Impaired aortic function in patients with coeliac disease

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Abstract

Background and aim: We aimed to investigate the association between aortic function (aortic stiffness index, aortic strain, and aortic distensibility), which is a predictor of atherosclerosis, and coeliac disease (CD).

Methods: Thirty-six patients with CD and 35 control subjects were included in the study. Serological screening was performed to determine the levels of auto-immune markers, including anti-gliadin immunoglobulin (Ig)A and IgG, and anti-tissue transglutaminase antibodies. Aortic distensibility, aortic strain, and aortic stiffness index were calculated using echocardiography.

Results: Aortic strain and aortic distensibility were significantly lower in patients with CD than in control subjects (0.07 [0.03–0.14] vs. 0.09 [0.06–0.15], p < 0.001; 0.0036 ± 0.0012 vs. 0.0051 ± 0.0014, p < 0.001, respectively). However, the aortic stiffness index was significantly higher in patients with CD than in controls (1.14 [0.57–2.69] vs. 0.91 [0.59–1.92], p = 0.002). Coeliac disease was the only independent parameter that was correlated with aortic strain, aortic stiffness index, and aortic distensibility (β = −0.427, p < 0.001; β = 0.375, p = 0.003; β = −0.434, p < 0.001, respectively).

Conclusions: In this study, we showed deteriorated aortic functions by echocardiography in CD patients, which predicted subclinical atherosclerosis. Because deteriorated aortic functions is a strong predictor of future cardiovascular events, close cooperation with cardiologists and gastroenterologists is needed in the management of CD patients, and increased awareness of ischaemic heart disease risk factors in these patients and healthcare providers is warranted.

Key words: aortic function, coeliac disease, echocardiography

INTRODUCTION

Coeliac disease (CD) is characterised by gluten intolerance that particularly affects the gastrointestinal system. The condition causes chronic mucosal inflammation of the proximal small intestine. CD is usually diagnosed during childhood and adolescence, but it can also be diagnosed in adults [1].

Previous studies have demonstrated an increased risk of incident ischaemic heart disease (IHD), mortality, or cardiovascular (CV) disease in CD patients [2–5].

Aortic stiffness (AS) has a direct effect on CV morbidity and mortality [6]. Major CV risk factors such as smoking, hypercholesterolaemia, and diabetes mellitus can increase AS [7–11].

Although some studies investigated the association between CD and CV disease, there was lack of evidence for an association between CD and early predictors of atherosclerosis, such as aortic function (AS index [ASI], aortic strain, and aortic distensibility) [12].
In this study, we aimed to investigate the association between aortic function (ASI, aortic strain, and aortic distensibility), which are predictors of atherosclerosis, and CD.

**METHODS**

The study included 36 biopsy-proven CD patients who were admitted to the Department of Gastroenterology and 35 age- and sex-matched control subjects who were admitted to the Department of Cardiology. Exclusion criteria were known history of moderate or severe valvular disease, heart failure (ejection fraction < 50%), rhythm disturbance, structural or congenital heart disease, coronary heart disease, active infection, malignancy, pregnancy, other systemic inflammatory diseases, diabetes mellitus, uncontrolled hypertension, and use of vasoactive drugs.

As part of gastrointestinal endoscopy studies, patients underwent upper gastrointestinal endoscopy with at least six biopsies in the descending duodenum using a Fujinon EG 450PE5 gastroscope (Fujinon, Japan). Histological findings were described using the modified Marsh classification [2]. The patients were enrolled to the study after diagnosis of CD.

During hospitalisation under fasting conditions, blood glucose levels, lipid profile (low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], triglycerides, and total cholesterol), renal and liver function tests, thyroid function tests, ferritin levels, vitamin B12, levels, and folate levels were measured (Beckman Coulter, Fullerton CA, USA). LDL-C was calculated using the Friedewald formula. A complete blood count was also obtained using a Beckman Coulter LH780 Haematology Analyser with the LH SlideMaker and LH SlideStainer (Fullerton CA, USA). Serological screening was performed to determine the levels of auto-immune markers, including anti-gliadin antibody (AGA) immunoglobulin (IgA), AGA IgG, and anti-tissue-transglutaminase (anti-tTG) antibodies. Antibodies were detected in CD patients using fluorescence patterns as auto-immune markers using Euroimmun (Medizinische Labordiagnostika AG) immune fluorescence auto-antibody determination kits.

