# Plasma Levels of Lipoproteins and Apolipoproteins in Congenital Hypothyroidism: Effects of L-Thyroxine Substitution Therapy

Carlo M. Barbagallo, Maurizio R. Averna, Andrea Liotta, Stefania La Grutta, Cristina Maggio, Lucia Casimiro, Angelo B. Cefalù, and Alberto Notarbartolo

**Thyroid status in humans is an important factor in the regulation of lipoprotein metabolism. There are several data on hypothyroidism in the adult population, but less information is available about congenital hypothyroidism. Since lipid metabolism at birth is substantially different from that of adults, it is not likely that the same abnormalities that occur in adult hypothyroidism are also present when this is diagnosed at early life. We studied 16 subjects with congenital hypothyroidism, seven at the time of diagnosis and also after normalization of thyroid hormone levels over a period of 2.0 ± 1.0 months of substitution therapy with L-thyroxine (5.9 ± 1.2 μg/kg/d) and nine already on L-thyroxine therapy for a period of 4.7 ± 3.2 months. Thirty-nine apparently healthy subjects matched for age were selected as controls. In all subjects, total cholesterol (CHO), triglycerides (TG), low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol (HDL-C), apolipoproteins (apo) A-I and B, lipoprotein(a) [Lp(a)] thyrotropin (TSH), (LDL-C), total and free thyroxine ($T_4$), and triiodothyronine ($T_3$) were determined. CHO, HDL-C, and apo A-I levels were significantly higher in patients at the time of diagnosis than in controls (respectively, $P = .0079$, .0007, and .0004), whereas TG, LDL-C, apo B, and Lp(a) levels were not significantly different. During L-thyroxine substitution therapy in these subjects, HDL-C and apo A-I levels significantly decreased (respectively, by a mean of −36.2% and −24.4%), with similar behavior in all subjects. To verify if these lipoprotein changes were due to L-thyroxine substitution therapy or to physiological modifications with time, we remeasured lipoprotein parameters also in 10 normal subjects approximately 2 months later than the first measurement, but no significant change was found. Moreover, all subjects with congenital hypothyroidism on L-thyroxine substitution therapy did not show any significant difference in lipoprotein profile in comparison to age-matched controls. Our data document that infants with congenital hypothyroidism mainly show high HDL-C levels, and that L-thyroxine substitution therapy completely restores a normal lipid profile. Since HDL plays a major role in newborns and in the first days of life, we suggest that thyroid hormones modulate the physiological development of lipoprotein metabolism after birth, and that the lack of thyroid hormones does not permit complete evolution of newborn lipid patterns toward an adult profile.**


THYROID STATUS in humans is an important factor in the regulation of lipoprotein metabolism. In the adult population, hypothyroidism is associated with an increase of total (CHO) and low-density lipoprotein (LDL) cholesterol (LDL-C), as well as triglyceride (TG) levels.[1-3] Also, high-density lipoprotein (HDL) cholesterol (HDL-C) seems to be affected by hypothyroidism.[4,5] Furthermore, a role in the regulation of lipoprotein(a) [Lp(a)] levels by thyroid hormones was recently suggested.[6,7] These abnormalities are the consequence of multiple alterations due to the lack of thyroid hormones: impairment of lipolytic enzymes, receptor pathways, or lipoprotein synthesis.[8-11] However, substitution therapy improves lipoprotein metabolism parameters and restores a normal lipid profile.[9,12-15] Although there are several studies on acquired hypothyroidism of adults, less data are available on congenital hypothyroidism.[16-19] It is not likely that the same abnormalities that occur in adult hypothyroidism are also present when this is diagnosed after birth. In the first weeks of life, lipoproteins are present in plasma concentrations and involved in metabolic roles substantially different from those of adults: in particular, HDLs, which in adults have the function of reverse transport of cholesterol, may be used as a source of cholesterol from the peripheral tissues.[20-22] Moreover, in many countries, including Italy, congenital hypothyroidism is currently screened in newborns, and early institution of substitution therapy avoids the clinical effects of the lack of thyroid hormones.[23,24]

In this study, we evaluated lipid, lipoprotein, apolipoprotein, and Lp(a) levels in a group of subjects with congenital hypothyroidism as compared with age-matched healthy controls, and the effects of substitution therapy with L-thyroxine.

