Hypothyroidism Results in Small Dense LDL Independent of IRS Traits and Hypertriglyceridemia

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Abstract. There is evidence of an association between hypothyroidism and coronary heart disease. We decided to look at the relationship between hypothyroidism and LDL subclasses' pattern including small, dense LDL to define a biochemical basis for better management of the CHD risk of these patients. We utilized a case-control design to evaluate differences in lipid parameters between cases and controls. Univariate analysis revealed that many factors were associated with LDL particle size. Binary logistic regression however revealed that only thyroid status and serum triglyceride (TG) levels were independently associated with LDL particle size. Results from this study support an independent association between LDL particle size phenotype and both plasma TG concentrations and thyroid status. After adjusting for TG levels, other insulin resistance syndrome (IRS) traits were not associated with LDL size phenotype, suggesting that the IRS related sdLDL is linked most strongly to alterations in TG levels.

Key words: Hypothyroidism, Small dense LDL, Atherosclerosis

(IN a number of cross-sectional and prospective epidemiological studies, the preponderance of small dense LDL (sdLDL) has been associated with the development of coronary heart disease (CHD). It has been accepted as an emerging cardiovascular risk factor by the National Cholesterol Education Program Adult Treatment Panel III [1–3]. An increase in the proportion of small, dense LDL may increase risk for any given level of LDL. This increased risk may be due in part to increased deposition in the sub-endothelial space where plaque forms. It may be due also to increased uptake by macrophages and increased susceptibility to oxidation, both early steps in atherogenesis, or to decreased clearance because of reduced affinity for the LDL receptor [4]. Observational and epidemiological studies suggest those having a predominance of small, dense particles may have an increase in risk over those having a predominance of large LDL particles[5, 6] and this observed increase in risk forms the basis of the rationale in using particle size as an adjunct to the standard proven means of risk assessment.

Since the knowledge of LDL subclasses pattern will have an impact on the management of primary and secondary dyslipidaemias and since hypothyroidism is one of the important causes of secondary dyslipidaemia, it may be important that lipid investigations in these patients be extended to include LDL subclass analysis, thus offering a better evaluation of cardiovascular risk. There are a limited number of reports on this topic in the literature with conflicting results. One study investigated overt hypothyroid patients [7] and found no significant discordance in percentages of B phenotype (that represents predominance of sdLDL) from the controls. Another study on subclinical hypothyroidism [8] observed a decreased level of sdLDL in spite of raised TC and LDL-C. These two studies

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however did not adjust for the major confounding expected from triglyceride levels and hence we can not be sure that they truly reflect a hypothyroid effect. In this case-control study we take a re-look at the relationship between atherogenic dyslipidaemia, small dense LDL and hypothyroidism after adjustment for known confounders.

**Subjects and Methods**

There were two groups of subjects. The first group were newly-diagnosed patients with hypothyroidism, attending the Endocrinology Clinic of Mubarak Al Kabeer Hospital, Kuwait, recruited for the study from December 2004–January 2006. They were classified as hypothyroid if serum TSH level was >5 mU/L regardless of FT4 level. The reference ranges in our laboratory are: (i) TSH (0.27–4.6 mIU/L); FT3 (3.3–7.2 pmol/L); FT4 (11.0–24.0 pmol/L). Exclusion criteria were other confounding risk factors for CHD, including diabetes mellitus, impaired fasting glycaemia, smoking, hypertension, and use of known lipid-lowering drugs. By using these criteria, 60 patients were eventually selected from 78 originally recruited for the study. The second group comprised of 54 healthy volunteers (controls) selected randomly from the Blood Bank. All had normal thyroid function, clinically and biochemically, and were healthy, without evidence of diabetes mellitus, impaired fasting glycaemia or any regular medication. The research proposal was approved by the Kuwait University Health Sciences Centre Ethical Committee. All patients and controls were recruited into the study after voluntary, informed consent.

