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LDL-cholesterol and arterial wall stiffness

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WHAT’S NEW?
Decreased arterial compliance (or increased stiffness) is an early marker of arteriosclerosis and an established predictor of cardiovascular morbidity and mortality. Non-invasive assessment of the elastic properties of arterial wall enables early detection of the vascular pathology before the clinical symptoms appear. Diagnosing atherosclerosis at this earliest possible stage can be crucial for treatment outcomes. Here we demonstrate that higher concentrations of serum LDL-cholesterol appear to contribute independently to stiffening of the peripheral arterial vasculature in otherwise healthy adults. Screening for dyslipidaemia in the general population and its prompt treatment are corroborated by the study outcomes.

Abstract
Background: Elevated serum LDL-cholesterol is a risk factor of atherosclerosis, which involves remodeling of the arterial walls with their subsequent stiffening.
Aim: The aim of the study was to evaluate the relationships between serum lipids and arterial wall elastic properties.
Methods: The study group comprised 315 men and women aged 55.84±9.44 years. Serum glucose and lipid concentrations were estimated. All subjects underwent blood pressure measurement,
transthoracic echocardiography and assessment of vascular compliance of large (C1) and small arteries (C2) using an HDI/Pulse Wave™ CR-2000 Research Cardiovascular Profiling Instrument. The subjects were divided into three groups: group I – LDL-cholesterol <2.6 mmol/L, group II – LDL-cholesterol ≥2.6 mmol/L and <4.0 mmol/L, and group III – LDL-cholesterol ≥4.0 mmol/L.

**Results:** There were no differences between the groups with regard to smoking status (p =0.56), serum glucose (p =0.13), BMI (p =0.96), systolic (p =0.17) and diastolic blood pressure (p =0.29), or C1 (p =0.09). On the other hand, C2 was higher in group I and II than in group III (5.12±2.57 vs. 5.18±2.75 vs. 4.20 ± 1.58 ml/mmHg×100, respectively, p < 0.01). The multivariate regression analysis negated independent associations between C1 and serum lipids. In contrast, C2 was associated independently inversely with serum LDL-cholesterol concentration (r = -0.18, p < 0.01).

**Conclusions:** Higher serum LDL-cholesterol concentration seems to contribute independently to stiffening of small arterial vasculature in otherwise healthy adults. Screening for dyslipidaemia in the general population and its prompt treatment are most desirable.

**Key words:** LDL-cholesterol, arterial wall stiffness, arterial wall compliance, arterial wall elasticity, small arteries, large arteries

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**INTRODUCTION**

Serum LDL-cholesterol is a well-known risk factor for cardiovascular diseases (coronary artery disease and peripheral arterial diseases) [1,2]. The prevalence of dyslipidemia in Poland continues to be high. The highest incidence of increased serum LDL-cholesterol levels was found in the 40–59 age group, similarly as in case of increased serum total cholesterol [3].

Atherosclerosis is a chronic inflammatory process, initiated by the damage of the vascular endothelium, which leads to remodeling of the artery wall. Serum LDL-cholesterol plays a significant role in this pathology, as oxidized LDL molecules activate a number of cellular responses in macrophages, endothelial cells, T-cells, and smooth muscle cells that promote inflammation and atherogenesis [4-6]. The initial phase of atherosclerosis involves arterial wall remodeling and a subsequent decrease of its compliance (or increased stiffness). Arterial stiffness is an early marker of arteriosclerosis and an established predictor of cardiovascular morbidity and mortality [7,8]. Assessment of the arterial wall elastic properties is a significant diagnostic tool that enables early detection of the vascular pathology before the clinical symptoms appear [9-11].

Diagnosing atherosclerosis at this earliest possible stage can be crucial for treatment outcomes. Assessment of arterial wall elastic properties with a non-invasive technique provides information about the functional and structural changes at the level of aorta, muscular conduit arteries, their peripheral branches, and the microvascular components [10].
The aim of the study was to evaluate the relationships between serum LDL-cholesterol concentration and arterial wall elasticity indices reflective of the large and small artery compliances.