## SUBJECTS AND METHODS

### *Subjects*

The total population consisted of 16 patients (eight males and eight females) aged 1 year or less with congenital hypothyroidism who were part of a larger group of outpatients evaluated by the Department of Pediatrics of the University of Palermo. Seven of them (four males and three females aged 0.5 to 3 months) found over a 15-month period were studied at the time of diagnosis (before any treatment) and also after a period of 2.0 ± 1.0 months of substitution therapy with L-thyroxine (5.9 ± 1.2 μg/kg/d), when thyroid hormones were restored to the normal range. Nine subjects (four males and five females) on L-thyroxine therapy (mean dose, 4.5 ± 1.2 μg/kg/d) for a period of 4.7 ± 3.2 months were included in the study as well. In all patients, congenital hypothyroidism was diagnosed by neonatal screening on a blood spot; diagnosis was further confirmed by clinical evaluation and measurement of thyrotropin (TSH) and thyroid hormone levels on a blood sample. The type of hypothyroidism (aplasia or hypoplasia of thyroid gland) was evaluated by thyroid scan with $^{99}Tc$.[25] Thirty-nine

*From the Department of Internal Medicine and Geriatrics and Department of Pediatrics, University of Palermo, Palermo; and the Department of Applied Pathophysiology, University of Catania, Catania, Italy.*

*Submitted July 19, 1994; accepted February 22, 1995.*

*Address reprint requests to Carlo M. Barbagallo, MD, Viale Francesco Scaduto 6/C, 90144 Palermo, Italy.*



*0026-0495/95/4410-0009$03.00/0*

apparently healthy subjects (19 males and 20 females) matched for age were selected as controls.

### *Methods*

In all subjects, a blood sample was collected in the morning in Na-EDTA tubes as long as possible after a fast (at least 5 to 6 hours). In every sample, CHO and TG levels were measured enzymatically,[26,27] HDL-C was assayed after precipitation of apolipoprotein (apo) B–containing lipoproteins by phosphotungstic acid/magnesium chloride and enzymatic determination of cholesterol,[28] apos A-I and B were determined by an immunonephelometric method,[29] LDL-C level was calculated by a modification of the Friedewald formula, ie, LDL-C = [CHO − (TG/5 − HDL-C)] − (Lp(a) · 0.3),[30] and Lp(a), TSH, total ($T_4$) and free thyroxine ($FT_4$), and triiodothyronine ($T_3$) levels were measured by radioimmunoassay.[31-33] Quality control of plasma lipid and apolipoprotein assays was performed as previously described.[34]

### *Statistical Analysis*

Statistical analysis was performed using Student's *t* test for paired or independent data when suitable. The log of TG and Lp(a) rather than raw data were used in all statistical analyses.[35]

## RESULTS

### *Clinical Characteristics*

Clinical characteristics of all subjects are shown in Table 1. All patients studied at the time of diagnosis were affected by aplasia of the thyroid gland, and aplasia was also the prominent defect in all subjects on L-thyroxine therapy. Despite substitution therapy, not all subjects in the group on L-thyroxine therapy, which included both patients recently treated (time of therapy, 2.0 ± 1.0 months) and patients treated for a longer time (time of therapy, 4.7 ± 3.2 months), were in a completely euthyroid state. However, thyroid hormone levels were markedly improved in comparison to levels in untreated subjects. There was an obvious difference in the mean age between untreated subjects at the time of diagnosis and subjects on L-thyroxine therapy; for this reason, controls aged 0.5 to 12 months were not considered all together but were divided into two groups matched for age with the two groups of hypothyroid individuals.

