Case Report

Two Long-Term Follow-Up Cases Preventing Atherosclerosis by Hormone Replacement Therapy-CETP Deficiency and Tangier Disease

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Abstract

We reported two cases being treated with HRT for the past 7~11 years presenting no progression in atherosclerosis. The first case was diagnosed of having CETP deficiency (homozygosity type) and fibromyalgia at the age of 52. The HDL-cholesterol level was around 200 mg/ ml, CETP DNA point mutation found in intron 14 variant type (A/A) and exon 15 wild type (A/A) were obtained. HRT relieved myalgia and joint pain as well as JFIQ baseline score 91 was reduced to 36, following a 3 months therapy. The second case was diagnosed as a Tangier disease, presenting 1~2 mg/dL of HDL cholesterol and a very low level of LDL-C at the age of 52. Her ANA with anti-centromere antibody 80 at the first visit rose to 640. Depression and shortness of breath disappeared while HRT was continued, However, HRT was discontinued for four years, which made osteoporosis and Alzheimer’s disease more progressive. The patient remained in good health as a result of the E3 2 mg/day and αtocopherol 600 mg/day that she has been receiving since 2015. In both cases, HRT served as a good therapy for mid aged women in the prevention of atherosclerosis.

Keywords: Tangier disease (TD); Cholesterol ester transfer protein (CETP); High density lipoprotein cholesterol (HDL-C); Estrogen progesterone replacement therapy (EPRT); Estradiol (E2); Estriol (E3); Atherosclerosis

Abbreviation: TD: Tangier Disease; CETP: Cholesterol Ester Transfer Protein; HDL-C: High Density Lipoprotein Cholesterol; EPRT: Estrogen Progesterone Replacement Therapy; E2: Estradiol; E3: Estriol; HRT: Hormone Replacement Therapy; CEE: Conjugated Equine Estrogen; FSH: Follicle Stimulating Hormone; CAVI: Cardio Ankle Vascular Index; ABI: Ankle Brachial Pressure Index; FMD: Flow Mediated Dilation; PCI: Percutaneous Coronary Intervention; IMT: Intima Media Thickness; CT: Computed Tomography; ERT: Estrogen Replacement Therapy; ANA: Anti-Nuclear Antibody; SRL: Special Reference Laboratory

Introduction

Atherosclerosis progression is common in mid-aged women [1]. Especially, in the case of ovarium resection and/or hysterectomy, menopausal symptoms including palpitation, sweating, insomnia, depression, dizziness, shortness of breath and so on are more prevalent and occur earlier in women who did operation than in those who performed no operation [2]. Tangier disease (TD) [3] is very rare. However, it is very important to know whether TD will become progressive or not in patients with atherosclerosis. HDL-C is extremely low such that atherosclerosis might develop, but low amount of LDL-C will not induce it. In contrast, CETP depletion [4] occurs with very high level of HDL-C, which is thought to be low activity of ABCA1-mediated cholesterol efflux. Therefore, high amount of HDL-C in case of CETP deficiency is not always protective of atherosclerosis. We have experienced two entirely different types of such diseases and treated with hormone replacement therapy (HRT) for the past ten years and reported the clinical significance of HRT for atherosclerosis. As control, 108 specimens from peri-/post-menopausal women were included to explore the influence of HRT for total cholesterol, LDL-C and HDL-C.
Methods

Influence of HRT for Levels of T Cholesterol, LDL-C and HDL-C

In addition to the two cases in particular, lipid analysis were performed at 0, 2, 6 and 12 months respectively, with a total of 108 specimen from 95 menopausal women under receiving tocopherol N 600 mg/day, ERT, estrogen progesterone replacement therapy (EPRT) cyclic, EPRT continuous, 17βE2 patch (0.72 mg/2days) and 17E2 oral(0.5 mg) as an estrogen source and dydrogesterone (5 mg) as a progestin source were used. Conjugated equine estrogen (CEE) was used exceptionally.

Consent

Two patients’ consent were obtained by documentation and the control patients’ consent were obtained orally. This study was approved by the Society of Health Care for Menopause and Ageing in Tokyo.

Detection of Autoantibodies

Anti-nuclear antibody (ANA) was measured by indirect immunofluorescence using Hep II cells as a substrate. Most autoantibodies including anti-U1RNP, anti-Sm, anti-SS-A/Ro, anti-SS-B/La, anti-jo1 and anti-Sd 70/Topo1 were measured by ELISA using commercial kit [5]. Anti-IP3Rs antibodies were detected by immunoblot, which has been previously described [6].

Determination of Post-Menopause

Postmenopausal conditions were estimated by simplified menopausal index (SMI) [7], menstrual condition, and sex hormone levels, including estradiol (E2) (less than 45 pg/mL) and/or follicle stimulating hormone (FSH) (more than 27 mIU/mL).

