Effect of Thyroid Function on LDL Oxidation

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Abstract—In this study, the effect of different levels of thyroid hormone and metabolic activity on low density lipoprotein (LDL) oxidation was investigated. Thus, in 16 patients with hyperthyroidism, 16 with hypothyroidism, and 16 age- and sex-matched healthy normolipidemic control subjects, the native LDL content in lipid peroxides, vitamin E, β-carotene, and lycopene, as well as the susceptibility of these particles to undergo lipid peroxidation, was assessed. Hyperthyroidism was associated with significantly higher lipid peroxidation, as characterized by a higher native LDL content in lipid peroxides, a lower lag phase, and a higher oxidation rate than in the other two groups. This elevated lipid peroxidation was associated with a lower LDL antioxidant concentration. Interestingly, hypothyroid patients showed an intermediate behavior. In fact, in hypothyroidism, LDL oxidation was significantly lower than in hyperthyroidism but higher than in the control group. Hypothyroidism was also characterized by the highest β-carotene LDL content, whereas vitamin E was significantly lower than in control subjects. In hyperthyroidism but not in the other two groups, LDL oxidation was strongly influenced by free thyroxine blood content. In fact, in this group, the native LDL lipid peroxide content and the lag phase were directly and indirectly, respectively, related to free thyroxine blood levels. On the contrary, in hypothyroidism LDL oxidation was strongly and significantly related to serum lipids. In conclusion, both hypothyroidism and hyperthyroidism are characterized by higher levels of LDL oxidation when compared with normolipidemic control subjects. In hyperthyroid patients, the increased lipid peroxidation was strictly related to free thyroxine levels, whereas in hypothyroidism it was strongly influenced by serum lipids. (Arterioscler Thromb Vase Biol. 1998;18:732-737.)

Key Words: thyroid hormone ▪ lipid peroxidation ▪ LDL oxidation ▪ antioxidant vitamins

Thyroid hormones play a crucial role in the regulation of mitochondrial oxidative metabolism; the synthesis and degradation of proteins and vitamins, such as vitamin E, vitamin A, and β-carotene; the sensitivity of tissues to catecholamines; and the regulation of antioxidant enzyme levels.1 Overt hyperthyroidism and hypothyroidism represent opposite clinical conditions characterized respectively by enhanced oxidative metabolism and reduced lipid and lipoprotein plasma levels and by reduced oxidative metabolism and markedly increased lipid and lipoprotein plasma levels. The hypermetabolic state that characterizes hyperthyroidism should accelerate free radical production in the mitochondria and induce changes in the antioxidant defense system.2 In contrast, the metabolic suppression brought about by hypothyroidism is associated with a decrease in free radical production, and it has also been suggested that hypothyroidism protects tissues against acceleration of lipid peroxidation.3-5 Increasing experimental and epidemiological evidence shows that high oxidative stress status favors oxidative modifications of LDL and plays an important role in the development of atherosclerosis.6-8 Nevertheless, hypothyroidism but not hyperthyroidism represents an important risk factor for atherosclerosis and coronary heart disease.9 In view of well-documented strong relationships between blood cholesterol, LDL oxidation, and atherosclerosis, we used two opposite metabolic conditions, overt hyperthyroidism and hypothyroidism, to better understand the relationships between metabolic activity, blood lipids, lipoprotein content, and LDL oxidation.

Methods

Sixteen patients with overt hyperthyroidism, 16 with overt hypothyroidism, and 16 control subjects were enrolled in the study. Subjects in accord with inclusion and exclusion criteria were consecutively selected from the population referred to the Regional Thyroid Unit of Chieti, Abruzzo, Italy. Groups were matched for age and sex. All control subjects had normal serum lipid levels, ie, serum TC ≤5.7 mmol/L and triglycerides ≤2.8 mmol/L. Overt hyperthyroidism was defined as a basal serum TSH concentration <0.1 μU/mL and a basal serum FT4 concentration >26 pmol/L. Overt hypothyroidism was defined as a basal serum TSH concentration >20 μU/mL and a basal serum FT4 concentration <8 pmol/L. The TSH normal range was 0.1 to 4.5 μU/mL, and the FT4 normal range was 11 to 26 pmol/L. Participants had to fulfill all of the following criteria to be entered into the study: nonsmokers; not taking any...
Biochemical Determinations

Fasting venous blood samples were obtained for a complete blood count, plasma glucose and protein determinations, and assessment of hepatic and renal function. All of these variables were assayed by standard laboratory techniques. Blood was also obtained for the determination of the lipid profile, serum thyroid hormone concentrations, and LDL isolation. In this study, LDL oxidation was evaluated as the susceptibility of LDL to undergo lipid peroxidation and as the n-LDL lipid peroxide content as assessed by fluorometrically detected TBARS and FPLPs.

