months (after L-T_4)	
Serum lipids			
TC			
mmol/L	4.466 ± 1.001	4.647 ± 0.693	NS
mg/dL	172.7 ± 38.7	179.7 ± 26.8	
TG			
mmol/L	1.370 ± 0.576	1.563 ± 0.627	NS
mg/dL	121.3 ± 51.0	138.4 ± 55.5	
HDLC			
mmol/L	1.810 ± 0.665	1.600 ± 0.546	↓ $P < .05$
mg/dL	70.0 ± 25.7	61.8 ± 21.1	
LDLC			
mmol/L	2.064 ± 0.760	2.322 ± 0.468	NS
mg/dL	79.8 ± 29.4	89.8 ± 18.1	
Serum apolipoproteins (mg/dL)			
A-I	150.4 ± 27.9	139.9 ± 22.7	↓ $P < .05$
A-II	32.8 ± 3.8	33.5 ± 2.8	NS
B	63.7 ± 15.1	76.9 ± 11.3	↑ $P < .01$
C-II	3.3 ± 1.6	3.6 ± 1.5	NS
C-III	8.9 ± 2.8	6.8 ± 1.8	↓ $P < .01$
E	6.69 ± 1.28	5.46 ± 0.78	↓ $P < .01$

NOTE. Arrows indicate a significant increase or decrease in the mean value at 3 months *v* 1 month.

With regard to other apolipoproteins, serum levels of apo E and C-III (both of which are smaller parts of the protein components of HDLC) decreased significantly after L-T_4 replacement. In hypothyroid rats, serum apo E levels were higher than in control rats and the HDL particles contained increased amounts of apo E.[25] In contrast, in hyperthyroid animals, there was a decrease in both the apo E and apo A-IV content of HDL with a reduction in the average size of apo A-I–containing particles.[25] Based on these findings, thyroid hormones appear to suppress serum apo E levels. By contrast, after L-T_4 replacement, there was no significant change in serum apo A-II, one of the major protein components of HDL. A possible explanation for this finding is provided by Strobl et al,[27] who demonstrated that apo A-I and apo A-II genes in rat liver respond differently to thyroid hormones.

In our study, the serum level of apo B, a major protein component of LDL, did not decrease after L-T_4 substitution; on the contrary, it showed a significant increase. This probably reflects the increase (albeit not statistically significant) in serum LDLC. The increase in apo B and the tendency for an increase in LDLC with L-T_4 therapy may reflect the normal increase during infancy or indicate a more rapid conversion of VLDL to LDL, with an elevation of LDLC in some patients but not all. It is generally accepted that serum LDLC concentrations are increased in the hypothyroid state; however, this hypocholesterolemic response of serum LDLC to L-T_4 replacement therapy is variable and is not demonstrated in up to 25% of patients.[3,8,28] Taken together with these studies, it is difficult to draw a firm conclusion about the observed increase in serum apo B with L-T_4 substitution in our hypothyroid infants.

In summary, this study on infants with congenital hypothyroidism, by eliminating many possible factors that affect the serum lipid profile, shows clear and significant serum lipid changes after L-T_4 replacement therapy. From these results, we conclude that in humans, thyroid hormone reduces the serum level of apo A-I, the principal protein component of HDLC, and this may contribute to the decline of serum HDLC concentrations after L-T_4 replacement therapy.

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