**Sample collection**

Blood samples (5 ml) were collected, from each of the subjects after 12 h overnight fast, into plain tubes. Serum was isolated after clot retraction and centrifugation (1500 g for 10 minutes) and subsequently divided into 3 aliquots and stored at –70°C until analysis. All analyses were performed within 1 month of sample collection.

**Assays**

The Beckman LX20 automated analytical system (Beckman-Coulter, USA) applying routine methods was used for the following measurements: glucose (hexokinase method), TC and HDL-C (cholesterol esterase method), TG (lipase method) and uric acid (uricase method). LDL-C was calculated by Friedewald equation (LDL-C (mmol/L) = TC – [HDL-C + TG/2.2]), where TG was <4.5 mmol/l. Apolipoprotein B (apoB) and apolipoprotein A1 (apoA) were measured by immunoturbidimetric methods on a Beckman Immage automated analytical system (Beckman-Coulter, USA), while the Thymune-M kit (Remel Europe Ltd, UK) was used for the semi-quantitative measurement of auto-antibodies to human thyroid microsomal antigen (antithyroid peroxidase).

For the thyroid function tests: (i) TSH, was analysed by the Coat-A-Count TSH IRMA (Diagnostic Product Corporation, USA) kit, a solid-phase immunoradiometric assay based on monoclonal and polyclonal anti-TSH antibodies. (ii) Free T4 (FT4) and free T3 (FT3) were analysed by the AMERLEX-MAB FT4, FT3 Kits (Trinity Biotech plc, Ireland) which utilize a direct, labeled antibody, competitive radioimmunoassay technique.

**LDL subclass analysis**

In most studies, so far, on LDL subclasses, particle size is commonly measured by gradient gel electrophoresis (GGE). Two of the older methods hitherto used for sdLDL quantitation were ultracentrifugation and nuclear magnetic resonance (NMR). Both are, however, too laborious, expensive and not suited to routine clinical use [9]. An alternative and less demanding approach to LDL subclasses study is a modified tube gel electrophoresis (TGE) technique which has been commercialized on the Lipoprint System (Quantimetrix Corporation. USA) [10]. It is relatively simpler to operate and fast compared with the gradient gel electrophoresis method, provides the particle size, allows quantitation of sdLDL fractions and correlates with the other methods [10–12].

In this method, VLDL remains in the origin [retention factor (Rf) = 0.0], whereas HDL migrates at the front (Rf = 1.0). In between, several bands can be detected including up to 7 LDL bands. The LDL1 and LDL2 bands correspond to large, buoyant LDL particles, whereas bands LDL3 to 7 correspond to sdLDL particles. Rf of LDL Subfraction = distance Between VLDL and LDL Subfraction Bands divided by distance
Between VLDL and HDL Bands. LDL subclasses designated as small have Rf>0.40, intermediate Rf = 0.38–0.40, and large Rf<0.38 by this method. Therefore, according to the LDL electrophoretic profile, 2 phenotypes can be defined: phenotype A with normal total cholesterol mass of the sdLDL subfractions and phenotype non-A (we call this phenotype B) where total cholesterol mass of the sdLDL subfractions is intermediate-low. The cutoff for elevated cholesterol mass of the sdLDL subfraction with this system is 0.155 mmol/L [13]. This system does not measure LDL particle size, but since older systems do, the Lipoprint System gives an estimate by means of the algorithm developed by Kazumi et al. [14]. The calculation is based on the equation: LDL-PPD = (1.429 – Rf) × 25 where PPD means peak particle diameter. The Average Particle Size reported by Lipoprint profile is the weighted average (calculated from the area under the curve for each sub fraction) of the particle sizes of all the LDL peaks present in the sample. Based on this the size cutoff works out to be above or equal to 26.8 nm for phenotype A (normal LDL size) and less than this for non-A (we call this B). It is likely that this TGE based calculation overestimates LDL particle size slightly in comparison with other methods and therefore this methods size cutoff’s are probably equivalent to the GGE cutoff of 26.3 nm for sdLDL [11]. Type B in this paper is therefore a combination of intermediate (25.8–26.3) and small (<25.8 nm) LDL in terms of GGE cutoffs [11]. In essence however, even though we report results in terms of estimated LDL size, the two phenotypic groups represent low and high cholesterol mass of the sdLDL subfractions respectively.