**Table 1. Clinical Characteristics of All Subjects**

| Characteristic | At Time of Diagnosis | On L-Thyroxine Therapy | Controls |
|---|---|---|---|
| No. of subjects | 7 | 16 | 39 |
| Age (mo) | | | |
| Mean ± SD | 1.2 ± 0.7 | 5.3 ± 3.0 | 3.5 ± 1.7 |
| Range | 0.5-3 | 2-12 | 0.5-12 |
| Males/females | 4/3 | 8/8 | 19/20 |
| Aplasia/hypoplasia | 7/0 | 13/3 | / |
| Body weight (kg) | 3.6 ± 1.0 | 7.4 ± 2.2 | 7.0 ± 2.4 |
| TSH (μIU/mL) | | | |
| Mean ± SD | 504.7 ± 237.3 | 12.6 ± 24.4 | 1.9 ± 0.9 |
| Range | 240-996 | 0.5-100 | 0.75-4.2 |
| $T_4$ (μg/dL) | 1.2 ± 1.3 | 12.7 ± 2.8 | 13.4 ± 3.1 |
| $FT_4$ (ng/dL) | 0.6 ± 0.5 | 1.7 ± 0.6 | 1.8 ± 0.3 |
| $T_3$ (ng/mL) | 0.7 ± 0.2 | 1.7 ± 1.5 | 1.2 ± 0.4 |
| L-Thyroxine dose (μg/kg/d) | — | 5.1 ± 1.5 | — |
| Time of therapy (mo) | — | 3.7 ± 2.6 | — |

**Table 2. Lipid, Lipoprotein, and Apolipoprotein Levels in Seven Untreated Subjects With Congenital Hypothyroidism at Time of Diagnosis and in 17 Age-Matched Controls**

| Parameter | Hypothyroid Patients | *P* | Controls |
|---|---|---|---|
| Age | | | |
| Mean ± SD | 1.2 ± 0.7 | .855 | 1.3 ± 0.4 |
| Range | 0.5-3 | | 0.5-2 |
| CHO | | | |
| Mean ± SD | 187.1 ± 61.3 | .0079 | 136.0 ± 26.1 |
| Range | 120-315 | | 93-188 |
| TG | | | |
| Mean ± SD | 163.7 ± 79.0 | .3164 | 122.4 ± 68.5 |
| Range | 75-300 | | 49-330 |
| HDL-C | | | |
| Mean ± SD | 79.5 ± 16.8 | .0007 | 49.5 ± 17.1 |
| Range | 62-115 | | 21-76 |
| LDL-C | | | |
| Mean ± SD | 70.9 ± 40.1 | .4727 | 62.0 ± 20.3 |
| Range | 20-135 | | 15-96 |
| Apo A-I | | | |
| Mean ± SD | 200.8 ± 18.6 | .0004 | 148.0 ± 30.9 |
| Range | 179-226 | | 78-186 |
| Apo B | | | |
| Mean ± SD | 73.6 ± 22.8 | .8701 | 72.1 ± 18.1 |
| Range | 46-116 | | 45-100 |
| Lp(a) | | | |
| Mean ± SD | 2.8 ± 1.8 | .2976 | 5.5 ± 5.2 |
| Range | 1.4-5.4 | | 1.2-13.7 |

NOTE. Age is expressed in months and lipid parameters in mg/dL.

### *Plasma Lipids in Untreated Patients and Effects of Substitution Therapy*

Lipid, lipoprotein, and apolipoprotein levels in seven untreated subjects with congenital hypothyroidism at the time of diagnosis and in 17 age-matched controls are shown in Table 2. CHO, HDL-C, and apo A-I levels were significantly higher in patients in comparison to controls (respectively, $P = .0079$, .0007, and .0004), whereas TG, LDL-C, apo B, and Lp(a) levels were not different. In these seven subjects, after normalization of thyroid hormone levels ($T_4$, $FT_4$, and $T_3$) over a period of treatment with L-thyroxine, during which a strong reduction of TSH levels was also observed (from 504.7 ± 237.3 to 23.8 ± 35.1 μU/L), a significant decrease of HDL-C and apo A-I levels was found (respectively, by −36.2% and −24.4%, $P = .0000$ and .0001; Table 3). Individual data before and during L-thyroxine substitution therapy are shown in Fig 1. It is possible to note that all patients presented a reduction of HDL-C and apo A-I levels. To verify if these lipoprotein changes were due to L-thyroxine substitution therapy or to physiological modifications with time, we remeasured lipoprotein parameters also in 10 normal subjects approximately 2 months later than the first measurement, but no significant change was found (data not shown). In Table 4, lipid, lipoprotein, and apolipoprotein levels in all subjects with congenital hypothyroidism on L-thyroxine substitution therapy and in age-matched controls are shown. We pooled subjects recently treated with L-thyroxine with patients with congenital hypothyroidism on substitution therapy for several months to evaluate the effects of replacement therapy