Seventy Abbreviations and Acronyms

FPLP = fluorescent product of lipid peroxidation
FT₃ = free thyroxine
HPLC = high-performance liquid chromatography
LDL-C = LDL cholesterol
n- = native
TBARS = thiobarbituric acid–reactive substances
TC = total cholesterol
TSH = thyrotropin

Serum Lipids and Lipoprotein Assay

TC and triglycerides were measured by standard automated enzymatic techniques. HDL cholesterol was assessed after precipitation of serum with dextran sulfate. The LDL-C level was calculated after precipitation of serum with dextran sulfate. The LDL-C level was calculated by the Friedewald formula: TC = HDL cholesterol + triglycerides/5.

Serum Hormone Concentrations

The serum TSH concentration was measured by immunoradiometric assay (RIA-gnost hTSH, CIS Bio-international). The serum FT₃ concentration was determined by radioimmunoassay (Coat-A-Count Free T₄, Diagnostic Products Corp).

LDL Isolation and Oxidation

After an overnight fast, blood was drawn into test tubes containing 1 mmol/L EDTA. Plasma was separated by low-speed centrifugation at 1500g for 15 minutes, immediately supplemented with 20 μmol/L BHT, stored at −80°C under N₂, and used for LDL isolation within 3 days. Previous studies have shown that plasma storage and freezing/thawing does not affect LDL isolation and its major chemical characteristics. LDL was isolated by single vertical-spin ultracentrifugation with a discontinuous NaCl/KBr density gradient. All solutions used for lipoprotein preparations contained 1 mmol/L EDTA. After 86 minutes at 397 700 g and 7°C in a Centrikon TVF 6513 vertical rotor (Kontron Instruments), LDL was recovered from the mid-upper part of the HPLC water and dried under a stream of N₂ gas at room temperature, resuspended in chloroform (2.5 mL), and exposed to UV light. Fluorescence values were estimated spectrally at 360 nm excitation and 430 nm emission using a Kontron SFM25 spectrophotometer calibrated with quinine sulfate. Results were expressed as units of relative fluorescence per milligram of LDL-C.

TBARS

The lipid peroxide content of n-LDL was also evaluated fluorometrically as TBARS. LDL (100 μg protein) was mixed with 1.5 mL of 0.67% TBA and 1.5 mL of 20% trichloroacetic acid containing 1 mg/mL EDTA. After the mixture was heated at 100°C for 30 minutes, fluorescent reaction products were estimated spectrophotometrically at 515 nm excitation and 553 nm emission using a Kontron SFM25 spectrophotometer. Freshly diluted tetramethoxypropane, which yields malondialdehyde, was used as a standard, and results were expressed as nanomoles of malondialdehyde equivalents per milligram of LDL-C.

LDL Antioxidant Determinations

The LDL contents in vitamin E, β-carotene, and lycopene were determined by HPLC. Vitamins were separated and quantified by using a Kontron system 450 equipped with a UV–visible wavelength variable Kontron detector 430. Analysis was performed by isocratic elution. The flow rate was 1.5 mL/min. The mobile phase, consisting of methanol/butanol/water (89.5:5.5:5, vol/vol/vol), was premixed and vacuum filtered through a 0.45-μm polypropylene membrane filter (Whatman) before use. Autoinjection of 10 μL of organic extract was performed with a Waters autoinjector (model 717 plus autosampler) refrigerated at 5°C. The analytical column used was a replaceable Partisil 5 C₅, cartridge (10×4.7 mm inner diameter, 5-μm particle size, Whatman) protected by a guard cartridge (15×5 μm) system and maintained at 45°C. Vitamin E, tocopherol acetate (internal standard), lycopene, and β-carotene were detected by the UV–visible light spectrophotometer at different wavelengths programmed for analysis as follows: at 0 minutes, 290 nm; 4.5 minutes, 280 nm; and 15 to 22 minutes, 450 nm. Vitamins were expressed as micrograms per milligram of LDL-C.