The process involves applying a serum sample (25 µl) to the ‘ready-to-use’ polyacrylamide gel tube along with 200 µl of a loading gel solution containing a lipophilic dye. The dye binds to the cholesterol in the lipoprotein particles permitting the visualization and measurement of lipoprotein fractions after electrophoretic separation. The sample loading gel mixture is photo-polymerized for 30 minutes prior to electrophoresis at a constant current of 3 mA/tube for one hour. This system ordinarily resolves up to 12 serum lipoprotein fractions as follows: VLDL (1), MID (3), LDL (7), HDL (1). HDL migrates the fastest (Rf = 1), while VLDL migrates the slowest to top of gel (Rf = 0). Mid bands and LDL subfractions migrate at various Rfs between VLDL and HDL. The Lipoware TM computer software (Quantiometrix Corporation, USA) is used to analyse the gel images. The bands are partitioned into discrete segments and the relative area under the curve is calculated for each lipoprotein band. The program also calculates the cholesterol concentration for each lipoprotein fraction using a total cholesterol value obtained for each sample by the method indicated previously.

Quality assurance

Internal quality of routine analyses was monitored at two levels of concentration, normal and pathological. Glucose, uric acid and lipid parameters were included in the Kuwait National and Biorad External Quality Assurance Schemes. For LDL subclass analysis, quality control material used was obtained from Quantiometrix Corporation, the makers of the Lipoprint gel tube electrophoresis system.

Data analysis

Statistical analysis was performed using SPSS 13.0. Descriptive statistics (median and inter quartile range) were used to present the data. Non-parametric statistical methods were used as the variables were not normally distributed. The Kruskal-Wallis test was used to compare medians for different groups. P-value<0.05 was considered as significant.

Results

Table 1 shows the demographic and anthropometric features of the subjects. BMI and waist circumference differed significantly between hypothyroid patients and the controls. The thyroid function parameters, as well as glucose, uric acid, lipid and lipoprotein parameters for both groups are shown in Table 2. As expected, pre-treatment TSH levels were much higher in hypothyroid, in comparison to the control group. FT3 levels did not differ between hypothyroid and controls. Also, as expected, FT4 levels were significantly lower in hypothyroid than the controls. There was a slightly higher fasting glucose level in the hypothyroid group but was not in the abnormal range since diabetes mellitus and impaired fasting glycaemia were among the exclusion criteria. Uric acid levels were significantly higher in hypothyroid than controls. The fasting values for total cholesterol, LDL-C, and apoB demonstrated
significant multi-colinearity and were significantly elevated in hypothyroid in comparison to controls. TG was significantly higher in hypothyroid than the controls. There were no significant differences in apoA levels and HDL between the two diagnostic groups (Table 2).

Although sdLDL was significantly associated with hypothyroidism in a univariate analysis, this could have been due to confounding by triglycerides, (Table 2) and a multivariate analysis was undertaken. LDL subclass as the dependent versus diagnosis (hypothyroid or not) and various lipid and biochemical parameters were entered into a forward stepwise logistic regression run. Only diagnosis and triglyceride levels were retained at the final step (Table 3). Hypothyroidism increased the odds of sdLDL 6-fold while each unit change in triglycerides increased the odds of sdLDL 15-fold. To help identify other factors independently associated with LDL size variation that are associated with thyroid status, the latter was removed from the logistic regression run and this time CRP and ApoB were significantly associated with LDL size in addition to TG. These results suggest that the hypothyroidism influence on size phenotype of LDL is reflected by changes in ApoB and CRP. Every unit change in CRP & apoB increased the odds of sdLDL 6 & 20-fold respectively. Post-treatment with thyroxine that normalized TSH, there was an improvement in all biochemical variables in univariate analysis except for triglycerides, HDL and LDL size (Table 4).

