S-5-2 Prevention of Aortic Calcification in Patients on Hemodialysis by Long-Term Administration of Vitamin E

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I. INTRODUCTION

It is well known that atherosclerosis is markedly pronounced in patients on hemodialysis [1, 2]. Atherosclerosis is an important risk factor for cardiovascular and cerebrovascular diseases. There is evidence that complications due to cardiovascular and cerebrovascular disorders are ranked high as the cause of death in Japanese hemodialysis patients [3]; therefore, prophylaxis or treatment of atherosclerosis is an important problem. We have reported our experimental studies on vitamin E [4] which has been found to have the possibility to suppress atherosclerosis in hemodialysis patients. In this study, we investigated the long-term clinical effect of vitamin E on atherosclerosis in hemodialysis patients by the evaluation method using aortic calcification index (ACI).

II. SUBJECTS AND METHODS

The subjects were 34 sex- and age-matched patients receiving regular hemodialysis treatment twice or three times a week, divided into two groups each consisting 17 patients; one treated with vitamin E (α-tocopherol, 200 - 600 mg/day) (group A) and other untreated with vitamin E (group B). The period of study was 4 years from 1986 to 1989, during which the patients were basically on dialysis diet and were not given any drugs capable of prophylaxis for atherosclerosis such as anti-hyperlipoproteinemic agent, except anti-hypertensive agent. ACI by CT scan on calcification in 10 slices of abdominal aorta and in 2 slices of iliac artery was quantitated by the method previously described [5]. Laboratory data on cephalo-thoracic ratio (CTR), body weight decrease in one dialysis (BWD), blood pressure (BP), calcium (Ca), phosphorus (iP), parathyroid hormone (PTH) and lipids were used to obtain mean values in each year period from 2 months at maximum, based on which mean values ± SD in each group were calculated. Ca, iP, total cholesterol (TC), triacylglycerols (TG), and high density TC (HDL-C) were determined by enzymatic methods, malondialdehyde (MDA) by Yagi's method [6] and PTH by enzyme-immunoassay (EIA), respectively. Statistical analysis was made with Student's t-test.

III. RESULTS

1. Clinical features of patients

Baseline clinical data of the patients are shown in Table 1. It was ascertained that there were no differences between both groups in age, sex, duration of hemodialysis, primary diseases, presence or absence of complication with diabetes mellitus, and combined use of calcium antagonist, calcium carbonate, alunigel and calcitonin which are closely related to calcium and phosphorus metabolism.
Table 1. Patients' background in this study.

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>PD (yr)</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>HDD (%)</th>
<th>DM (%)</th>
<th>S</th>
<th>Ca (%)</th>
<th>CaCO₃ (%)</th>
<th>AL (%)</th>
<th>Cal (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VE (+)</td>
<td>17</td>
<td>100</td>
<td>52/11</td>
<td>70.6</td>
<td>9.1/4.1</td>
<td>5.8</td>
<td>35.3</td>
<td>17</td>
<td>70.6</td>
<td>6</td>
<td>18</td>
</tr>
<tr>
<td>VE (-)</td>
<td>17</td>
<td>94</td>
<td>49/12</td>
<td>64.7</td>
<td>7.1/2.6</td>
<td>5.8</td>
<td>41.2</td>
<td>12</td>
<td>82.4</td>
<td>18</td>
<td>6</td>
</tr>
</tbody>
</table>

VE (+), group A; VE (-), group B; N, number of cases; PD, primary disease (glomerulonephritis); /, mean ± SD; HDD, duration of hemodialysis; DM, diabetes mellitus; S, history of smoking; OD, other drugs concomitantly used; Ca, Ca-antagonist; AL, alumigel; Cal, calcitonin.

2. Changes of ACI

1) Changes of ACI for 4 years

ACI values at baseline and 4 years later were 15.6 ± 20.4 and 18.1 ± 24.6 in group A, and 21.3 ± 20.6 and 39.1 ± 27.1 in group B. Group B showed a significant increase 4 years later compared to group A (p<0.05).

