Serum High-Density Lipoprotein Cholesterol Concentrations in Hypo- and Hyperthyroidism

Alfred G. Scottonini,1 Nadhipuram V. Bhagavan, Thelma H. Oshiro, and Suzanne Y. Abe

We studied alterations in the concentration of high-density lipoprotein cholesterol and of other lipid categories (total cholesterol, low-density lipoprotein cholesterol, very-low-density lipoprotein cholesterol, and triglycerides) in serum in hypo- and hyperthyroid states, and compared these findings with those for a control group. In the latter group the lipids showed an age-related increase in concentration but with a decrease in the eighth decade in all categories. In untreated hypo- and hyperthyroid subjects, all of the lipid values differed significantly from those of the controls but promptly returned to normal values upon treatment. In hypothyroid patients who are prone to develop coronary heart disease, the concentrations of high-density lipoprotein cholesterol were high, suggesting protection against heart disease, while the ratio to total cholesterol indicated the contrary. The exact opposite of these relationships was seen in hyperthyroid disorders. This apparent paradox suggests that the low-density lipoprotein cholesterol in serum, with its established atherogenic effect, should be given at least equal, if not more, weight than the concentration of high-density lipoprotein cholesterol in serum, with its alleged protective effect.

Additional Keyphrases: factors related to risk of coronary heart disease • lipoproteins • sex-and-age-related effects • reference intervals • atherosclerosis

Besides measuring components directly related to thyroid function—i.e., some representation of thyroid hormone concentration—physicians have also measured indirect indicators such as serum cholesterol concentration, basal metabolic rate, tendon reflexes, and, more recently, activities or concentrations in serum of creatine kinase (EC 2.7.3.2), lactate dehydrogenase (EC 1.1.1.27), aspartate aminotransferase (EC 2.6.1.1), protein, and albumin. In recent years, investigators have begun examining the whole lipid profile, including triglycerides, but especially serum cholesterol and its fractions (2-4). In 1978, we began a study of concentrations of various lipids in health and disease, especially in those diseases predisposing to heart disorders.

Materials and Methods

We examined serum concentrations of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), very low-density lipoprotein cholesterol (VLDL-C), triglycerides (TG), and the ratio of TC to HDL-C. The control subjects were 136 apparently healthy women and 158 apparently healthy men, ranging in age from their 20's to 70's. They were recruited from medical and paramedical personnel and health-plan members referred for multiphasic screening. Anyone with a suspected illness or known medical problem was excluded.

The test sample consisted of patients referred to the Kaiser Foundation Hospital clinical laboratory for specific thyroid-function tests, to assess suspected thyroid dysfunction. Whenever thyroid dysfunction was corroborated, we also requested these patients to fast when possible before collection of additional serum for lipid studies. The patients were 41 men and 200 women, ranging in age from their teens to the 80's.

The basic screening test for thyroid function in our laboratory is the effective thyroid index (Res-O-Mat ETR; Mallinckrodt, Inc., St. Louis, MO 63134), a double competitive-protein-binding technique yielding a so-called "normalized T4," in which effects of drugs, hormones, pregnancy, and variations in thyroxine-binding globulin have been corrected for (5, 6). The reference interval for this index in our laboratory is 0.86 to 1.13. Its one limitation, of course, is that it will not measure triiodothyronine (T3) and, hence, triiodothyronine thyrotoxicosis. All cases of suspected hypothyroidism and hyperthyroidism were confirmed by serum thyrotropin concentrations and radioactive iodine uptake, respectively. In equivocal cases additional laboratory tests were performed (T3 and T4 radioimmunoassay and T3 uptake). All gamma counting was done with an Auto-Logic gamma counter (Abbott Laboratories, Inc., North Chicago, IL 60064).

Serum cholesterol concentrations were measured by an enzymic method with a Bichromatic Chemical Analyzer ABA-100 (Abbott Laboratories, Inc.). HDL-C was determined by a polyaminoc acid precipitation technique with dextran sulfate-magnesium salt (Mg++) (7). The precipitate removes all the apoprotein-B-associated lipoproteins (LDL and VLDL) so that HDL-C can be measured in the supernate. Warnick et al. (8) found this method to have the lowest coefficient of variation of all the polyamic procedures, and results from it correlated well with results by the ultracentrifugation method. We estimated VLDL as one-fifth of the triglycerides in the sera of patients who had fasted for 14 h (if TG exceeds 4.00 g/L, this relationship between VLDL and TG is not valid). HDL-C was estimated as TC - (TG/5) - LDL-C.