**Discussion**

Many epidemiological studies have shown an association between hypothyroidism and coronary heart disease (CHD). Indeed even sub-clinical hypothyroidism (SCH) is a risk factor for CHD as demonstrated in a cross-sectional study of 1149 women aged ≥55 yr [15] and in large studies, subjects with subclinical hy-

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**Table 1.** Characteristics of study participants

<table>
<thead>
<tr>
<th>Group</th>
<th>Controls</th>
<th>Hypothyroid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>IQR</td>
</tr>
<tr>
<td>Age, years</td>
<td>32</td>
<td>24–39</td>
</tr>
<tr>
<td>BMI, Kg/m²</td>
<td>25.36</td>
<td>22.72–30.43</td>
</tr>
<tr>
<td>Waist, cm</td>
<td>84</td>
<td>76–90</td>
</tr>
<tr>
<td>Sex, F/M</td>
<td>44/10</td>
<td></td>
</tr>
</tbody>
</table>

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**Table 2.** Baseline values for thyroid function parameters, and glucose, uric acid, lipid and lipoprotein levels for both groups of subjects.

<table>
<thead>
<tr>
<th>Group</th>
<th>Controls</th>
<th>Hypothyroid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>IQR</td>
</tr>
<tr>
<td>TSH, mIU/l*</td>
<td>1.3</td>
<td>1–2</td>
</tr>
<tr>
<td>Free T3, pmol/l</td>
<td>4.1</td>
<td>3.7–4.5</td>
</tr>
<tr>
<td>Free T4, pmol/l*</td>
<td>14.8</td>
<td>13.2–16.9</td>
</tr>
<tr>
<td>Glucose, mmol/l*</td>
<td>5</td>
<td>4.6–5.2</td>
</tr>
<tr>
<td>Uric acid, µmol/l*</td>
<td>234</td>
<td>202–328</td>
</tr>
<tr>
<td>Cholesterol, mmol/l*</td>
<td>4.78</td>
<td>4.22–5.42</td>
</tr>
<tr>
<td>Triglyceride, mmol/l*</td>
<td>0.78</td>
<td>0.58–1.27</td>
</tr>
<tr>
<td>LDL-C, mmol/l</td>
<td>3.12</td>
<td>2.50–3.76</td>
</tr>
<tr>
<td>HDL-C, mmol/l</td>
<td>1.24</td>
<td>1.06–1.5</td>
</tr>
<tr>
<td>ApoA, g/l</td>
<td>1.3</td>
<td>1.12–1.42</td>
</tr>
<tr>
<td>ApoB, g/l*</td>
<td>0.85</td>
<td>0.69–1.04</td>
</tr>
<tr>
<td>LDL size, (nm)*</td>
<td>27.04</td>
<td>26.90–27.29</td>
</tr>
<tr>
<td>Normal/small LDL</td>
<td>44/10</td>
<td></td>
</tr>
<tr>
<td>CRP, mg/dl*</td>
<td>0.22</td>
<td>0.11–0.40</td>
</tr>
<tr>
<td>Insulin, µU/l</td>
<td>7</td>
<td>6–10</td>
</tr>
<tr>
<td>C-peptide, pmol/l</td>
<td>703</td>
<td>562–938</td>
</tr>
</tbody>
</table>

* Significantly different via the Kruskal-Wallis test, P<0.05
HYPOTHYROIDISM RESULTS IN SMALL DENSE LDL INDEPENDENT OF IRS TRAITS AND HYPERTRIGLYCERIDEMIA