Echocardiographic recordings were obtained by standard ultrasonography (Vivid 7, GE, Horten, Norway) and a 2.5–3.5-Hz transducer at parasternal and apical windows by a single experienced observer who was blinded to clinical and laboratory data. Apical four-chamber and parasternal views of the left ventricle were obtained at end-expiratory apnoea. The left ventricular ejection fraction was measured with M-mode recordings using the Teichholz method [13].

Aorta (Ao) diameters were measured from the same view on the M-mode tracing at a level of 3 cm above the aortic valve. The systolic diameter (AoSD) was measured at the maximum anterior motion of the Ao, while the diastolic diameter (AoDD) was measured at the peak of the QRS complex on a simultaneously recorded electrocardiogram. Blood pressure (systolic [SBP] and diastolic [DBP]) was simultaneously measured by sphygmomanometry during echocardiography.

Aortic function was measured by sphygmomanometry during echocardiography. The aortic function (ASI, aortic strain, and aortic distensibility) was defined as the relative compliance or relative change in diameter as pressure increases.

The following indices of aortic function were calculated.

- **Aortic strain (%)** = 100 × \( \frac{(\text{AoSD} – \text{AoDD})}{\text{AoDD}} \)
- **Aortic distensibility** = \( \frac{2 \times (\text{AoSD} – \text{AoDD})}{(\text{AoDD})^2} \) [cm² × dyn⁻¹ × 10⁻⁶]
- **Aortic stiffness index (ASI)** = \( \ln \left( \frac{\text{PP}}{(\text{AoSD} – \text{AoDD})/\text{AoDD}} \right) \)
- **Pulse pressure (PP)** was calculated as SBP – DBP [16]
- **Mean blood pressure (MBP)** was calculated as \( \frac{1}{2} (\text{SBP} + \text{DBP}) \)

The study protocol was approved by the local ethics committee, and informed consent was obtained from each subject before study enrolment.

**Statistical analysis**

The International Business Machines Statistical Package for the Social Sciences for Windows 15.0 was used for all statistical analyses. Continuous variables are presented as means ± standard deviations or medians (minimum–maximum). Categorical variables are summarised as frequencies and percentages. Normality of the continuous variables was evaluated by the Shapiro–Wilks test. Differences between groups according to continuous variables were determined by an independent samples t-test or the Mann–Whitney U-test as appropriate. Categorical variables were compared by Pearson’s \( \chi^2 \) or Fisher’s exact test. Factors affecting aortic function were verified by multiple linear regression analysis. A p-value < 0.05 was considered statistically significant.

**RESULTS**

Clinical and demographic variables of the groups are summarised in Table 1. There were no significant differences in gender, age, body mass index, hyperlipidaemia, smoking status, and blood pressure. LDL-C, serum triglyceride, and serum thyroid stimulating hormone levels were significantly higher in the CD group than in controls: 103.65 ± 25.63 vs. 89.82 ± 32.23, \( p = 0.049 \); 109.88 ± 39.28 vs. 83.14 ± 41.22, \( p = 0.007 \); 2.1 (0.74–17.9) vs. 1.44 (0.39–4.65), \( p = 0.001 \), respectively. HDL-C and free tri-iodothyronine levels were significantly higher in controls than in the CD group: 52.08 ± 13.16 vs. 45.28 ± 10.34, \( p = 0.002 \); 3.40 ± 0.39 vs. 3.07 ± 0.76, \( p = 0.026 \). respectively.

Echocardiographic variables of the groups are shown in Table 2. The left atrial diameter and aortic root diameter were significantly greater in CD patients than in controls: 3.25 (2.5–3.6) vs. 3.0 (2.3–3.9), \( p = 0.005 \); 2.30 (2.0–3.3) vs. 2.10 (2.0–2.6), \( p = 0.006 \), respectively.
Table 1. Demographic and laboratory characteristics of subjects by study groups