All computed ranges are based upon the mean (±) and one standard error of the mean (±SEM). Statistical significance of differences between group means was assessed by use of Student's t-test.

Results

Table 1 shows that for apparently normal women, values for all lipid categories progressively increase with age until the eighth decade, when mean values resemble those of the high decade. We can speculate that those persons who lived beyond the eighth decade were in some way protected, perhaps by a higher than normal HDL-C concentration; however, the average HDL-C in the eighth decade is 40 (±SEM 11) mg/dL and the TC/HDL-C ratio is 5.1 (±SEM 0.3). Castelli and coworkers (9, 10) found that for women who are at lower risk of coronary heart disease than men, the average HDL-C is 550 mg/dL and that the average

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2. Nonstandard abbreviations used: TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; VLDL-C, very low-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.
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TC/HDL-C ratio is 4.4 and 5.3 for the average normal woman and heart-attack victim, respectively. Note the significant decrease in LDL-C in the eighth decade in our population.

Table 1 also lists values for 158 healthy men. For them, the age-related progression and decrease in the eighth decade is the same as for women. Although women generally appear to be protected from coronary heart disease to the sixth decade (the average HDL-C is 550 mg/L in women and 450 mg/L in men), the risk is comparable in both sexes thereafter; in fact, men may have an advantage in the eighth decade and beyond.

The sex and age distribution of patients with thyroid disease is shown in Table 2. Although the average age of onset of disease and the incidence by age is comparable in both sexes, hyperthyroidism appears about a decade earlier than hypothyroidism in both sexes. In addition, the well-known fact that thyroid dysfunction is more common in women than men is clearly apparent here, the ratio being 5 to 1.

* Numbers in parentheses represent number of subjects.

The results in Table 3 demonstrate significant differences in mean values between hypo- and hyperthyroid subjects—except for HDL-C in men. The lack of a significant difference may be a consequence of the small number of men in each category.

Note how misleading and even contradictory various indexes can be in evaluating risk factors, e.g., the HDL-C and TC/HDL-C in each sex. The average hypothyroid woman appears to be protected as judged from her HDL-C (av. normal = 550 mg/L) but at increased risk as judged from her TC/HDL-C (av. normal = 4.4); these factors are reversed in the average hyperthyroid woman. Though less striking, these observations apply to the average man as well. The well-known changes in TC between hypo- and hyperthyroidism are confirmed in this study.

Table 4 demonstrates very graphically the return to normal ranges of all lipid values in women patients who have been treated for thyroid disorders; there is no significant difference between mean values for the hypo- and hyperthyroid groups. We cannot compare all the values measured—especially LDL, VLDL, and TG—in the treated and untreated states, because most patients in this series, when seen for the initial thyroid function test, had not been fasting for the required 14 h (currently, all cases of suspected thyroid dysfunction are subject to serum lipid panels as part of their initial work-up). However, the changes in TC, HDL-C, and TC/HDL-C are dramatic. Furthermore, when one follows the changes in individual cases (Table 5), a striking inverse relationship between the effective thyroxine ratio and lipids becomes apparent; i.e., when the effective thyroxine ratio decreases, values for all lipid categories increase, and vice versa. We found unusually high HDL-C concentrations in most of the hypothyroid patients—clearly at or above the "longevity

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**Table 1. Lipid Concentrations in Sera of Healthy Subjects**