Hypothyroidism had a significantly higher prevalence of CHD than euthyroid subjects [16, 17]. It is clear therefore that hypothyroidism, regardless of severity, is associated with increased CHD risk. Such hypothyroid patients tend to have multiple CHD risk factors. These include: (i) increased prevalence of hypertension [18]; (ii) increased vascular resistance associated with raised cardiac afterload and cardiac work [19, 20]; (iii) impairment of flow-mediated endothelium-dependent vasodilatation, that is considered an early sign in atherogenesis [21]; (iv) increased arterial wall stiffness [22, 23]; and finally (v) atherogenic dyslipidaemia. The induction of atherogenic dyslipidaemia seems to be a major component of the association between hypothyroidism and CHD risk. Although it is well known that hypothyroidism results in reduced LDL clearance and hence raised levels of LDL and apoB, an important predictor of cardiovascular events and progression of CHD could be LDL subclass pattern and particle size which go beyond assay of total LDL-C, thus sharpening the scope of cardiovascular risk assessment [2, 24, 25]. LDL comprises subpopulations of particles that vary in size (22.0–27.2 nm diameter), density, cholesterol content and apoB conformation. The 7 LDL subspecies separated by nondenaturing gradient gel electrophoresis have been grouped into 4 major subclasses LDL I–IV from the largest, most buoyant to the smallest, most dense particles [4]. Two phenotypes have been identified—(i) phenotype A, comprising large, less dense LDL (>26.3 nm diameter if by GGE or >26.8 nm if by TGE) [11], present at low TG levels, and; (ii) phenotype B, with abundant sdLDL coupled with elevated TG and decreased HDL-C levels. Phenotype B is the hallmark of ‘atherogenic lipoprotein profile’, a term used to describe the syndrome of sdLDL, elevated TG and low HDL-C [4]. It has been suggested that sdLDL atherogenicity is relatively dichotomous [26], perhaps due to exposure of specific epitopes when particle lipid content is reduced past a certain point, corresponding to 26.3–26.8 nm in diameter (GGE vs TGE). However, such a model has not been confirmed and one group reported a continuum of increasing oxidative susceptibility of LDLs, suggesting pro-atherogenic property of small LDLs, with decreasing particle size [27]. It seems likely that LDL atherogenicity increases continuously with decreasing particle size and, therefore, that in this population small LDLs will tend to be more atherogenic than large LDLs.

It has been reported that TG concentrations account for a significant proportion of LDL size variation [28,
and this was documented in this study too. In fact, this relationship was strong enough for us to use TG levels as a reasonable predictor of LDL size phenotype category in addition to thyroid status. A TG concentration of less than 1 mmol/l (88% sensitivity) or greater than 1.5 mmol/L (93% specificity) was optimal for classifying LDL size phenotype as normal or dense respectively in samples from this population. Using just the TG concentration and thyroid status, approximately 84% of LDL phenotypes were correctly predicted across all samples (Table 3a), but about 13.5% of large LDL samples and 20% of small LDL samples were misclassified (Table 3b). The association of TG with small, dense LDL therefore suggests a possible means of establishing the presence of predominant small, dense LDL by use of TG measurement and it has been suggested that those with TG above 1.6 mmol/L have small, dense LDL and may be classified as LDL phenotype B on the basis of TG alone [30]. Consequently, a separate test of LDL particle size to identify individuals at increased risk from small, dense LDL would be generally unnecessary for such individuals. Others too concur that small dense LDL tend to be the rule with triglycerides >1.5 mmol/l [31] and small, dense LDL particles are usually found in association with high triglycerides (TG) and low HDL. The mechanism of this association seems to be that when TG, in a 12 h fasting specimen, is increased in the serum, it is usually a result of increased VLDL (very low density lipoprotein). Under these conditions, TG are transferred from VLDL to LDL in exchange for cholesterol ester by CETP (cholesterol ester transfer protein). These TG enriched, cholesterol ester depleted LDL particles are then acted upon by hepatic lipase which cleaves out the TG leaving cholesterol ester depleted LDL particles [32]. The depleted LDL particles are physically smaller and because of the resultant relative increase in protein also denser. While it is true that hepatic lipase activity is decreased in hypothyroidism, the only explanation we may suggest as to the association with sdLDL is that it is not the rate limiting factor in the hydrolysis of LDL triglycerides. Indeed, it has been reported that in the absence of hypertriglyceridemia, the amount of VLDL triglycerides exchanged become limiting on the LDL size [33]. We can however attribute the lack of improvement in the small dense LDL state in the initial treatment of hypothyroidism to the increase in HL activity by thyroxine therapy leading to increasing hydrolysis of LDL triglycerides. It is of interest to note that the median levels of cholesterol, LDL-C and Apo A after the treatment with thyroxine are similar to those in controls (Table 4). This suggests that short-term treatment of hypothyroidism is sufficient to normalize quantitative lipid profiles, but not qualitative lipid profiles, and it is possible that the latter may need longer-term treatment with thyroxine to improve.