**Table 3. Lipid, Lipoprotein, and Apolipoprotein Levels in Seven Subjects With Congenital Hypothyroidism at Time of Diagnosis and During L-Thyroxine Substitution**

| Parameter | At Time of Diagnosis | P | During |
|---|---|---|---|
| TSH | 504.7 ± 237.3 (240-996) | .0001 | 23.8 ± 15.1 (0.5-100) |
| CHO | 187.1 ± 61.3 | .1852 | 146.0 ± 34.1 |
| TG | 163.7 ± 79.0 | .6410 | 148.8 ± 46.4 |
| HDL-C | 79.5 ± 16.8 | .0000 | 50.7 ± 13.7 |
| LDL-C | 70.9 ± 40.1 | .7720 | 65.5 ± 24.2 |
| Apo A-I | 200.8 ± 18.6 | .0001 | 151.8 ± 23.5 |
| Apo B | 73.6 ± 22.8 | .6439 | 68.6 ± 17.0 |
| Lp(a) | 2.8 ± 1.8 | .6671 | 3.2 ± 2.1 |

NOTE. TSH is expressed in μIU/mL, and lipid parameters in mg/dL. Parenthetical values for TSH are ranges.

on lipoprotein parameters in relation to a normal lipoprotein profile, but no significant difference was found.

## DISCUSSION

The main finding of this study is that congenital hypothyroidism leads to a selective impairment of the HDL system. Although there are a number of studies evaluating relationships between thyroid function and lipids in adults,[1-17] fewer data are available on congenital hypothyroidism,[18,19] a disorder with a prevalence of one in 4,000 births, mostly due to thyroid dysgenesis (aplasia or hypoplasia).[25] In adults, hypothyroidism represents one of the most common causes of secondary hyperlipidemia.[36] In particular, both very-low-density lipoprotein (VLDL) and LDL metabolism are affected. Impaired VLDL transport and fractional catabolic rates were found, and apo B and E receptor activity was documented to be greatly reduced; also, enzymatic activities involved in lipid metabolism, like lipoprotein and hepatic lipase (HL) or lecithin cholesterol acyltransferase (L-CAT), may be low.[8-12,14,15] Therefore, in hypothyroidism plasma levels of LDL and VLDL fractions and apo B levels are considerably increased, but all these alterations are completely reversible after L-thyroxine substitution therapy.[12-15] Moreover, several studies investigated relationships between thyroid hormones and HDL metabolism. HDL-C was generally reported to be increased in hypothyroidism, with a selective elevation of $HDL_2$.[4,5,9,11,14] Hepatic apo A-I synthesis should be sensitive to thyroid status, but in hypothyroid rats a defective clearance of HDL from plasma was documented.[37,38] Also, activity of cholesterol ester transfer protein, which is involved in the exchange of esters of cholesterol between lipoproteins, was