<table>
<thead>
<tr>
<th></th>
<th>Celiac patients (n = 36)</th>
<th>Controls (n = 35)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male/female)</td>
<td>6/30</td>
<td>5/30</td>
<td>0.783</td>
</tr>
<tr>
<td>Age [years]*</td>
<td>28.5 (17–53)</td>
<td>27 (18–52)</td>
<td>0.682</td>
</tr>
<tr>
<td>Body mass index [kg/m²]</td>
<td>22.52 ± 4.13</td>
<td>21.42 ± 3.51</td>
<td>0.235</td>
</tr>
<tr>
<td>Pulse [bpm]</td>
<td>72.08 ± 6.83</td>
<td>75.51 ± 8.32</td>
<td>0.062</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>5 (13.9%)</td>
<td>3 (8.6%)</td>
<td>0.710</td>
</tr>
<tr>
<td>Smoking</td>
<td>5 (13.9%)</td>
<td>8 (22.9%)</td>
<td>0.503</td>
</tr>
<tr>
<td>Systolic blood pressure [mm Hg]*</td>
<td>110 (90–120)</td>
<td>110 (90–130)</td>
<td>0.489</td>
</tr>
<tr>
<td>Diastolic blood pressure [mm Hg]*</td>
<td>69 (60–80)</td>
<td>70 (60–80)</td>
<td>0.675</td>
</tr>
<tr>
<td>Antiendomysium ab. (+/-)</td>
<td>19/17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antigliadin IgA (+/-)</td>
<td>14/23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antigliadin IgG (+/-)</td>
<td>11/25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol [mg/dL]</td>
<td>164.25 ± 34.16</td>
<td>159 ± 37.98</td>
<td>0.542</td>
</tr>
<tr>
<td>HDL cholesterol [mg/dL]</td>
<td>45.28 ± 10.34</td>
<td>52.08 ± 13.16</td>
<td>0.019</td>
</tr>
<tr>
<td>LDL cholesterol [mg/dL]</td>
<td>103.65 ± 25.63</td>
<td>89.82 ± 32.23</td>
<td>0.049</td>
</tr>
<tr>
<td>Triglyceride [mg/dL]</td>
<td>109.88 ± 39.28</td>
<td>83.14 ± 41.22</td>
<td>0.007</td>
</tr>
<tr>
<td>Haemoglobin [g/dL]</td>
<td>12.97 ± 1.71</td>
<td>13.16 ± 1.62</td>
<td>0.633</td>
</tr>
<tr>
<td>Vitamin B₁₂ [pg/mL]</td>
<td>353.05 ± 125.07</td>
<td>320.68 ± 181.26</td>
<td>0.383</td>
</tr>
<tr>
<td>Ferritin [mg/mL]*</td>
<td>59 (5-214)</td>
<td>69 (11-251)</td>
<td>0.154</td>
</tr>
<tr>
<td>Folate [ng/dL]</td>
<td>6.77 ± 3.80</td>
<td>6.40 ± 2.61</td>
<td>0.637</td>
</tr>
<tr>
<td>Free T₃ [pmol/L]</td>
<td>3.07 ± 0.76</td>
<td>3.40 ± 0.39</td>
<td>0.026</td>
</tr>
<tr>
<td>Free T₄ [pmol/L]</td>
<td>1.98 ± 1.75</td>
<td>1.12 ± 0.21</td>
<td>0.376</td>
</tr>
<tr>
<td>TSH [mU/mL]*</td>
<td>2.1 (0.74–17.9)</td>
<td>1.44 (0.39–4.65)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Median (minimum–maximum), variables without normal distribution; mean ± standard deviation, variables with normal distribution; HDL — high density lipoprotein; LDL — low density lipoprotein; TSH — thyroid-stimulating hormone