<table>
<thead>
<tr>
<th>Age group, yr</th>
<th>No. of subjects</th>
<th>TC (Mean, SEM), mg/L</th>
<th>LDL-C (Mean, SEM), mg/L</th>
<th>HDL-C (Mean, SEM), mg/L</th>
<th>VLDL-C (Mean, SEM), mg/L</th>
<th>TG (Mean, SEM), mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-29</td>
<td>19</td>
<td>1900 (128)</td>
<td>1200 (124)</td>
<td>550 (37)</td>
<td>170 (11)</td>
<td>800 (55)</td>
</tr>
<tr>
<td>30-39</td>
<td>26</td>
<td>2120 (116)</td>
<td>1390 (100)</td>
<td>520 (25)</td>
<td>210 (24)</td>
<td>1050 (120)</td>
</tr>
<tr>
<td>40-49</td>
<td>22</td>
<td>2330 (111)</td>
<td>1560 (100)</td>
<td>500 (26)</td>
<td>270 (32)</td>
<td>1370 (166)</td>
</tr>
<tr>
<td>50-59</td>
<td>31</td>
<td>2770 (118)</td>
<td>1860 (110)</td>
<td>530 (25)</td>
<td>360 (27)</td>
<td>1800 (135)</td>
</tr>
<tr>
<td>60-69</td>
<td>28</td>
<td>2970 (95)</td>
<td>2030 (98)</td>
<td>580 (30)</td>
<td>340 (30)</td>
<td>1730 (149)</td>
</tr>
<tr>
<td>70 and above</td>
<td>10</td>
<td>2410 (142)</td>
<td>1610 (120)</td>
<td>480 (41)</td>
<td>310 (28)</td>
<td>1570 (136)</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-29</td>
<td>19</td>
<td>1770 (99)</td>
<td>1140 (87)</td>
<td>450 (21)</td>
<td>180 (23)</td>
<td>870 (108)</td>
</tr>
<tr>
<td>30-39</td>
<td>32</td>
<td>2160 (118)</td>
<td>1470 (113)</td>
<td>430 (18)</td>
<td>260 (27)</td>
<td>1300 (131)</td>
</tr>
<tr>
<td>40-49</td>
<td>36</td>
<td>2420 (85)</td>
<td>1650 (83)</td>
<td>450 (18)</td>
<td>330 (32)</td>
<td>1660 (157)</td>
</tr>
<tr>
<td>50-59</td>
<td>35</td>
<td>2360 (103)</td>
<td>1530 (85)</td>
<td>480 (22)</td>
<td>400 (24)</td>
<td>1640 (146)</td>
</tr>
<tr>
<td>60-69</td>
<td>25</td>
<td>2410 (138)</td>
<td>1640 (112)</td>
<td>440 (18)</td>
<td>330 (26)</td>
<td>1660 (134)</td>
</tr>
<tr>
<td>70 and above</td>
<td>11</td>
<td>2180 (175)</td>
<td>1410 (166)</td>
<td>520 (45)</td>
<td>260 (39)</td>
<td>1320 (193)</td>
</tr>
</tbody>
</table>

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**Table 2. Sex and Age (in Years) Distribution of Patients**

<table>
<thead>
<tr>
<th>Sex</th>
<th>Average Age (Range)</th>
<th>Average Age (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (41)</td>
<td>41 (19) 21-76</td>
<td>41 (22) 14-88</td>
</tr>
<tr>
<td>Female (200)</td>
<td>52 (69) 18-82</td>
<td>44 (131) 18-74</td>
</tr>
</tbody>
</table>

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**Table 3. Total Cholesterol, HDL-Cholesterol, and TC/HDL-C Ratios in Sera of Untreated Hypo- and Hyperthyroid Patients**

<table>
<thead>
<tr>
<th>Hypothyroid</th>
<th>Hyperthyroid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (and SEM)</td>
<td>Mean (and SEM)</td>
</tr>
</tbody>
</table>

**Table 4. Lipid Values in Sera of Women Patients Treated for Thyroid Disorders**

<table>
<thead>
<tr>
<th>Hypothyroid</th>
<th>Hyperthyroid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (and SEM)</td>
<td>Mean (and SEM)</td>
</tr>
</tbody>
</table>

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* The difference between the two thyroid states is significant (p < 0.001).
syndrome” concentration described by Glueck et al. (11); yet it is well established that patients with hypothyroidism are prone to develop accelerated arteriosclerosis.

**Discussion**

Tables 3-5 indicate an inverse relationship between thyroid function and the concentration of various lipids in the serum. This relationship is especially apparent when one follows the fluctuations during the management of individual cases of either hyper- or hypothyroidism. With treatment, lipid values returned to normal in almost all cases. Other investigators have studied serum lipoprotein concentrations in hypothyroidism (2, 4, 12), but their main objective was to phenotype hyperlipidemia and to reverse it with therapy. None, to our knowledge, has examined total cholesterol and its fractions in relationship to hypo- and hyperthyroidism. Mishkel and Crowthers (4) found that hypothyroidism is followed by hyperlipidemia in approximately 1.6% of cases and may be preceded by it for several years, during which time the patient will appear to be euthyroid (normal serum concentration of thyroid but above-normal thyrotropin). This state has been dubbed “compensated hypothyroidism.” Most cases of hyperlipidemia associated with hypothyroidism mimic types II A, II B, or IV; on occasion, a case is associated with a rare type III. All of these usually regress with thyroxine therapy.

A paradoxical finding in our study is that in most cases of hypothyroidism the concentration of HDL-C is strikingly increased, as is TC. This suggests that these patients are protected against coronary heart disease by virtue of the former. However, the TC/HDL-C ratios are much higher than normal, implying that these patients are at greater risk. On the other hand, in hypothyroidism values for TC, HDL-C, and TC/HDL-C are low, thus creating another seeming contradiction: the HDL-C values indicate these patients are at risk, while the TC/HDL-C ratios imply they are not. What is the truth under these circumstances?

