Correlations Between Serum Cholesterol and Vascular Lesions in Fabry Disease Patients

Hiroki Katsuta, MD; Kazuya Tsuboi, MD, PhD; Hiroshi Yamamoto, MD, PhD; Hiromi Goto, MD, PhD

Background: Fabry disease is an X-linked lysosomal storage disorder and shows globotriosylceramide (Gb3) accumulation in multiple organs, resulting from a deficiency of α-galactosidase. In patients with Fabry disease, cardiovascular disease occurs at an early age. Previous studies have shown that serum levels of high-density lipoprotein-cholesterol (HDL-C) increase in this disease, yet its clinical significance for cardiovascular disease remains unclear.

Methods and Results: In order to determine why the serum HDL-cholesterol is high in various cardiovascular diseases of Fabry disease patients, we evaluated the serum lipid profiles, ocular vascular lesions, and levels of serum vascular endothelial growth factor (VEGF) and intercellular adhesion molecule-1 in 69 patients with Fabry disease diagnosed by genetic examination. The serum HDL-C/total cholesterol (T-Chol) ratio was significantly high, especially in male patients (41.5±1.7%) regardless of body mass index. Ocular vascular lesions were more likely to occur in female patients with a high HDL-C/T-Chol ratio compared with most male patients. Female patients with a high HDL-C/T-Chol ratio also presented a high serum VEGF level, suggesting that vascular endothelium dysfunction and arteriosclerotic changes progress more severely than in patients with a normal HDL-C/T-Chol ratio. In most patients, enzyme replacement therapy improved serum Gb3 and lyso-Gb3 levels, but these Gb3 and lyso-Gb3 still remained higher than in healthy controls, which appears to result in continuous vascular arteriosclerotic changes.

Conclusions: We concluded that increased low-density lipoprotein-cholesterol uptake to the vascular wall caused by endothelial dysfunction is likely to contribute to the high HDL-C/T-Chol ratio observed in Fabry disease patients.

Key Words: Enzyme replacement therapy; Fabry disease; High-density lipoprotein-cholesterol; Microvascular lesions; Sphingolipidosis

Fabry disease (OMIM no. #301500) is an X-linked lysosomal storage disease caused by loss-of-function mutations of α-galactosidase (GLA). In patients with Fabry disease, globotriosylceramide (Gb3) and other glycosphingolipids progressively accumulate in different tissues. The specific symptoms of this disease are angiokeratoma, acroparesthesia and hypohydrosis, but other organs, such as the heart, kidneys and blood vessels are also affected, resulting in multiorgan failure and premature death. For example, in cardiac systems, Gb3 accumulates in heart muscle cells and vascular endothelial and smooth muscle cells, which causes chronic heart failure, left ventricular hypertrophy and arrhythmia. In vascular, endothelial and smooth muscle cells are affected by Gb3, resulting in vascular endothelial dysfunction and wall thickening. Previous studies have shown increased carotid intima-media thickness (IMT) and decreased brachial flow-mediated dilation (FMD). Although the GLA gene is on the X chromosome, female carriers can be also affected because of lyonization, which results in as many kinds of symptoms as in male patients. The only treatment at present for Fabry disease is enzyme replacement therapy (ERT). ERT is effective for acroparesthesia, left ventricular hypertrophy (most common heart lesion in Fabry disease) and renal dysfunction. However other studies suggest progression of vascular lesions, and autopsies of Fabry disease patients have shown Gb3 accumulation in vascular walls even after ERT.