Table 4. Descriptive Statistics post therapy of 31 cases

<table>
<thead>
<tr>
<th>Post treatment variable**</th>
<th>P value (post minus pre treatment)*</th>
<th>Minimum</th>
<th>Maximum</th>
<th>25th</th>
<th>50th (Median in controls given for comparison)</th>
<th>75th</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHOLESTEROL</td>
<td>0.02</td>
<td>3.65</td>
<td>8.43</td>
<td>4.79</td>
<td>5.4 (4.78)</td>
<td>6.26</td>
</tr>
<tr>
<td>TSH</td>
<td>&lt;0.001</td>
<td>0.2</td>
<td>4.1</td>
<td>1.3</td>
<td>2.10 (1.3)</td>
<td>2.7</td>
</tr>
<tr>
<td>FT4</td>
<td>&lt;0.001</td>
<td>4.4</td>
<td>27.8</td>
<td>12.3</td>
<td>15.5 (14.8)</td>
<td>18.3</td>
</tr>
<tr>
<td>TRIGLYCERIDE</td>
<td>0.59</td>
<td>0.61</td>
<td>4.27</td>
<td>0.88</td>
<td>1.24 (0.78)</td>
<td>2.16</td>
</tr>
<tr>
<td>LDL</td>
<td>0.02</td>
<td>2</td>
<td>7</td>
<td>2.92</td>
<td>3.87 (3.12)</td>
<td>4.57</td>
</tr>
<tr>
<td>HDL</td>
<td>0.3</td>
<td>0.81</td>
<td>1.73</td>
<td>1</td>
<td>1.13 (1.24)</td>
<td>1.24</td>
</tr>
<tr>
<td>APOA</td>
<td>0.006</td>
<td>0.96</td>
<td>1.69</td>
<td>1.07</td>
<td>1.25 (1.3)</td>
<td>1.4</td>
</tr>
<tr>
<td>APOB</td>
<td>0.001</td>
<td>0.53</td>
<td>2.26</td>
<td>0.86</td>
<td>1.12 (0.85)</td>
<td>1.33</td>
</tr>
<tr>
<td>LDLSIZE</td>
<td>0.17</td>
<td>25.91</td>
<td>27.52</td>
<td>26.25</td>
<td>26.66 (27.04)</td>
<td>26.99</td>
</tr>
</tbody>
</table>

Treatment for a mean of 15.7 weeks (range 6–40 weeks).

* Wilcoxon signed ranks test

** Units as in table 1

TG may also be used to track treatment because the approaches which lower TG also convert small, dense LDL to large, less atherogenic LDL [34–37]. Thus, weight loss, exercise, niacin, and fibrates which, independently, have been shown to reduce TG, also convert
small, dense LDL to larger LDL. As a class, statin drugs do not change particle size appreciably. Thus, once patients achieve their NCEP LDL targets on statin treatment, if they also need pharmaceutical treatment of TG to achieve NCEP TG target (<1.7), then a test of LDL particle size would not be needed. If the TG were between 0.8 and 1.6 and the individual was a CAD risk equivalent, or had established CAD and, more so, if he or she had progressing CAD, consideration may be given to measuring LDL particle size before the addition of niacin or fibric acid derivatives.