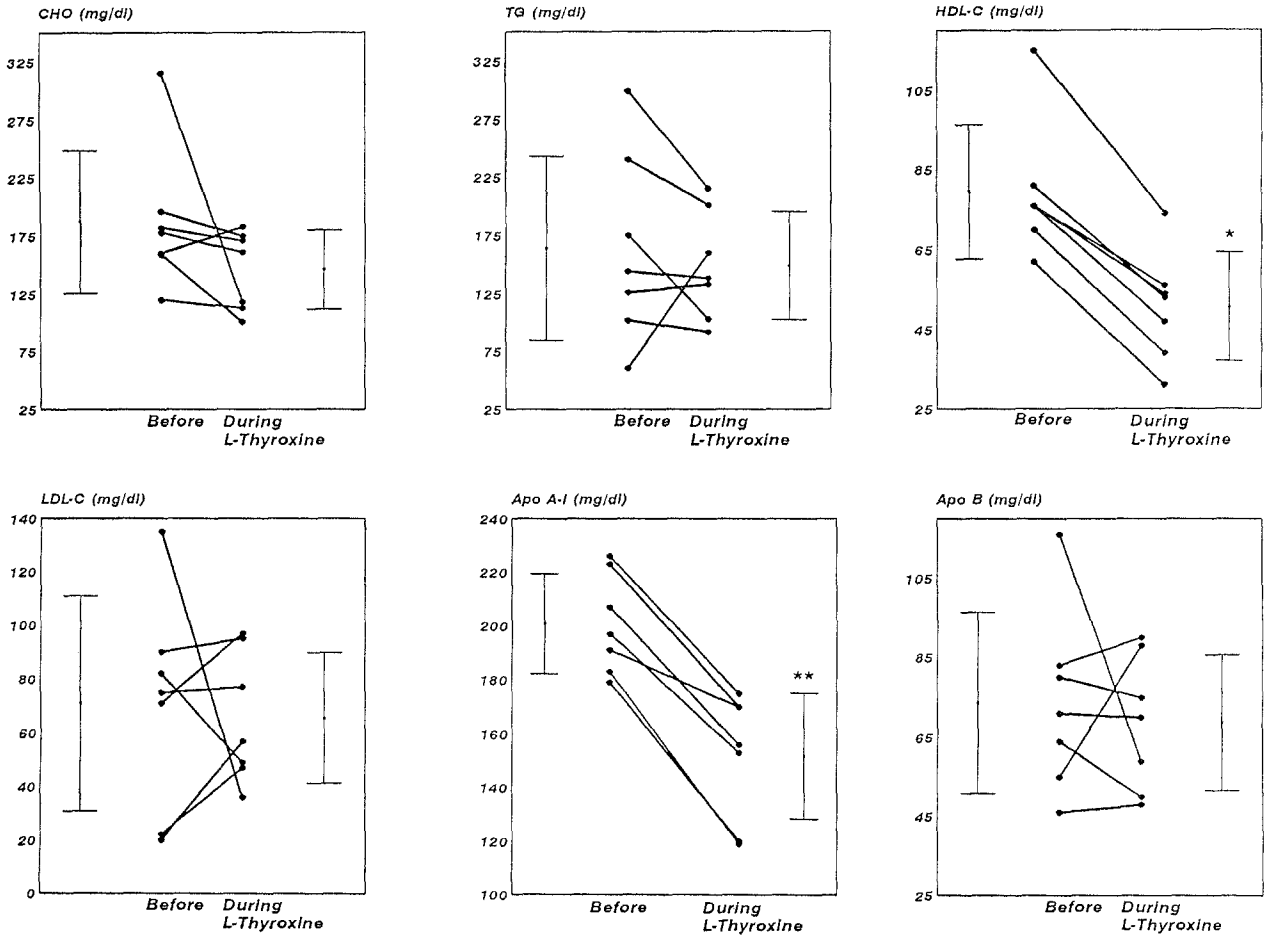


**Fig 1. CHO, TG, HDL-C, LDL-C, apo A-I, and apo B levels in 7 subjects with congenital hypothyroidism before and during L-thyroxine substitution. *P = .0000, **P = .0001: *v* before.**

**Table 4. Lipid, Lipoprotein, and Apolipoprotein Levels in 16 Subjects With Congenital Hypothyroidism on L-Thyroxine Substitution-Therapy and in 22 Age-Matched Controls**

| Parameter | Hypothyroid Patients | P | Controls |
|---|---|---|---|
| Age | 5.3 ± 3.0 (2-12) | .7635 | 5.0 ± 2.8 (2-12) |
| CHO | 151.1 ± 29.8 | .5926 | 145.3 ± 29.0 |
| TG | 148.6 ± 78.7 | .4806 | 130.6 ± 59.5 |
| HDL-C | 48.8 ± 13.5 | .4790 | 45.5 ± 15.5 |
| LDL-C | 72.5 ± 28.4 | .9419 | 73.7 ± 25.2 |
| Apo A-I | 144.0 ± 18.6 | .1089 | 131.1 ± 33.3 |
| Apo B | 81.5 ± 22.7 | .7262 | 84.1 ± 22.3 |
| Lp(a) | 7.3 ± 9.0 | .5937 | 8.2 ± 12.6 |

NOTE. Age is expressed in months, and lipid parameters in mg/dL. Parenthetical values for age are ranges.