Previous studies have shown that serum high-density lipoprotein-cholesterol (HDL-C) levels are higher in Fabry disease patients than in healthy controls. The HDL-C levels remained high even after ERT in those studies. On the other hand, high HDL-C level is related to elimination of the risk of cardiovascular disease. It remains unclear why serum HDL-C levels are high in Fabry disease patients and why cardiovascular diseases occur earlier than in other people despite high HDL-C levels. In order to figure out the clinical meaning of serum cholesterol levels in Fabry disease, we analyzed the relationship between serum cholesterol level and vascular lesions. We evaluated vascular lesions by ocular vascular features, and levels of serum vascular endothelial growth factor (VEGF) and intercellular
adhesion molecule-1 (ICAM-1), because serum VEGF and ICAM-1 are useful for detecting the early stages of atherosclerotic lesions\(^8\)\(^{,}\)\(^9\) and are thought to be related to diabetic microangiopathy.\(^{21}\) In previous studies, these cytokines were higher in this disease than in healthy controls.\(^{22,}\)\(^{23}\) We also measured serum Gb3 and lyso-Gb3 levels before and after ERT based on our hypothesis that the cholesterol profile is affected by these factors.

**Methods**

We carried out an observational study of Fabry disease patients at Nagoya Central Hospital who were confirmed by clinical manifestation and genetic testing. The mutation of E66Q is now thought to be a genetic polymorphism,\(^{24,}\)\(^25\) so this mutation was excluded. Patients with no test results for HDL-C and low-density lipoprotein-cholesterol (LDL-C) were also excluded. The sex proportions in this study were 30 males and 37 females. The study was conducted in accordance with the Declaration of Helsinki and applicable local laws and regulations. Patients provided written informed consent before inclusion in the study.

In previous studies, serum cholesterol levels have shown no obvious changes before and after ERT, so we used the blood test results from the first visit to hospital regardless of ERT. The serum lipid profile was determined by enzymatic method. The reference ranges were: 120–219 mg/dL for total cholesterol (T-Chol); 40–85 mg/dL in men and 40–95 mg/dL in women for HDL-C; 65–139 mg/dL for LDL-C; 30–149 mg/dL for triglycerides (TG); and 25–35% for HDL-C/T-Chol ratio. Serum VEGF and ICAM-1 levels were measured by enzyme immunoassay (EIA). The normal range of serum VEGF is <38.3 pg/mL, and for serum ICAM-1 is 82.5–276 ng/mL. Gb3 and lyso-Gb3 levels were measured by liquid chromatography–tandem mass spectrometry (LC-MS/MS). Ocular vascular lesions were evaluated by ophthalmologists. The Scheie classification was used for hypertensive and arteriosclerotic lesion assessments.\(^{26}\)

All data are described as mean±SD or median (95% CI). Fisher’s exact test, paired t-test and Mann-Whitney U-test were used in the statistical analysis. We defined P<0.05 as statistically significant.

**Results**

**Patients’ Characteristics**

The age of patients included in this study ranged from 6 to 55 years (median 33) in the males and from 14 to 64 years (median 43) in the females. None of the male patients had dyslipidemia, but 2 female patients did and were treated with statins. Average body mass index (BMI) was 20.1±0.6 kg/m\(^2\) in the males and 21.5±0.5 kg/m\(^2\) in the females.

**Serum Lipid Profiles (Table 1)**

In male and female patients, respectively, the serum lipid profiles were as follows: T-Chol, 166.8±5.2 mg/dL (4.32±0.13 mmol/L) and 203.8±5.4 mg/dL (5.28±0.14 mmol/L), which was almost the same as in previous studies of Fabry disease patients.\(^{26,}\)\(^{16}\) TG, 77.1±6.4 mg/dL (0.87±0.07 mmol/L) and 105.4±10.4 mg/dL (1.19±0.12 mmol/L); LDL-C, 87.5±4.8 mg/dL (2.27±0.12 mmol/L) and 119.0±4.4 mg/dL (3.08±0.11 mmol/L); HDL-C, 67.8±2.3 mg/dL (1.74±0.12 mmol/L) and 70.2±2.0 mg/dL (1.78±0.11 mmol/L). A total of 10 female patients had dyslipidemia; all showed only high LDL-C.