**METHODS**

The trial was conducted as part of the Silesian Cardiovascular Study which is an investigation designed to examine risk factors underlying cardiovascular disorders and which was approved by the Bioethical Committee of the university. All subjects (Polish white) were recruited from the general population in three reference centers for cardiovascular diseases in the south of Poland.

Serum fasting total cholesterol, HDL-cholesterol, triglycerides, LDL-cholesterol and glucose were measured. The compliance of large and small arteries was assessed non-invasively and automatically using an HDI/Pulse Wave™ CR-2000 Research Cardiovascular Profiling Instrument. Subjects were tested lying down with the head raised no higher than 30°. The measurement was started after a 5-minute rest. Blood pressure was measured automatically with the oscillometric method. Analysis of the shape of the pulse wave of the radial artery was performed on the right limb with use of a piezoelectric sensor (applanation tonometry method). In order to minimize artifacts, the wrist was stabilized in supination with a dedicated tool. The principle of the applied method takes into account blood pressure changes during cardiac diastole and is based on the analogy to an electric current circuit according to a modified windkessel model [12]. Two vascular systems are distinguished in this model – a high pressure one, that includes aorta with its main branches, and the low pressure one containing peripheral arteries. As a result, the following parameters are obtained: systolic (SBP) and diastolic (DBP) blood pressures, large artery elasticity index reflective of large artery compliance (C1, expressed in ml/mmHg×10), and small artery elasticity index reflective of small artery compliance (C2, expressed in ml/mmHg×100) [9].

Echocardiography was performed in all subjects by one experienced sonographer using a Vivid 4 system equipped with a 3.5 MHz transducer.

Healthy subjects aged ≥18 years who granted written informed consent were included in the study. Exclusion criteria were: occurrence of any disease or treatment with any medication. Subjects whose serum fasting glucose was elevated (≥100 mg/dL) in the baseline tests were also excluded from the study.

**Statistical analysis**

Statistical analysis was performed using the GraphPad InStat version 3.05 (GraphPad Software, San Diego, California, USA, www.graphpad.com). The demographic, anthropometric, clinical, as well as the analyzed hemodynamic and biochemical parameters were compared between the groups with Kruskal-Wallis analysis of variance and Mann-Whitney test for the post-hoc comparisons. Simple
correlations between serum total cholesterol, HDL-cholesterol, triglycerides, LDL-cholesterol and arterial parameters were assessed with Pearson’s correlation test. Backward stepwise multivariate regression analysis was used to elucidate the independent determinants of the large artery elasticity index (C1) and small artery elasticity index (C2). The p-value <0.05 was considered statistically significant.

RESULTS
315 males and females, at the average age of 55.84 ± 9.44 years, were included in the study and divided into three groups according to their serum LDL-cholesterol concentration (group I – LDL-cholesterol < 2.6 mmol/L, group II – LDL-cholesterol ≥ 2.6 mmol/L and < 4.0 mmol/L, and group III – LDL-cholesterol ≥ 4.0 mmol/L). The demographic and clinical characteristics of the study participants are reported in Table 1. There were no differences between the groups in body mass index (BMI) (p = 0.96), serum triglycerides (p = 0.09), glucose (p = 0.13), smoking (p = 0.56), systolic blood pressure (SBP) (p = 0.17), and diastolic blood pressure (DBP) (p = 0.29). There was no statistically significant difference between the groups with regard to the large artery elasticity index (C1) (14.16 ± 4.52 vs 15.35 ± 4.84 vs 15.83 ± 6.29 ml/mmHgx10, p = 0.09). The small artery elasticity index (C2) was higher in group I and II than in group III (5.12 ± 2.57 vs 5.18 ± 2.75 vs 4.20 ± 1.58 ml/mmHg×100, p = 0.005) (Table 1). Moreover, the subjects did not differ significantly in terms of the parameters of the left atrium and left ventricle (Table 2). The correlation test revealed univariate positive associations between C1 and serum total cholesterol (r = 0.15, p < 0.01), as well as C1 and serum LDL-cholesterol (r = 0.12, p = 0.03), whilst no significant correlations between C1 and serum HDL-cholesterol (p = 0.08) or triglycerides (p = 0.28). In the multivariate regression analysis the correlations of C1 with serum cholesterol concentrations were lost, and only female sex, younger age, lower SBP, but higher BMI were independently associated with higher large artery compliance (Table 3). On the other hand, inverse univariate correlations were found between C2 and serum total cholesterol (r = - 0.13, p = 0.02), as well as LDL-cholesterol (r = - 0.15, p < 0.01, Figure 1). Moreover, lower serum LDL-cholesterol concentration, along with younger age, female sex, but higher BMI, correlated independently with higher C2 in the multivariate regression analysis (Table 3).