Free Fatty Acid Measurements in LDL

The fatty acid composition of LDL was determined by HPLC according to the method of Miwa and Yamamoto. In brief, 1 mL LDL was extracted with 8 mL chloroform/methanol (2:1, vol/vol). The extracts were washed with 2 mL of HPLC water and dried under N₂ at 25 μL of ethanol containing 2 mmol/L marginal (heptadecanoic) acid as the internal standard was then added. Fatty acids were converted into their 2-nitrophenylhydrazide forms by the addition of 100 μL of 2-nitrophenylhydrazine HCl (20 mmol/L) and 200 μL of equal volumes of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide HCl (250 mmol/L) and 13% ethanolic pyridine. The mixture was then heated at 60°C for 20 minutes. After the addition of 50 μL of KOH solution (KOH 15% in methanol/water, 4:1, vol/vol), the mixture was heated further at 60°C for 15 minutes. To the resulting mixture of hydrazides, 2 mL of 1/30 mol/L phosphate buffer (pH 6.4)–0.5 mol/L HCl (3.8:0.4, vol/vol) and 1.5 mL of n-hexane were
added. After vortexing and centrifugation, the n-hexane layer was taken and evaporated under N₂. The residue was dissolved in 50 μL methanol, and aliquots were injected into the HPLC utilizing a Supelcosil LC-8 reversed-phase column. The samples were eluted with acetonitrile/water (85:15, vol/vol, pH 4.5), and the chromatograms were recorded with a Perkin-Elmer Sigma 15 data station utilizing a Perkin-Elmer LC-75 monitor set at 400 nm.

Statistical Analysis
Data are reported as mean±SD. Differences between the three groups were analyzed by one-way ANOVA, followed by the Scheffe test for multiple comparisons. Simple linear regression analysis was also used where appropriate. Statistical significance was defined as P<.05. Statistical analyses were performed using STATVIEW software (Abacus Concepts Inc) for the Apple Macintosh computer.

Results
Clinical and Laboratory Data
Serum FT₄ and TSH concentrations are reported in Table 1. Serum TC, LDL-C, and triglycerides were significantly higher in hyperthyroid patients when compared with either hypothyroid patients or control subjects (Table 1). Hyperthyroid patients showed lower TC, LDL-C, and triglyceride serum contents than the control group (Table 1). HDL cholesterol was significantly higher in hyperthyroid and control groups when compared with the hypothyroid group; no significant difference was present between hypothyroid patients and control subjects.

Lipid Peroxidation Indices
Hyperthyroidism was associated with significantly higher FPLP and TBARS n-LDL contents than in the other two groups (Table 2). Hypothyroid patients showed significantly higher FPLP and TBARS n-LDL content than control subjects (Table 2). LDL susceptibility to oxidation was significantly increased in hyperthyroid patients when compared with the other two groups (Table 2). In hypothyroid patients, the lag phase was shorter than in the control group, but this difference was not statistically significant. Interestingly, when the oxidation rate was taken into account, both hyperthyroid and hypothyroid groups showed significantly higher values than the control group, but no significant difference was found between hyperthyroidism and hypothyroidism. The cholesterol to protein ratio (Table 2) was significantly higher in the hypothyroid group than in the other two groups. This ratio was not significantly different between hyperthyroid and control groups.

LDL Content in Antioxidant Vitamins
Vitamin E LDL content was significantly lower in the hyperthyroid group than in the other two groups (Table 3). The hypothyroid group showed significantly lower vitamin E LDL contents than did control subjects. The β-carotene LDL content was significantly higher in the hypothyroid group than in the other two groups (Table 3); moreover, β-carotene was significantly lower in the hyperthyroid group than in the control group. Lycopene LDL level was significantly lower in hyperthyroid patients than in control subjects; no significant difference was found between hypothyroid and control groups (Table 3) or between hypothyroid and hyperthyroid groups.