The HDL-C/T-Chol ratio was higher than the reference range in 22 of the 30 male patients and in 20 of the 37 female patients. The HDL-C/T-Chol ratio was 41.5±1.7% in males and 35.2±1.2% in females. We also analyzed whether this cholesterol profile correlated with age (Figure S1), but did not find a clear correlation in either sex. Male patients aged >50 years were also included in the high HDL-C/T-Chol ratio group, but they had significant heart atrophy and renal dysfunction, which suggested that a high HDL-C/T-Chol ratio does not contribute to cardiovascular protection.

We also analyzed the relationship between BMI and the HDL-C/T-Chol ratio. As shown in Figure 1 the correlation coefficient was −0.097 in males and −0.231 in females, which is not a clear correlation.

**Ocular Vascular Lesions and Relationship to Serum Cholesterol**

Abnormal findings in the ocular vessels were identified in 23 of the 27 male patients and in 17 of 34 female patients. Common vascular lesions were arteriolar tortuosity, arteriolar narrowing, broadening of the light reflex with minimal arteriovenous compression in fundic vessels. Conjunctival microaneurysms, vessel overswellling or irregularities of the vessel’s caliber were found in 4 patients. The ocular vascular lesions of the patients in this study are shown in Table 2. A previous study reported tortuosity of retinal vessels, venous vascular aneurysmal dilatation and caliber irregularities.\(^{26}\) However, aneurysms of the conjunctival vessels were much fewer (4 of 61 patients) compared with previous studies reporting that aneurysms were observed in 68–97% patients.\(^{26,}\)\(^{28}\)

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**Table 1. Serum Lipid Profiles of Fabry Disease Patients**

<table>
<thead>
<tr>
<th>Laboratory reference range</th>
<th>Male (n=30)</th>
<th>Female (n=37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>31.4±4.1 (6–55)</td>
<td>45.6±7±4.8 (14–64)</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>20.1±1.2</td>
<td>21.5±1.0</td>
</tr>
<tr>
<td>T-Chol (mg/dL)</td>
<td>130–220</td>
<td>166.8±5.2</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>65–139</td>
<td>87.5±4.8</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>40–150</td>
<td>77.1±6.4</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>40–85 (M)/40–95 (F)</td>
<td>67.8±2.3</td>
</tr>
<tr>
<td>HDL/Total (%)</td>
<td>25–35</td>
<td>41.5±1.7*</td>
</tr>
</tbody>
</table>

*P<0.05. BMI, body mass index; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; T-Chol, total cholesterol.
Clinical Meaning of Cholesterol in Fabry Disease

In this study, only 3 male and 4 female patients showed hypertension and only 10 female patients showed dyslipidemia; hypertensive and arteriosclerotic changes occurred in most of the male patients and half of the female patients, suggesting that Fabry disease, but not the more common diseases such as hypertension and dyslipidemia, causes arteriolar lesions.

We also analyzed the correlation between the HDL-C/T-Chol ratio and ocular vascular lesions (Table 3). We divided our patients into 2 groups according to the HDL-C/T-Chol ratio (≤35% vs. >35%). In male patients, ocular vascular lesions were found at almost the same rate in both groups. However, female patients with a high HDL-C/T-Chol ratio (>35%) were more likely to have ocular vascular lesions, although not statistically significant in Fisher’s exact test. Our results suggested that a high HDL-C level does not play a vascular protective role in Fabry disease patients.