found to be decreased in hypothyroidism.[11] These mechanisms might contribute to the increase of HDL-C levels in adult hypothyroidism. However, in newborns and in the early life, lipoprotein metabolism is consistently different from that of adults. HDL is the main lipoprotein class in cord blood, and significant differences occur in plasma concentrations and distributions of apolipoproteins in neonates as compared with adults.[20] At birth, a distinct HDL fraction enriched in apo E could be detected.[21] This particle might represent an additional source of cholesterol for peripheral tissues via the apo (B, E) receptor, while both VLDL and LDL concentrations are low.[20-22] After the onset of enteral feeding, several factors, including VLDL synthesis, lipolytic and esterification enzymes, and lipid-exchange activities, may be related to modification of the lipid profile.[39] We designed this study to verify which lipid abnormalities might occur in congenital hypothyroidism. The lipoprotein profile rapidly changes during the first weeks of life[40]; for this reason, we always compared hypothyroid subjects with strictly age-matched normal controls. We found that untreated subjects showed a significant increase of total and HDL-C and apo A-I levels, and that normalization of thyroid hormones by L-thyroxine substitution therapy was followed by a significant decrease of HDL-C and apo A-I levels. In the same period (~2 months), a group of age-matched normal controls did not show significant modification of lipoprotein profile (data not shown), and this suggests that changes observed in hypothyroid subjects were due to L-thyroxine substitution therapy and normalization of thyroid status. It is otherwise remarkable that there was a reduction in HDL-C and apo A-I levels in all subjects (Fig 1), which supports the metabolic relevance of these data. In contrast, other parameters like LDL-C or apo B, which are usually affected by hypothyroidism in adults,[1,2,6,13] were not increased at the time of diagnosis and did not significantly change during treatment. Also, Tenenbaum et al[18] previously documented that large-size HDL subfractions were increased in congenital hypothyroidism before treatment and decreased significantly after L-thyroxine therapy, but did not find any modification in LDL apo B levels. They also found that lipoprotein lipase and HL activities were significantly reduced in hypothyroid infants as compared with adult reference values, but only HL increased after therapy. In contrast, Moorjani et al,[19] as stated by the same investigators, surprisingly did not observe any lipid abnormalities in hypothyroid neonates, but did not provide any data about substitution therapy. In the present study, we also evaluated Lp(a) levels. Plasma concentrations of this lipoprotein particle are low at birth and increase during the first years of life.[41] Even if Lp(a) levels are mostly genetically determined,[42] some data seem to document that thyroid status should be able to modulate them due to the effects on the apo (B, E) receptor, but this is still being debated.[6,7] However, we were unable to demonstrate any influence of congenital hypothyroidism, as well as substitution therapy, on Lp(a) levels in our patients. When we evaluated lipid, lipoprotein, and apolipoprotein parameters in a group of infants with congenital hypothyroidism on treatment with L-thyroxine, we observed that even without achievement of a complete euthyroid status in all subjects, they did not show any difference in comparison to age-matched controls. These data suggest that although congenital hypothyroidism markedly affects lipoprotein metabolism, L-thyroxine substitution therapy is able not only to produce a reduction of impaired parameters but also to completely restore the lipoprotein profile within the normal range, and that at this age, subclinical hypothyroidism could affect lipoprotein metabolism less than in adults.[12,16] Therefore, thyroid hormones seem to be important in the physiological development of lipoprotein metabolism after birth.[39] This could be due to the modulation of the apo (B, E) receptor,[8] which in early life should mainly be reflected in the HDL system. Alternatively, other factors found to be impaired in hypothyroidism, particularly cholesterol ester transfer protein activity,[11] might contribute to increase HDL, which represents the main lipoprotein particle in the first weeks of life.

In conclusion, our data document that infants with congenital hypothyroidism mainly show high HDL-C and apo A-I levels, without any modifications of TG, LDL-C, apo B, or Lp(a) levels, and that L-thyroxine substitution therapy is able to restore a normal lipid profile. Since HDL plays a major role in newborns and in the first days of life, we suggest that thyroid hormones modulate the physiological development of lipoprotein metabolism after birth, and that the lack of thyroid hormones does not permit complete evolution of the newborn lipid pattern toward the adult profile.

## ACKNOWLEDGMENT

The authors thank Dr Gisella Marino, Dr Lia Caldarella, and Dr Angela Rao Camemi for technical assistance.