LDL Composition in Free Fatty Acids
Hyperthyroidism showed a significantly higher relative arachidonic acid LDL content than the other two groups (Table 4). Hypothyroidism was characterized by a significantly higher LDL total fatty acid content than the other two groups (Table 4). The control group showed a significantly higher relative oleic acid content than the other two groups (Table 4). Linoleic acid LDL content was significantly higher in

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**TABLE 1. Clinical Data, Serum Lipids and Lipoproteins, TSH, and FT₄ Concentrations**

<table>
<thead>
<tr>
<th>Group</th>
<th>Hyperthyroid (n=16)</th>
<th>Hypothyroid (n=16)</th>
<th>Control (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>49±16</td>
<td>56±15</td>
<td>51±11</td>
</tr>
<tr>
<td>Sex M/F, n/n</td>
<td>3/13</td>
<td>3/13</td>
<td>3/13</td>
</tr>
<tr>
<td>TC, mmol/L</td>
<td>3.64±0.64</td>
<td>7.22±1.10†</td>
<td>4.86±0.64*</td>
</tr>
<tr>
<td>LDL-C, mmol/L</td>
<td>2.01±0.57</td>
<td>5.1±0.83†</td>
<td>3.05±0.5*</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>1.08±0.14</td>
<td>1.47±0.29*</td>
<td>1.36±0.19*</td>
</tr>
<tr>
<td>TG, mmol/L</td>
<td>1.18±0.44</td>
<td>2.15±0.86†</td>
<td>0.98±0.35</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>5.15±0.70</td>
<td>4.9±0.82</td>
<td>4.77±0.70</td>
</tr>
<tr>
<td>TSH, μU/mL</td>
<td>0.02±0.035</td>
<td>61±27†</td>
<td>1.5±0.57*</td>
</tr>
<tr>
<td>FT₄, pmol/L</td>
<td>53±15</td>
<td>4.4±1.5†</td>
<td>14±2.2*</td>
</tr>
</tbody>
</table>

-C indicates cholesterol; TG, triglyceride. Values are mean±SD by one-way ANOVA plus the Scheffe test for multiple comparisons.

**TABLE 2. n-LDL Content in Lipid Peroxides, LDL Susceptibility to Oxidation, and Cholesterol-Protein Ratio**

<table>
<thead>
<tr>
<th>Group</th>
<th>Hyperthyroid (n=16)</th>
<th>Hypothyroid (n=16)</th>
<th>Control (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPLP, URF/mg LDL-C</td>
<td>19.2±5.7</td>
<td>12.7±6.5†</td>
<td>7.7±1.2*</td>
</tr>
<tr>
<td>TBARS, nmol MDA/mg LDL-C</td>
<td>0.81±0.13</td>
<td>0.69±0.12†</td>
<td>0.58±0.11*</td>
</tr>
<tr>
<td>Oxidation rate</td>
<td>7.2±2.2</td>
<td>6.1±2.7†</td>
<td>3.9±1.6*</td>
</tr>
<tr>
<td>Cholesterol/Protein</td>
<td>1.05±0.19</td>
<td>1.34±0.25†</td>
<td>1.12±0.23</td>
</tr>
</tbody>
</table>

URF indicates units of relative fluorescence; MDA, malondialdehyde. Values are mean±SD by one-way ANOVA plus the Scheffe test for multiple comparisons. Cholesterol/protein is the ratio between the LDL content in cholesterol and protein. *P<.05 hyperthyroid vs hypothyroid and control group; †P<.05 hypothyroid group vs control group.