Genetic Analysis

Gene analysis of TD was done in Fukuoka University School of Medicine and reported in 2009 [8]. CETP deficiency (Reference No:4SSU0001) was determined in Tokyo by Special Reference Laboratory (SRL) in 2009.

LDL-Cholesterol Estimation

In 2008~2009, the amount of cholesterol in LDL was not directly tested, therefore, it was estimated using Fried Ewald’s formula [9].

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\text{LDL-cholesterol} = \frac{\text{Total cholesterol} - \text{HDL-C} - \text{Triglyceride}}{5}
\]

Atherosclerosis Examination

Atherosclerosis examination included ECG, CAVI (Cardio Ankle Vascular Index), ABI (Ankle Brachial Pressure Index), FMD (Flow Mediated Dilatation) [10], PCI (Percutaneous Coronary Intervention), performing first in early visiting, while the second time was after 8~10 years.

Results

Case 1 Female (1955)

a) Past history: 29y ovariectomy and hysterectomy,

b) Family history: young sister, high HDL-cholesterol

c) Present illness: She had complained of knee joint pain for over 30-years, but knee x ray revealed no evidence of abnormality.
In summer 2009, she complained of bilateral knee, wrist and ankle pains and in September 2009, because of bilateral wrist joint swelling, she could not take a walk with a dog. In January 2011, she visited the clinic owing to fatigue, multiple joint pains and myalgia. She was diagnosed as having fibromyalgia and menopausal arthralgia because of depletion in E2 level (16.0 pg/mL) and FSH level (66.7 mIU/mL). Estrogen replacement therapy reduced Japanese Fibromyalgia Impact Questionnaire (J-FIQ) [11] score from 91 to 36 after two weeks therapy and joint pain reduced by 22% after receiving HRT for 6 months. Laboratory findings and clinical course were presented. For the past 8 years, HDL-cholesterol level was always around 200 mg/mL. LDL-C levels were not so high and maintained the normal range. LDL-C/HDL-C was 0.68 on the first visit. E2 levels after receiving ERT were maintained at 40~90 pg/mL and FSH levels were maintained at 35~70 mIU/mL and the wide spreading pain was reduced to 50%. However, it did not disappear completely (Figure 1). CAVI and ABI revealed 8.9(rt. side)/ 8.6(lt. side) and 1.12(rt. side)/ 1.17(lt. side) in August 2016, suggesting that they were within normal limit. Further FMD showed 11.1% that was normal range (limit level above 6%). Findings from the study of images revealed that carotid artery echogram had no intima media thickness (IMT) hyperplasia and stenosis. Coronary artery computed tomography (CT) scan had no stenosis (in January 2017). Gene analysis was completed in 2011 as shown. One was Intron 14-point mutation (G>A) which causes abnormal splicing (Int 14A mutation). The other was amino acid change (aspartic acid>Glycine) at the position of 442 caused by base change (A>G) at the position of 1506 (D442G mutation)

Case 2, Female, (1953), sales woman

- a) Chief complaint: lethargy
- b) Family history: np
- c) Personal history: np

In case 2, the patient was a 1953 female saleswoman. The patient's chief complaint was lethargy. Her family and personal histories were not notable. She reported a history of low serum cholesterol level during a routine health check in 1990. In 1996, she was found to have uterine myoma and ovarian cyst. She underwent hysterectomy and ovarian cyst resections. She noticed dry mouth and in 2004, she had hemorroid surgery and her platelet count was found to be low. In January 2005, she visited the Keigu Clinic due to Raynaud’s phenomenon. During her first visit in October 2005, total cholesterol was 82 mg/dL, HDL-C 2 mg/dL, triglyceride 144 mg/dL, and estimated LDL-C 52 mg/dL were obtained. LDL-C/HDL-C was 25.5. ANA 40 with discrete speckle and platelet 8.9x10^4 /μl were shown. As sex hormone such as E2 9.0 pg/mL and FSH 42.3 mIU/mL was presented at postmenopausal stage, estrogen replacement therapy (ERT) began. Menopausal symptoms including depression, general fatigue and shortness of breath gradually improved when she started taking low dose of ERT in June 2008. She was referred to another hospital because of cognitive disorder and she remained there until January 2012. As soon as she started noticing depression and general fatigue, she returned to receive E3 2 mg/day and tocopherol 600 N mg/day (Figure 2). Moreover, she received bilateral total hip replacement (THR) in February and August 2017 because of walking difficulty owing to osteoporosis. She is now active, but Alzheimer’s disease is progressing. CAVI and ABI revealed 8.2(both sides) and 1.07(rt. side)/ 1.09(lt. side) in August 2016, suggesting that they were within normal limit. Further FMD showed 7.9% that fell within normal range. From the study of images, it was revealed that carotid artery echogram had no IMT hyperplasia and stenosis, but coronary artery CT scan presented significant stenosis in the right coronary artery proximal site (in January 2017). Gene analysis was completed in 2011 and shown in previous study [8].