## REFERENCES

1. Ballantyne FC, Epenetos AA, Caslake M, et al: The composition of low-density lipoprotein subfractions in primary hypothyroidism and the effect of hormone-replacement therapy. Clin Sci 57:83-88, 1979

2. Abrams JJ, Grundy SM: Cholesterol metabolism in hypothyroidism and hyperthyroidism in man. J Lipid Res 22:323-338, 1981

3. Nikkila EA, Kekki M: Plasma triglyceride metabolism in thyroid disease. J Clin Invest 51:2103-2114, 1972

4. Verdugo C, Perrot L, Ponsin G, et al: Time-course of alterations of high density lipoproteins (HDL) during thyroxine administration to hypothyroid women. Eur J Clin Invest 17:313-316, 1987

5. Muls E, Rosseneu M, Lamberigts G, et al: Changes in the distribution and composition of high-density lipoproteins in primary hypothyroidism. Metabolism 34:345-353, 1985

6. De Bruin TW, Van Barlingen H, Van Linde-Sibenius Trip M, et al: Lipoprotein(a) and apolipoprotein B plasma concentrations in hypothyroid, euthyroid, and hyperthyroid subjects. J Clin Endocrinol Metab 76:121-126, 1993

7. Klausen IC, Nielsen FE, Hegedus L, et al: Treatment of hypothyroidism reduces low-density lipoproteins but not lipoprotein(a). Metabolism 41:911-914, 1992

8. Thompson GR, Soutar AK, Spengel FA, et al: Defects of receptor-mediated low density lipoprotein catabolism in homozygous familial hypercholesterolemia and hypothyroidism in vivo. Proc Natl Acad Sci USA 78:2591-2595, 1981

9. Kuusi T, Taskinen MR, Nikkila EA: Lipoproteins, lipolytic enzymes and hormonal status in hypothyroid women at different levels of substitution. J Clin Endocrinol Metab 66:51-56, 1988

10. Abrams JJ, Grundy SM, Ginsberg H: Metabolism of plasma triglycerides in hypothyroidism and hyperthyroidism in man. J Lipid Res 22:307-322, 1981

11. Dullaart RP, Hoogenberg K, Groener JE, et al: The activity of cholesterol ester transfer protein is decreased in hypothyroidism: A possible contribution to alterations in high-density lipoproteins. Eur J Clin Invest 20:581-587, 1990

12. Lithell H, Boberg J, Hellsing K, et al: Serum lipoprotein and apolipoprotein concentrations and tissue lipoprotein-lipase activity in overt and subclinical hypothyroidism: The effect of substitution therapy. Eur J Clin Invest 11:3-10, 1981

13. Muls E, Rosseneu M, Blaton V, et al: Serum lipids and apolipoproteins A-I, A-II and B in primary hypothyroidism before and during treatment. Eur J Clin Invest 14:12-15, 1984

14. Packard CJ, Shepherd J, Lindsay GM, et al: Thyroid replacement therapy and its influence on postheparin plasma lipases and apolipoprotein-B metabolism in hypothyroidism. J Clin Endocrinol Metab 76:1209-1216, 1993

15. Valdemarsson S, Hedner P, Nilsson-Ehle P: Reversal of decreased hepatic lipase and lipoprotein lipase activities after treatment of hypothyroidism. Eur J Clin Invest 12:423-428, 1982

16. Arem R, Patsch W: Lipoprotein and apolipoprotein levels in subclinical hypothyroidism. Effect of levothyroxine therapy. Arch Intern Med 150:2097-2100, 1990

17. Agdeppa D, Macaron C, Mallik T, et al: Plasma high density lipoprotein cholesterol in thyroid disease. J Clin Endocrinol Metab 49:726-729, 1979

18. Tenenbaum D, Gambert P, Fischbach M, et al: Alterations of serum high-density lipoproteins and hepatic lipase activity in congenital hypothyroidism. Biol Neonate 54:241-245, 1988

19. Moorjani S, Dussault JH, Lupien PJ, et al: Plasma lipid and lipoprotein concentrations are normal in congenital hypothyroidism. Clin Chem 30:158-159, 1984

20. Averna MR, Barbagallo CM, Di Paola G, et al: Lipids, lipoproteins and apolipoproteins $A_I$, $A_{II}$, B, $C_{II}$, $C_{III}$ and E in newborns. Biol Neonate 60:187-192, 1991