Serum lipid concentrations reflect thyroid hormone effect on synthesis, catabolism, and mobilization. Cholesterol synthesis in the liver is enhanced in hyperthyroidism and depressed in hypothyroidism. However, hepatic cholesterol catabolism is depressed even more in hypothyroidism, so that the resulting concentration of serum cholesterol is increased. Others (13, 14) have shown that hypothyroid individuals excrete less fecal bile acid, neutral sterols, and total steroids than do normals. Administration of thyroxine produced the opposite effect, and at the same time the above-normal concentrations of serum cholesterol returned to normal. Hypothyroidism is also associated with a decreased rate of catabolism of LDL, and restoration to normal occurs with euthyroid state (15). Tullock et al. (16) found the triglycerides were increased in nine of 10 hypothyroid patients, but returned to normal on administration of thyroxine. The increased TG is attributable to decreased clearance. After treatment with heparin, lipolytic activity is also reduced and usually returns to normal. In short, hypertriglyceridemia of hypothyroidism is the result of decreased clearance of VLDL rather than of increased hepatic production of VLDL from circulating free fatty acids. Presumably, all effects are reversed with hyperthyroidism. Another finding in our work and that of others (17-21) is the age-related increase in serum cholesterol. These same authors found that serum concentration of T4 remains the same throughout life. However, T3 decreased significantly in older subjects. Kinetic analysis of T4 and T3 strongly suggests that low serum T3 in older subjects is due to decreased peripheral conversion of T4 to T3. Ikejiri et al. (17) have studied the relationship between serum cholesterol and T3 concentrations. They found an inverse correlation between serum cholesterol concentration and serum T3 concentration when the latter is below normal. It appears, therefore, that the progressive increase in serum cholesterol with age is due in part to a progressive decrease of serum T3.
Our seemingly contradictory data suggest that hypothyroid subjects are protected by a relatively high HDL-C, only to be at jeopardy as a result of a higher than normal ratio of TC/HDL-C, while hyperthyroid subjects appear simultaneously vulnerable by virtue of low HDL-C and protected by a low ratio of TC/HDL-C. We know that hypothyroid subjects are prone to develop coronary heart disease, whereas hyperthyroid subjects are not. Why? Have the epidemiologic data correlating high HDL-C with protection against coronary heart disease been misinterpreted? Is this a chance relationship? Are there other factors that deserve scrutiny? The TC/HDL-C ratio (or even LDL-C) may be a better predictor of risk than HDL-C alone. As indicated above, approximately 80% of serum TC is carried by LDL and most of the remainder by HDL. Table 3 makes clear that although values for all lipid categories are different in hypo- and hyperthyroid patients from those for normal subjects (Table 1), the most dramatic changes are in mean serum TC and mean ratio of TC/HDL-C. In fact, the HDL-C data from the men (Table 3) are not significantly different from the mean value of 450 mg/L for normal men. We are forced to conclude, therefore, that it is the predominant LDL-C moiety that is responsible for the striking changes in both serum TC and ratios of serum TC/HDL-C.

We suggest, then, that the concentration of serum LDL-C, with established atherogenic effect, should be given at least as much weight as the concentration of serum HDL-C, with its alleged protective effect, in the assessment of risk for coronary heart disease.

Addendum

Our attention has been directed to the recently published work of Agdeppa et al. (22) regarding HDL-C in thyroid disease. Our results differ from theirs in one important aspect; namely, HDL-C concentrations are lower in their hypothyroid patients than in the euthyroid subjects (43.4 ± 15.5 vs 51.5 ± 13; p < 0.05) but still higher than the HDL-C of the hyperthyroid group. We are as surprised by this finding as the authors were, in view of our own strikingly contrasting results and the expectation of slower catabolism of HDL-C in hypothyroidism than in the euthyroid state. Although we have no satisfactory explanation for this discrepancy, we are constrained to point out that the authors firstly, by their own admission, studied a small population of patients with hypothyroidism (22 women vs 69 women and 19 men in our study) and, secondly, utilized a different polyanimic precipitation technique (sodium phosphotungstate–Mg2+). Warnick et al. (8) have indicated that precipitation by this method appears more sensitive to reagent concentration and temperature variations than the heparin–Mn2+ or dextran sulfate–Mg2+ (our technique) methods, and gives rise to significant systematic differences in HDL-C quantitation (CVs of 6–7% for the former and 4% for the latter).

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References