**TABLE 3. LDL Vitamin E, β-Carotene, and Lycopene Concentrations**

<table>
<thead>
<tr>
<th>Group</th>
<th>Hyperthyroid (n=16)</th>
<th>Hypothyroid (n=16)</th>
<th>Control (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin E, μg/mg LDL-C</td>
<td>2.8±0.5</td>
<td>3.6±0.6†</td>
<td>4.5±0.6*</td>
</tr>
<tr>
<td>β-Carotene, μg/mg LDL-C</td>
<td>0.31±0.10</td>
<td>0.64±0.18†</td>
<td>0.44±0.10*</td>
</tr>
<tr>
<td>Lycopene, μg/mg LDL-C</td>
<td>0.18±0.12</td>
<td>0.32±0.19</td>
<td>0.36±0.21*</td>
</tr>
</tbody>
</table>

Values are mean±SD by one-way ANOVA plus the Scheffe test for multiple comparisons. *P<.05 hyperthyroid vs hypothyroid and control group; †P<.05 hypothyroid group vs control group.
hypothyroidism than in the control group, but no significant difference was found between hyperthyroidism and hypothyroidism as well as between hyperthyroidism and control (Table 4). Eicosapentaenoic acid was significantly higher in the hypothyroid group than in control subjects; no significant difference was observed between hyperthyroid and hypothyroid groups or between the hyperthyroid group and control subjects. Docosahexaenoic acid was significantly higher in hyperthyroid patients than in the other two groups but similar between the hypothyroid and control groups. The ratio of the LDL content in oleic to that in linoleic acid was significantly lower in hyperthyroid and hypothyroid groups than in the control group; no significant difference was found between hyperthyroidism and hypothyroidism (Table 4).

Correlations

In hyperthyroid patients, the n-LDL content in FPLPs and TBARS and the oxidation rate values were significantly and directly related to FT4 serum levels (r = .87, P < .0001, Fig 1; r = .80, P < .001; and r = .56, P < .05). Moreover, in this group, FT4 concentration was also significantly and inversely related to the lag phase (r = -.93, P = .0001, Fig 1). On the contrary, no significant correlation was present between FT4 and LDL oxidation indices in the hypothyroid group.

In the control group a weak but nonsignificant correlation was present between FT4 values and n-LDL contents in FPLPs, TBARS, the lag phase, and the oxidation rate. No significant relationship was found between FT4 and LDL contents in vitamin E, β-carotene, and lycopene in the three groups. In the hypothyroid group, TC and LDL-C were significantly and directly related to n-LDL content in FPLPs (r = .75, P < .01, Fig 2; r = .74, P < .01) and TBARS (r = .74, P < .01; r = .73, P < .01). In this group, TC and LDL-C were also significantly and inversely related to the lag phase (r = -.53, P < .05; r = -.59, P < .05, Fig 2). On the contrary, in hyperthyroid and control groups, TC, and LDL-C were not significantly related to FPLPs, TBARS, and the lag phase.

In all groups the n-LDL content in FPLPs and TBARS was significantly and inversely related to the lag phase (hyperthyroidism, r = -.86, P < .01 and r = -.82, P < .01; hypothyroidism: r = -.68, P < .01 and r = -.72, P < .01; and control subjects: r = -.60, P < .05 and r = -.58, P < .05). Vitamin E LDL content was significantly and directly related to the lag phase in all groups (hyperthyroid group: r = .54, P < .05; hypothyroid group: r = .54, P < .05; and control group: r = .58, P < .05). Vitamin E LDL content was also significantly and inversely related to n-LDL content in FPLPs and TBARS in all groups (hyperthyroidism: r = -.52, P < .05 and r = -.53, P < .05; hypothyroidism: r = -.52, P < .05 and r = -.54, P < .05; and control subjects: r = -.50, P < .05 and r = -.54, P < .05). Finally, the oxidation rate was significantly and inversely related to the oleic to linoleic acid ratio in hyperthyroid and hypothyroid groups (r = -.66, P < .01; r = -.68, P < .01).

**Discussion**

Our study confirms that LDL oxidation is markedly higher in hyperthyroidism than in hypothyroidism or control subjects. The increased oxidative stress was associated with higher consumption of lipid-soluble antioxidant vitamins. Accordingly, it is well known that hyperthyroidism accelerates mitochondrial oxidative metabolism, resulting in increased free radical production and lipid peroxidation. Moreover, inspection of the fatty acid composition of LDL particles reveals a higher relative arachidonic acid content in this group (Table 4). Arachidonic acid is a polyunsaturated fatty

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**TABLE 4. Fatty Acid Composition of LDL**