21. Van Biervliet JP, Rosseneu M, Bury J, et al: Apolipoprotein and lipid composition of plasma lipoproteins in neonates during the first month of life. Pediatr Res 20:324-328, 1986

22. Carr BR, Parker CR Jr, Milewich L, et al: The role of low density, high density, and very low density lipoproteins in steroidogenesis by the human fetal adrenal gland. Endocrinology 106:1854-1860, 1980

23. La Franchi SH, Hanna CE, Krainz PL, et al: Screening for congenital hypothyroidism with specimen collection at two time periods: Results of the Northwest Regional Screening Program. Pediatrics 76:734-740, 1985

24. Glorieux J, Dussault JH, Morissette J, et al: Follow-up at ages 5 and 7 years on mental development in children with hypothyroidism detected by Quebec screening program. J Pediatr 107:913-915, 1986

25. Fisher DA: Management of congenital hypothyroidism. J Clin Endocrinol Metab 72:523-529, 1991

26. Roschlau P, Bernt E, Gruber W: Enzymatische bestimmung des gesamte-cholesterins in serum. Klin Chem Biochem 12:403-407, 1974

27. Wahlefeld AW: Triglycerides determination after enzymatic hydrolysis, in Bergmeyer HU (ed): Methods of Enzymatic Analysis, vol 4. New York, NY, Academic, 1974, pp 1831-1835

28. Lopez-Virella MF, Stone P, Ellis S, et al: Cholesterol determination in high density lipoproteins separated by three different methods. Clin Chem 23:882-884, 1977

29. Becker W, Schafer W, Ziegenbein W: Standardization of immunochemical quantitation of human apolipoproteins A and B. Ric Clin Lab 10:203-212, 1980

30. Sandkamp M, Funke H, Schulte H, et al: Lipoprotein(a) is an independent risk factor for myocardial infarction at a young age. Clin Chem 36:20-23, 1990

31. Albers JJ, Adolphson JL, Hazzard WR: Radioimmunoassay of human plasma Lp(a) lipoprotein. J Lipid Res 18:331-338, 1977

32. Pekary AE, Hershman JM, Parlow AF: A sensitive and precise radioimmunoassay of human thyroid-stimulating hormone. J Clin Endocrinol Metab 41:676-684, 1975

33. Weeke J, Orskov H: Evaluation of thyroid function, in Alberti KGMM (ed): Recent Advances in Clinical Biochemistry. Edinburgh, UK, Churchill Livingstone, 1978, pp 111-128

34. Averna MR, Barbagallo CM, Galione A, et al: Serum apolipoprotein profile of hypertriglyceridemic patients with chronic renal failure on hemodialytic therapy: A comparison with type IV hyperlipoproteinemia. Metabolism 38:601-602, 1989

35. Snedecor GW, Cochran WG: Statistical Methods. Ames, IA, Iowa State University Press, 1964

36. Mishkel MA, Crowther SM: Hypothyroidism, an important cause of reversible hyperlipidemia. Clin Chim Acta 74:139-151, 1977

37. Gross G, Sykes M, Arellano R, et al: HDL clearance and receptor-mediated catabolism of LDL are reduced in hypothyroid rats. Atherosclerosis 66:269-275, 1987

38. Wilcox HG, Frank RA, Heimberg M: Effects of thyroid status and fasting on hepatic metabolism of apolipoprotein A-I. J Lipid Res 32:395-405, 1991

39. Genzel-Boroviczeny O, D'Harlingue AE, Kao LC, et al: High-density lipoprotein subclass distribution in premature newborns before and after the onset of enteral feeding. Pediatr Res 23:543-547, 1988

40. Ginsburg BE, Zetterstrom R: Serum cholesterol concentration in early infancy. Acta Paediatr Scand 69:581-585, 1980

41. Van Biervliet JP, Labeur C, Michiels G, et al: Lipoprotein(a) profiles and evolution in newborns. Atherosclerosis 86:173-181, 1991

42. Boerwinkle E, Menzel HJ, Kraft HG, et al: Genetics of the quantitative Lp(a) lipoprotein trait. Hum Genet 82:73-78, 1989