Serum VEGF and ICAM-1 Levels and Relationship to Serum Cholesterol

In order to determine whether serum VEGF and ICAM-1 levels change after ERT, we compared 14 patients with serum VEGF and ICAM-1 data before and after ERT using the Wilcoxon rank sum test. Neither VEGF nor ICAM-showed a decrease after ERT, so we used the serum VEGF and ICAM-1 data from the first hospital visit regardless of administration of ERT. The serum VEGF level was >38.3 pg/mL in 12 of 18 male patients and in 12 of 22 female patients. ICAM-1 was higher than the reference range in 16 of 18 male patients and in 13 of 22 female patients. We analyzed the correlation between these cytokines and the HDL-C/T-Chol ratio. Serum VEGF was significantly higher in patients with a high HDL-C/T-Chol ratio, especially in female patients (P=0.138 in males; P=0.047 in females) (Figure 2). Serum ICAM-1 did not show a clear correlation with the HDL-C/T-Chol ratio. Previous studies have shown that serum VEGF and ICAM-1 levels increase from an early stage of atherosclerosis. So it is likely that a high HDL-C/T-Chol ratio reflects some vascular lesions in Fabry disease. In addition, patients with ocular vascular lesions had more tendency towards a high serum VEGF level. Our results suggested that a high HDL-C/T-Chol ratio and high serum VEGF indicate

**Table 2. Ocular Vascular Lesions in Fabry Disease Patients**

<table>
<thead>
<tr>
<th>Vascular lesion</th>
<th>Male (%)</th>
<th>Female (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fundic vascular tortuosity</td>
<td>20 (74)</td>
<td>8 (24)</td>
</tr>
<tr>
<td>Scheie classification</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H0</td>
<td>11 (41)</td>
<td>21 (62)</td>
</tr>
<tr>
<td>H1</td>
<td>13 (48)</td>
<td>11 (32)</td>
</tr>
<tr>
<td>H2</td>
<td>3 (11)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>H3</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>S0</td>
<td>10 (37)</td>
<td>21 (62)</td>
</tr>
<tr>
<td>S1</td>
<td>15 (56)</td>
<td>12 (35)</td>
</tr>
<tr>
<td>S2</td>
<td>1 (4)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>S3</td>
<td>1 (4)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

In addition to these vascular lesions, conjunctiva microaneurysms (1 patient), vessel overswellin (1 patient) and irregularities of the vessel caliber (2 patients) were observed.

**Table 3. Relationship Between Ocular Vascular Lesions and HDL-C/T-Chol Level**

<table>
<thead>
<tr>
<th>HDL-C/T-Chol</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;35% (%)</td>
<td>(17 (85))</td>
<td>(12 (71))</td>
</tr>
<tr>
<td>≤35% (%)</td>
<td>(7 (100))</td>
<td>(7 (41))</td>
</tr>
</tbody>
</table>

In this study, only 3 male and 4 female patients showed hypertension and only 10 female patients showed dyslipidemia; hypertensive and arteriosclerotic changes occurred in most of the male patients and half of the female patients, suggesting that Fabry disease, but not the more common diseases such as hypertension and dyslipidemia, causes arteriolar lesions.

**Figure 1.** Relationship between body mass index (BMI) and HDL-C/T-Chol ratio shows no correlation in either male or female patients. HDL-C, high-density lipoprotein-cholesterol; T-Chol, total cholesterol.

**Figure 2.** Serum ICAM-1 did not show a clear correlation with the HDL-C/T-Chol ratio. Previous studies have shown that serum VEGF and ICAM-1 levels increase from an early stage of atherosclerosis. So it is likely that a high HDL-C/T-Chol ratio reflects some vascular lesions in Fabry disease. In addition, patients with ocular vascular lesions had more tendency towards a high serum VEGF level. Our results suggested that a high HDL-C/T-Chol ratio and high serum VEGF indicate
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Other studies have shown that accumulated Gb3 in vascular endothelial cells induces vascular damage in Fabry disease patients.