DISCUSSION
In this study we aimed to define the relationship between serum LDL-cholesterol concentration and arterial wall compliance/stiffness. Based on the presented results we found a negative correlation between serum LDL-cholesterol and small artery compliance (C2). The results of our research partially coincide with those obtained by Schillinger et al., who have shown an association between
high serum concentrations of lipoprotein (a) (a modified low-density lipoprotein particle with strong pro-inflammatory and pro-atherogenic effects [14]) and reduced compliance of the small artery walls [13]. In a group of subjects with atherosclerosis, the observed negative correlation between serum lipoprotein (a) and C2 was independent of other risk factors such as: sex, smoking and diabetes. Moreover, no independent correlation between serum lipoprotein (a) and C1 was shown. On the other hand, Miao et al. did not reveal any independent relationships between serum total cholesterol or LDL-cholesterol and the elastic properties of the vascular wall [15]. In turn, they ascertained associations of low serum HDL-cholesterol or elevated triglycerides and the reduced compliance of the arterial wall. Moreover, they were able to show a relationship between the compliance of the vascular wall and left ventricular diastolic function [15]. In our study, in line with that of Canepa et al. [16], we did not corroborate any correlations between the artery wall elasticity indices and left ventricular end-diastolic diameter. This is in contrast to the majority of clinical studies that showed an association between reduced compliance (or increased stiffness) of the arterial walls and LV diastolic dysfunction [17]. With decreasing arterial wall compliance, cardiac afterload increases because of the accelerated return of the arterial reflection wave from the periphery during systole, which augments the SBP and results in an excess stress to the left ventricle [17]. In our work, similar to Canepa et al. [16], the average age of the studied subjects was lower in comparison to other studies, which may partially explain the discrepancy between the study findings.

The pathophysiology of arterial stiffening involves extracellular matrix remodelling with fragmentation of elastin and deposition of collagen in the arterial walls. Elastin fibres provide mechanical properties of elasticity, whereas collagen is significantly stiffer than elastin [18]. Importantly, elastin contains hydrophobic domains, which makes it attractive for interactions with ligands such as cholesterol. Bilici et al. revealed detrimental modifications of elastin due to cholesterol exposure in vitro [19]. It may be assumed that such changes occur in vivo in the course of dyslipidaemia and contribute to arterial stiffening. Biochemical analyses have revealed that lipids accumulating on the membranes of atherosclerotic lesions are bonded with elastin already at the early stages of atherosclerosis [19,20].