<table>
<thead>
<tr>
<th></th>
<th>Hyperthyroid Group (n=16)</th>
<th>Hypothyroid Group (n=16)</th>
<th>Control Group (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palmitic acid (16:0)</td>
<td>21.1±0.83</td>
<td>21.7±1.5</td>
<td>21.1±1.18</td>
</tr>
<tr>
<td>Palmitoleic acid (16:1)</td>
<td>2.3±0.17</td>
<td>2.6±0.57</td>
<td>3.2±1*</td>
</tr>
<tr>
<td>Stearic acid (18:0)</td>
<td>4.7±0.56</td>
<td>4.5±0.74</td>
<td>4.4±0.31</td>
</tr>
<tr>
<td>Oleic acid (18:1)</td>
<td>21.6±2.33</td>
<td>22.4±2.70†</td>
<td>24.9±1.66*</td>
</tr>
<tr>
<td>Linoleic acid (18:2)</td>
<td>34±3.20</td>
<td>35.8±4.74†</td>
<td>31.7±2.48</td>
</tr>
<tr>
<td>Arachidonic acid (20:4)</td>
<td>8.4±2.1</td>
<td>6.5±1.23*</td>
<td>5.2±1*</td>
</tr>
<tr>
<td>Eicosapentaenoic acid (20:5)</td>
<td>0.65±0.11</td>
<td>0.69±0.13†</td>
<td>0.48±0.30</td>
</tr>
<tr>
<td>Docosahexaenoic acid (22:6)</td>
<td>2.2±0.21</td>
<td>1.7±0.37*</td>
<td>1.8±0.30*</td>
</tr>
<tr>
<td>Oleic/linoleic</td>
<td>0.64±0.12</td>
<td>0.64±0.15†</td>
<td>0.81±0.18*</td>
</tr>
<tr>
<td>Total fatty acids, μmol/L</td>
<td>316±65</td>
<td>507±147*†</td>
<td>410±103</td>
</tr>
</tbody>
</table>

Oleic/linoleic indicates the ratio between the LDL content in oleic and linoleic acid. Values are mean±SD by one-way ANOVA plus the Scheffé test for multiple comparisons. Values are mean±SD in percentages of total fatty acids. *P < .05; †P < .005 hyperthyroid group vs control group.
acid with four double bonds, which are easily oxidized and thus contribute to increased lipid peroxidation.\(^2^5\)

Unexpectedly, hypothyroid patients showed higher lipid peroxidation than did healthy normocholesterolemic control subjects. This higher oxidative stress was characterized by a significantly higher LDL content in preformed lipid peroxides and a higher oxidation rate, whereas the lag phase was shorter but not statistically different than in control subjects. Interestingly, hypothyroid patients showed oxidation rates not significantly different from those found in the hyperthyroid group, despite significantly longer lag phases. These data suggest that in hypothyroidism the LDL oxidation process is delayed compared with that in the hyperthyroid group, but once the autocatalytic chain reaction of lipid peroxidation begins, it propagates very quickly inside the particle. This phenomenon is difficult to explain. In hypothyroid patients, vitamin E LDL content was significantly lower in those found in the hyperthyroid group, whereas the lag phase was shorter but not statistically different than in control subjects. Interestingly, hypothyroid patients showed oxidation rates not significantly different from those found in the hyperthyroid group, despite significantly longer lag phases. These data suggest that in hypothyroidism the LDL oxidation process is delayed compared with that in the hyperthyroid group, but once the autocatalytic chain reaction of lipid peroxidation begins, it propagates very quickly inside the particle. This phenomenon is difficult to explain. In hypothyroid patients, vitamin E LDL content was significantly lower in those found in the hyperthyroid group, whereas the lag phase was shorter but not statistically different than in control subjects.

In conclusion, a marked increase of metabolic activity can favor a pro-oxidant environment capable of significantly increased antioxidant consumption and LDL oxidation. Nevertheless, high serum cholesterol levels seem to represent a very strong pro-oxidant factor that can also favor LDL oxidative modification in patients with a very low metabolic rate, such as in hypothyroidism. Finally, considering the different prevalence
of atherosclerosis in hyperthyroidism and hypothyroidism, we can speculate that without a sufficiently high blood cholesterol content, even a very high level of oxidative stress is rarely associated with atherosclerotic lesions.

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References

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