**Serum Gb3 and Lyso-Gb3 Levels**

In order to determine why the HDL-C/T-Chol ratio and VEGF levels remain high, we analyzed the serum Gb3 and lyso-Gb3 levels before and after ERT (Table 4). For the data from “after ERT”, we used the latest blood test results from all patients who underwent this treatment for at least 3 months. In male patients, Gb3 decreased from 15.7 ng/mL to 6.49 ng/mL and lyso-Gb3 decreased from 83.4 pg/mL to 32.3 pg/mL on average. In female patients, Gb3 decreased from 9.00 ng/mL to 5.61 ng/mL and lyso-Gb3 decreased from 10.5 pg/mL to 6.84 pg/mL on average. These results suggested that ERT can decrease Gb3 and lyso-Gb3 levels. However, the reference range for Gb3 is 4.6±2.0 ng/mL and that of lyso-Gb3 is <1.2±0.1 pg/mL, so the serum levels were still higher in the present study patients than in healthy people, even after ERT. Based on our results, it is possible that high Gb3 and lyso-Gb3 levels may affect the continually high HDL-C/T-Chol ratio, and thus vascular lesions, even after ERT.

**Discussion**

In this study, we analyzed the correlations between serum cholesterol levels and vascular lesions in Fabry disease patients. Our results showed that these patients had a high HDL-C/T-Chol ratio, vascular hypertensive and arteriosclerotic changes of the fundus and high serum VEGF and ICAM-1 levels. In the study by Cartwright et al, the average of serum HDL-C concentration in male patients was 1.46 mmol/L and 1.93 mmol/L in female patients. Stepien et al also reported almost the same cholesterol levels. In our results, the male HDL-C level was 1.74 mmol/L, which was higher than in the 2 previous studies. So the high HDL-C level in our study is consistent and unlikely to be affected by ethnic differences.

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Because LDL-C is essential for lipid raft formation, may contribute to the formation of focally distributed HDL-C. Moreover, the vascular tortuosity observed in which is likely to result in a relative increase of serum utilization might be increased in Fabry disease patients, level is also low.

vascular damage. sheds new light on Fabry disease, especially in relation to damage. Despite these limitations, we believe our study the risk of stroke, acute coronary syndrome etc. need to be further evaluated. In our study, serum lyso-Gb3 showed a significant decrease after ERT, but remained much higher than in healthy people, suggesting that present ERT protocols are still not effective enough because of high lyso-Gb3 levels. In fact, other ways of evaluating vascular lesions and endothelial functions, such as IMT and FMD, have not shown outstanding improvement after ERT.4

Recent in vitro studies suggested other mechanisms of vascular damage caused by this disease. In GLA-silencing cells, lipid raft domains show a significant increase.36 Because LDL-C is essential for lipid raft formation,37 LDL utilization might be increased in Fabry disease patients, which is likely to result in a relative increase of serum HDL-C. Moreover, the vascular tortuosity observed in this disease is likely to cause turbulent blood flow, which may contribute to the formation of focally distributed incipient atherosclerotic lesions.38

It is known that other lysosomal storage disorders are associated with HDL-C decrease. In Gaucher disease, this low HDL-C improves with ERT towards the normal range.39 In Niemann-Pick A, B and C disease, the HDL-C level is also low.40,41 One possible reason is the contribution of liver function. HDL-C is not only produced in peripheral tissues but also re-secreted by the liver. As with many other organs, liver function is affected in most lysosomal storage diseases, but not in Fabry disease,42 which may contribute to the high serum HDL-C level in this disease. However, further study is necessary to clarify more why HDL-C increases only in Fabry disease.

The limitation of this study is that the number of patients was small, especially those who had serum VEGF, ICAM-1, Gb3 and lyso-Gb3 levels measured. In addition, the relationships between the serum cholesterol profile and the risk of stroke, acute coronary syndrome etc. need to be further studied. By evaluating ocular vascular lesions or the serum VEGF level, we may be able to follow-up vascular damage. Despite these limitations, we believe our study sheds new light on Fabry disease, especially in relation to vascular damage.

Grants
No grants are provided in this study, but Kazuya Tsuboi receives consulting fee from Sumitomo Dainippon Pharma Co., Ltd.

References


**Supplementary Files**

**Supplementary File 1**

Figure S1. Correlation between age and HDL/T-Chol ratio in Fabry disease patients.

Please find supplementary file(s):

http://dx.doi.org/10.1253/cirj.CJ-18-0378