**Figure 2:** Long term follow-up of cases with Tangier disease.

She received CEE from October 2005 to April 2006 and changed 17βestradiol patch (estrana) 0.72 mg/2days from June 2006 to July 2008. Since then, HRT was completely terminated for 4 years. She restarted 0.36 mg/2days from January 2012 to July 2013, however, she visited intermittently for two years and has received E3 2 mg/day and α-tocopherol 600 mg since March 2015. Total cholesterol, LDL-C and HDL-C level as baseline 100% in October 2005 were changed to 97.5%, 76% and 150% in December 2005.
Discussion

Menopausal women were popularly known to have abnormal lipid and atherosclerosis. In recent times, HRT at onset of menopause is very useful for the prevention of disease progression such as atherosclerosis and osteoporosis [12]. Regarding association with estrogen and lipid, sufficient estrogen (E2) at child bearing stage maintains normal level of total (T)- cholesterol and LDL-C, in contrast to higher levels in menopausal women. Several reasons were considered. The first reason was that, E2 can regulate the function of 3-hydroxy-3 methylglutaryl coenzyme A reductase, consequently maintaining T-cholesterol level [13]. The second reason is that, E2 decreases the function of hepatic lipase and level of LDL-C, resulting from the interfering conversion of LDL-C to LDL-C [14]. The third reason is that, E2 upgrades LDL-receptor on the surface of the hepatic cell and helps the influx of LDL-C to hepatic cell [15]. The fourth, E2 decreases the function of lipo-protein lipase (LPL) to divide triglyceride into free fatty acid and glycerol, and consequently to low level of LDL-C [16].

The fifth, estrogen enhances the synthesis of Apo-A1 as a major part of HDL-C [17], leading to higher HDL-C. Finally, 17βE2 activates CETP, consequently, transporting cholesterol ester in HDL-C to LDL-C, in order to prevent atherosclerosis [18]. In this study, we present two different types of lipidosis. One is TD and the other is CETP deficiency. The HDL-C level ranges from 2 to 200 mg/dL and the LDL-C level ranges from 40 to 140 mg/dL in CETP deficiency. When we saw these patients for the first time, we wondered whether they could remain for a very long time in good health under these conditions of lipid unbalance. Especially, in the second case of Tangier disease, LH ratio was 25.5, indicating the highly progressive condition of atherosclerosis. Almost ten years have passed since we met them, so we decided to assess their health under these conditions of lipid unbalance. Probably, micro-coronary artery will be well circulated in such conditions [20].

ECG showed a slight abnormality in ST wave depression, but there is no difference between that of 2009 and 2016. In addition, more test such as cardiac echogram, cervical neck echogram, CAVI, and ABI are not significantly changed. We think ERT is useful for the prevention of atherosclerosis in this case. As for Tangier disease (TD), she had symptomatic Sjogren’s syndrome without anti-SS-A/Ro, but high titer of ANA with centromere type. In addition, alpha tocopherol N (600 mg/day)/day. Clinically, it was observed that shortness of breath diminished in both patients undertaking ERT. Probably, micro-coronary artery will be well circulated in such conditions [20].

<table>
<thead>
<tr>
<th>Case No</th>
<th>T-Chol 10%&lt; down</th>
<th>LDL-C 10%&lt; down</th>
<th>HDL-C 5%&lt; up</th>
</tr>
</thead>
<tbody>
<tr>
<td>TF alone</td>
<td>57</td>
<td>7.0%</td>
<td>17.5%</td>
</tr>
<tr>
<td>ERT alone</td>
<td>10</td>
<td>30.0%</td>
<td>40.0%</td>
</tr>
<tr>
<td>EPRT cyclic or EPRT cont alon</td>
<td>41</td>
<td>19.5%</td>
<td>26.8%</td>
</tr>
</tbody>
</table>

Acknowledgement

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Biographical note

Kiyomitsu Miyachi. MD. Chief doctor for this whole study
Minoru Ihara. MD. Cardiologist performing atherosclerosis tests.
Toshitsugu Ishikawa.MD. An expert for atherosclerosis and lipidosis
Belinda Sasse. MD. Rheumatologist following these patients for 6 months in Japan in 2015

Toshikon Igarashi. PhD. Technician conducting statistical work
Takao Koyama. MD. Advisor for this work regarding HRT
Keijiro Saku. MD. An expert for atherosclerosis and Tangier disease.
Katsuhiko Mikoshiba. MD. Assisted in the detection of anti-IP3R antibody
Akihiro Inazu. MD. Advisor for the study of CETP deficiency

Reference