Table 2. Echocardiographic characteristics of subjects by study groups

<table>
<thead>
<tr>
<th></th>
<th>Celiac patients (n:36)</th>
<th>Controls (n:35)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV end-diastolic diameter [cm]</td>
<td>4.52 ± 0.41</td>
<td>4.51 ± 0.37</td>
<td>0.909</td>
</tr>
<tr>
<td>LV end-systolic diameter [cm]</td>
<td>2.83 ± 0.28</td>
<td>2.73 ± 0.31</td>
<td>0.174</td>
</tr>
<tr>
<td>Ejection fraction [%]</td>
<td>67 ± 4.27</td>
<td>67.97 ± 3.82</td>
<td>0.317</td>
</tr>
<tr>
<td>Left atrium diameter [cm]*</td>
<td>3.25 (2.5–3.6)</td>
<td>3.0 (2.3–3.9)</td>
<td>0.005</td>
</tr>
<tr>
<td>Septal wall thickness [cm]*</td>
<td>0.9 (0.7–1.0)</td>
<td>0.90 (0.7–1.1)</td>
<td>0.672</td>
</tr>
<tr>
<td>Posterior wall thickness [cm]*</td>
<td>0.90 (0.7–1.10)</td>
<td>0.90 (0.6–1.1)</td>
<td>0.908</td>
</tr>
<tr>
<td>Aortic root [cm]*</td>
<td>2.30 (2.0–3.3)</td>
<td>2.10 (2.0–2.6)</td>
<td>0.006</td>
</tr>
<tr>
<td>Aortic velocity [m/sn]*</td>
<td>1.22 (1.0–1.6)</td>
<td>1.20 (1.0–1.5)</td>
<td>0.169</td>
</tr>
<tr>
<td>Pulmonary velocity [m/sn]*</td>
<td>0.90 (0.7–1.1)</td>
<td>0.90 (0.6–1.0)</td>
<td>0.447</td>
</tr>
<tr>
<td>Mitral E wave [m/sn]*</td>
<td>0.90 (0.5–1.3)</td>
<td>0.90 (0.6–1.3)</td>
<td>0.338</td>
</tr>
<tr>
<td>Mitral A wave [m/sn]*</td>
<td>0.60 (0.5–1.0)</td>
<td>0.60 (0.4–0.8)</td>
<td>0.174</td>
</tr>
<tr>
<td>Aortic strain [%]*</td>
<td>0.07 (0.03–0.14)</td>
<td>0.09 (0.06–0.15)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Aortic stiffness index*</td>
<td>1.14 (0.57–2.69)</td>
<td>0.91 (0.59–1.92)</td>
<td>0.002</td>
</tr>
<tr>
<td>Aortic distensibility</td>
<td>0.0036 ± 0.0012</td>
<td>0.0051 ± 0.0014</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

*Median (minimum–maximum), variables without normal distribution; mean ± standard deviation, variables with normal distribution; LV — left ventricle
The degree of aortic strain and aortic distensibility was significantly smaller in CD patients than in controls: 0.07 (0.03–0.14) vs. 0.09 (0.06–0.15), p < 0.001; 0.0036 ± ± 0.0012 vs. 0.0051 ± 0.0014, p < 0.001, respectively, but the ASI was significantly higher in CD patients than in controls: 1.14 (0.57–2.69) vs. 0.91 (0.59–1.92), p = 0.002.

As shown in Table 3, although we found that age and celiac disease were correlated both with aortic strain (p = 0.036, p < 0.001, respectively), and aortic distensibility (p = 0.028, p < 0.001, respectively), celiac disease was the only parameter that correlated with ASI (p = 0.002). After multivariate analysis, celiac disease was the sole independent factor for aortic strain, aortic distensibility, and ASI (β = –0.437, p < 0.001; β = 0.369, p = 0.002; β = 0.451, p < 0.001, respectively).

**DISCUSSION**

Celiac disease is characterised by life-long intolerance to gluten found in dietary cereals. The prevalence of CD is 1% in the general population, but the prevalence in patients with autoimmune disorders is higher than that in the normal population (8–20%) [1, 17]. In CD patients, regular ingestion of wheat, rye, and barley induces T-cell-mediated inflammation in the gut and an autoimmune response to self proteins, mainly tissue type-2-transglutaminase, leading to the production of anti-tTG antibodies [18].

The aetiopathological mechanisms of CV outcomes in CD patients can be chronic inflammation or augmented levels of plasma homocysteine because of the malabsorption of folic acid and vitamin B12 [19, 20]. In our study, the underlying mechanism of CD may be chronic inflammation because there were no significant differences in folate and vitamin B12 levels between groups.

AS has a strong effect on CV prognosis. This association can be explained by three primary mechanisms [21]. First, increased AS may contribute to atherosclerotic progression to other arteries such as the coronary and carotid arteries. Second, in addition to AS, SBP and pressure on vital organs is increased, contributing to the risk of atherosclerotic complications. Last, endothelial dysfunction can lead to AS and atherosclerotic progression. Therefore, AS plays an important role in CV events [22–24].