As mentioned above, the non-invasive measurement of the compliance of the vascular wall makes it possible to detect pathologies before the clinical symptoms of the cardiovascular disease appear. The decreased compliance of small artery walls reflects the disturbed vascular endothelium function and has been established as an independent cardiovascular risk factor [21,22]. Panaich et al. have shown that both small and large artery compliances were associated with subclinical coronary atherosclerosis in subjects free from symptomatic angina. This association was independent of cardiovascular risk factors i.e. age, sex, race, systolic blood pressure, diabetes,
smoking, serum total cholesterol, HDL-cholesterol, and high-sensitivity C-reactive protein [23]. In a prospective study, Grey et al. demonstrated an association between the increased stiffness of the small arteries and occurrence of cardiovascular events. Like in our work, the methodology of the measurement of elasticity indices of the small and large arteries was based upon the modified Windkessel model. In a long-term observation cardiovascular events occurred in 41% of the studied subjects and both C1 and C2 were their univariate predictors, whereas only C2 was found to predict cardiovascular events after taking into account the effect of age [24].

In our study we have shown that higher serum LDL-cholesterol appears to contribute independently to small artery stiffening in otherwise healthy adults. A decreased compliance (or increased stiffness) of these arteries in subjects without diagnosed cardiovascular disease, can suggest a very early disease course and be the indication to extend patient diagnostics.

Limitations of the study
Other parameters such as serum CRP, aminotransferases, uric acid, creatinine, GFR, oxLDL, which may influence the elastic properties of the arteries, were not taken into consideration in our study.

CONCLUSIONS
The small artery compliance (C2) is lower among subjects with higher serum LDL-cholesterol. There is an inverse correlation between serum LDL-cholesterol and the small artery compliance (C2).

Acknowledgements
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Conflict of interest: none to declare

References


Table 1. Demographic, biochemical and clinical characteristics of the study group

<table>
<thead>
<tr>
<th></th>
<th>Group I (serum LDL-cholesterol &lt;2.6 mmol/L) n = 83</th>
<th>Group II (serum LDL-cholesterol ≥2.6 and &lt;4.0 mmol/L) n = 134</th>
<th>Group III (serum LDL-cholesterol ≥4.0 mmol/L) n = 98</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/Female</td>
<td>59 / 24</td>
<td>85 / 49</td>
<td>63 / 35</td>
<td>0.48</td>
</tr>
<tr>
<td>Age (years)</td>
<td>58.28 ± 10.49</td>
<td>55.01 ± 9.71</td>
<td>54.91 ± 7.71</td>
<td>0.03</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>27.36 ± 3.97</td>
<td>27.39 ± 3.79</td>
<td>27.51 ± 4.13</td>
<td>0.96</td>
</tr>
<tr>
<td>Serum total cholesterol (mmol/L)</td>
<td>3.79 ± 0.49</td>
<td>5.09 ± 0.54</td>
<td>6.83 ± 1.02</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Serum HDL-cholesterol (mmol/L)</td>
<td>0.87 ± 0.33</td>
<td>1.00 ± 0.32</td>
<td>1.03 ± 0.31</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Serum triglycerides (mmol/L)</td>
<td>1.83 ± 1.02</td>
<td>1.64 ± 0.92</td>
<td>1.81 ± 0.95</td>
<td>0.09</td>
</tr>
<tr>
<td>Serum LDL-cholesterol (mmol/L)</td>
<td>2.08 ± 0.40</td>
<td>3.35 ± 0.39</td>
<td>4.97 ± 0.84</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Serum glucose (mg/dL)</td>
<td>83.28 ± 11.62</td>
<td>83.36 ± 9.82</td>
<td>85.88 ± 9.94</td>
<td>0.13</td>
</tr>
<tr>
<td>Smokers/Nonsmokers</td>
<td>52 / 31</td>
<td>74 / 60</td>
<td>60 / 38</td>
<td>0.56</td>
</tr>
<tr>
<td>number percentage (%)</td>
<td>62.65 / 37.35</td>
<td>55.22 / 44.78</td>
<td>61.22 / 38.78</td>
<td></td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>123.46 ± 13.77</td>
<td>124.49 ± 11.69</td>
<td>121.30 ± 13.37</td>
<td>0.17</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>71.89 ± 9.04</td>
<td>72.80 ± 8.78</td>
<td>70.87 ± 9.95</td>
<td>0.29</td>
</tr>
<tr>
<td>C1 (ml/mmHg×10)</td>
<td>14.16 ± 4.52</td>
<td>15.35 ± 4.84</td>
<td>15.83 ± 6.29</td>
<td>0.09</td>
</tr>
<tr>
<td>C2 (ml/mmHg×100)</td>
<td>5.12 ± 2.57</td>
<td>5.18 ± 2.75</td>
<td>4.20 ± 1.58</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Data are presented as means ± standard deviations, numbers or percentages.