Worsening the already bad atherogenic milieu, hypothyroidism also results in increases in Apo-B and LDL. Despite the strong association between ApoB and LDL, ApoB is better associated with sdLDL because the amount of cholesterol in LDL particles can vary substantially, and LDL cholesterol does not necessarily equal LDL particle number [4]. This discrepancy makes apoB more informative in patients with predominantly small dense cholesterol-depleted LDL particles in whom LDL cholesterol would understate LDL particle number, the latter being more important in terms of atherosclerosis [38]. The higher the ApoB levels were, the more likely this was to be associated with sdLDL with fewer subjects having normal LDL beyond ApoB of 1.2 g/L (90% specificity) but sensitivity (58%) was poor and a lot of the sdLDL’s in this study were not associated with such ApoB levels. Finally, since elevated ApoB levels were induced by the hypothyroid state, this may not necessarily be directly involved in the pathogenesis of sdLDL.

To further compound the risks created by sdLDL and elevated ApoB, CRP was also elevated in hypothyroidism in this study. Inflammation appears to be pivotal in all phases of atherosclerosis from the fatty streak lesion to acute coronary syndromes. An important down-stream marker of inflammation is C-reactive protein (CRP). Numerous studies have shown that CRP levels predict cardiovascular disease in apparently healthy individuals [39]. This has resulted in a position statement recommending cutoff levels of CRP <1.0 mg/dl equating to low risk for subsequent cardiovascular disease [39]. In keeping with this we found that beyond a CRP of 1.1 mg/dl most subjects had sdLDL (95% specificity) but nevertheless, the vast majority of subjects with sdLDL had CRP levels below this threshold (20% sensitivity). This association again reflects thyroid status and may not be causal in the pathogenesis of sdLDL. Although LDL too was elevated in the hypothyroid group with elevated CRP, it is known that CRP concentrations correlate only minimally with LDL-C, and the predictive value of CRP (on atherogenesis) has been largely independent of LDL-C [40]. Our study too found such independence suggesting that disorders of LDL metabolism and inflammatory processes promote atherogenesis by distinct pathways.

Insulin resistance, defined as the decreased ability of insulin to perform its biological functions, is likely to represent the primary physiologic defect underlying the insulin resistance syndrome (IRS), which includes insulin resistance/hyperinsulinemia, glucose intolerance and/or type 2 diabetes mellitus, visceral obesity, hypertension, and dyslipidemia (low HDL cholesterol, and hypertriglyceridemia). This constellation of traits is a leading cause of cardiovascular mortality and morbidity. A number of studies have reported strong associations between LDL particle size phenotype and certain IRS-related traits such as adiposity, plasma glucose and plasma insulin concentrations. We were unable to show such a relationship here with parameters other than elevated TG suggesting that the relationship between LDL size and IRS [29] may be more strongly reflected by changes in TG concentrations and thus the small sample size did not allow other relationships to emerge. Supporting this interpretation is the univariate association of BMI with LDL size. Many studies have also reported sex-specific differences in lipoprotein phenotypes which could confound the present observations. However, sex differences did not contribute to LDL size distribution. Furthermore, the correlations of LDL size phenotype with lipoprotein and IRS-related traits were basically similar when considered in each sex separately. Thus, although there are important sex differences in LDL size phenotype, these did not appear to be responsible for the patterns of correlation observed in the pooled group.

In summary, results from this study support the strong association between hypothyroidism and sdLDL, elevated ApoB and elevated CRP. Also there was a strong association between LDL particle size phenotype and plasma TG concentrations independent of thyroid status. Though the risk of sdLDL was also linked to increases in CRP and ApoB levels (independent of changes in LDL particle size, each other and TG), these increases were hypothyroidism related and may not be causal in the pathogenesis of sdLDL. After adjusting for TG levels, other IRS traits were not associated with LDL size phenotype, suggesting that the
IRS related sdLDL is most strongly linked to alterations in TG levels. Finally, short-term treatment of hypothyroidism does not improve sdLDL status probably due to the initial increases in hepatic lipase activity.

References