Previous studies have shown a higher CD prevalence among patients with idiopathic dilated cardiomyopathy and myocarditis [25–27]. Moreover, Makhdoom et al. [28] demonstrated the association between gluten restriction and improvement of cardiac function in patients with CD. In our study, there were significant differences in the diameter of the left ventricle between the CD patients and controls. Left atrial diameters were greater in the CD group; this condition could be related to left ventricular diastolic dysfunction.

Ludvigsson et al. [29] found a positive association between CD and IHD; they also found an elevated risk of IHD that was independent of small intestinal histopathology in CD patients. Also, Wei et al. [5] reported a 2.5-fold increased risk of CV disease in celiac patients without prior CV disease. Endothelial dysfunction is a marker of vascular involvement in any disease affecting the vascular structures that can be linked with vascular involvement in atherosclerosis [30]. In our previous study, we demonstrated macrovascular endothelial dysfunction in CD patients using a flow-mediated dilatation method [31].

This is the first study to investigate aortic function using echocardiography in CD patients, which revealed deteriorated aortic function. These results suggest that the consumption of gluten-free diets from childhood may play a preventive role in the development of further atherosclerotic diseases in CD patients.

**Limitations of the study**

This study has some limitations. This study is a single-centre, nonrandomised study. The sample size was relatively small. Other limitations of the study were the fact that no inflammation markers were used and that the blood pressure was measured from the brachial artery instead of the aorta.
CONCLUSIONS
In conclusion, our findings suggest that CD is associated with impaired aortic function. This finding helps to explain why celiac subjects have increased CV risk. Because deteriorated aortic function is a strong predictor of future CV events, close cooperation with cardiologists and gastroenterologists is needed in the management of CD patients, and increased awareness of IHD risk factors in these patients and healthcare providers is warranted.

Conflict of interest: none declared

References

Nieprawidłowa czynność aorty u pacjentów z chorobą trzewną

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Streszczenie

Wstęp i cel: Badanie przeprowadzono w celu oceny powiązań między czynnością aorty (wskaźnik sztywności aorty i rozszerzalność aorty), będącą czynnikiem predykcyjnym miażdżycy, a chorobą trzewną (CD).

Metody: Do badania włączono 36 pacjentów z CD i 35 osób stanowiących grupę kontrolną. W celu określenia stężeń wskaźników autoimmunologicznych, w tym miana przeciwciał przeciw gliadynie IgA i IgG oraz przeciw transglutaminazie tkankowej, przeprowadzono badania serologiczne. Rozszerzalność aorty, odkształcenie aorty i wskaźnik sztywności aorty obliczono na podstawie badania echokardiograficznego.

 Wyniki: Odkształcenie i rozszerzalność aorty były istotnie mniejsze u pacjentów z CD niż u osób z grupy kontrolnej [odpowiednio 0,07 (0,03–0,14) vs. 0,09 (0,06–0,15), p < 0,001; 0,0036 ± 0,0012 vs. 0,0051 ± 0,0014, p < 0,001]. Z kolei wskaźnik sztywności aorty był istotnie wyższy u pacjentów z CD niż w grupie kontrolnej [1,14 (0,57–2,69) vs. 0,91 (0,59–1,92), p = 0,002]. Choroba trzewna była jedyną niezależną zmienią skorelowaną z odkształceniem aorty, wskaźnikiem sztywności aorty i rozszerzalnością aorty (odpowiednio β = −0,427; p < 0,001; β = 0,375, p = 0,003; β = −0,434; p < 0,001).

Wnioski: Na podstawie badania echokardiograficznego wyказанo, że u pacjentów z CD występuje nieprawidłowa czynność aorty, która jest czynnikiem predykcyjnym subklinicznej miażdżycy. Ze względu na fakt, że upośledzenie czynności aorty jest silnym czynnikiem predykcyjnym wystąpienia w przyszłości zdarzeń sercowo-naczyniowych, w leczeniu osób z CD konieczna jest ścisła współpraca między kardiologami a gastroenterologami. Potrzebne jest również zwiększenie wśród pacjentów i lekarzy wiedzy na temat związanych z tym schorzeniach czynników ryzyka choroby niedokrwiennej serca.

Słowa kluczowe: czynność aorty, choroba trzewna, echokardiografia

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