BMI – body mass index, C1 – large artery elasticity index, C2 – small artery elasticity index, SBP – systolic blood pressure, DBP – diastolic blood pressure.
### Table 2. Echocardiographic parameters of the study group

<table>
<thead>
<tr>
<th></th>
<th>Group I (serum LDL-cholesterol &lt;2.6 mmol/L)</th>
<th>Group II (serum LDL-cholesterol ≥2.6 and &lt;4.0 mmol/L)</th>
<th>Group III (serum LDL-cholesterol ≥4.0 mmol/L)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA (mm)</td>
<td>38.85 ± 4.69</td>
<td>38.43 ± 4.04</td>
<td>38.5 ± 3.76</td>
<td>0.75</td>
</tr>
<tr>
<td>IVSDd (mm)</td>
<td>11.04 ± 1.76</td>
<td>10.51 ± 1.8</td>
<td>11.05 ± 1.63</td>
<td>0.07</td>
</tr>
<tr>
<td>PWDd (mm)</td>
<td>10.68 ± 1.55</td>
<td>10.22 ± 1.43</td>
<td>10.64 ± 1.29</td>
<td>0.04</td>
</tr>
<tr>
<td>LVESd (mm)</td>
<td>33.94 ± 8.49</td>
<td>33.39 ± 6.54</td>
<td>34.16 ± 7.48</td>
<td>0.64</td>
</tr>
<tr>
<td>LVEDd (mm)</td>
<td>50.55 ± 6.00</td>
<td>50.97 ± 4.96</td>
<td>51.15 ± 5.25</td>
<td>0.18</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>54.87 ± 6.40</td>
<td>56.10 ± 8.92</td>
<td>56.97 ± 7.64</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Data are presented as means ± standard deviations.

IVSDd - intraventricular septum diastolic diameter, LA - left atrium, LVEDd - left ventricular end-diastolic diameter, LVEF - left ventricular ejection fraction, LVESd - left ventricular end-systolic diameter, PWDd - posterior wall diastolic diameter.

### Table 3. Multivariate regression analysis with large artery compliance (C1) and small artery compliance (C2) as dependent variables

<table>
<thead>
<tr>
<th>Dependent variables</th>
<th>Independent variables</th>
<th>beta-coefficient</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1</td>
<td>Male sex</td>
<td>- 0.33</td>
<td>-0.29 to -0.37</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>- 0.22</td>
<td>-0.18 to 0.26</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td></td>
<td>BMI</td>
<td>0.23</td>
<td>0.19 to 0.27</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td></td>
<td>SBP</td>
<td>- 0.37</td>
<td>-0.32 to -0.42</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>C2</td>
<td>Male sex</td>
<td>- 0.26</td>
<td>-0.21 to -0.31</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>- 0.24</td>
<td>-0.19 to -0.29</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td></td>
<td>BMI</td>
<td>0.20</td>
<td>0.15 to 0.25</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td></td>
<td>Serum LDL-cholesterol concentration</td>
<td>- 0.18</td>
<td>-0.13 to -0.23</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

CI - confidence interval, other abbreviations - see Table 1 and Table 2.
Figure 1. Pearson’s correlation between small artery elasticity index (C1) and serum LDL-cholesterol

$r = -0.15$
$p < 0.01$