2) Time-course of changes in ACI

The time-course of changes in ACI was examined in each 9 cases from both groups in which the evaluation by ACI was performed every year during the period from 1986 to 1989. As shown in Fig. 1, a time-dependent increase in ACI was observed in both groups. The increments of ACI in group A vs. group B were 2.2 ± 2.9 vs. 7.1 ± 3.4 in the first year, 1.7 ± 1.0 vs. 4.3 ± 3.0 in the next year and 2.4 ± 1.5 vs. 5.5 ± 3.2 in the last year. The increments of ACI in group A were lower in each year than those in group B.

3. Changes of other parameters

There were no significant changes in all testing items of blood chemistry at baseline and in each year during the period of study except that MDA value in group A showed a significant decrease in 4 years later (group A vs. group B; 2.5 ± 0.3 vs. 2.9 ± 0.5 nmol/ml, p<0.05). CTR, BWD and BP also showed no differences in both groups throughout the study period (data not shown).

![Fig. 1. A time-course of an increase in ACI a year with and without vitamin E treatment. VE(+), group A; VE (-), group B; n, number of cases. ΔI, ΔII and ΔIII represent the increase value of ACI/year from 1986 to 1989. Significance between VE (+) and VE (-): P <0.01, P <0.05 and P <0.02 were observed in *, ** and ***, respectively.](image-url)
Atherosclerosis is caused by numerous factors, and it is well known that hyperlipidemia, especially increased levels of low density lipoproteins (LDL) in plasma, is one of the important causative factors [7] and the degenerated LDL has been presumed to play a major role in causing the diseases [8]. Culture experiments support the view that the LDL would be an oxidized LDL [9]. The oxidized LDL may be produced by free radical reaction with active oxygen species [9]; it has been confirmed that a series of reactions involving LDL are suppressed by an anti-oxidant, butylated hydroxytoluene or vitamin E [9].

Our previous study [4] indicated that oral administration of vitamin E in hemodialysis patients decreased MDA concentrations in LDL, and that the accelerated metabolism of LDL before vitamin E treatment in macrophage was improved, suggesting possible prophylaxis of atherosclerosis in hemodialysis patients by vitamin E treatment. It is suggested that the MDA formation in LDL begins after vitamin E exhaustion [10]. In hemodialysis patients, vitamin E in LDL as well as high density lipoproteins (HDL) is decreased and the supply of vitamin E to erythrocyte seems to be insufficient [11, 12]. These findings suggest that the long-term administration of vitamin E may clinically suppress the progress of atherosclerosis in hemodialysis patients. In this study we employed ACI in the estimation of the progress of atherosclerosis because the increased ACI seemed to reflect the pathological atherosclerosis [13]. The present results demonstrated that ACI values were increased with year, irrespective of vitamin E treatment, while the increments of ACI in group A (treated with vitamin E) were significantly suppressed compared to those in group B (untreated with vitamin E), suggesting that vitamin E may prevent the progress of atherosclerosis in hemodialysis patients.

Hypertension and volume overload are risk factors for atherosclerosis in hemodialysis patients. The results of this study showed that hypertension alone was unable to become a factor exacerbating ACI. In addition, there were no differences between both groups in BWD as well as in CTR representing the degree of cardiomegaly. Furthermore, no appreciable differences were found between both groups in baseline values and time-course of changes in Ca, iP and PTH which are closely related to ectopic calcification in hemodialysis patients. Plasma lipid levels, a risk factor for atherosclerosis, also showed no differences between two groups. However, only MDA level showed a significant decrease in patients treated with vitamin E at the last year of the study period. This result is consistent with the experimental data [4] earlier showing the improvement of LDL metabolism in macrophage. The concentrations of MDA in LDL were not determined in the present study, and it is necessary to confirm it in further investigations. It still remains unclear to what extent atherosclerosis evaluated by ACI as general concept would reflect other atherosclerosis-related diseases such as coronary atherosclerosis or cerebrovascular sclerosis. Our earlier studies [5] revealed close relationship with ischemic heart disease and cerebral infarction. However, the relation between ACI and atherosclerosis-related diseases in hemodialysis patients is not fully clarified. It has been pathologically demonstrated that the increase ACI suggests the progress of atherosclerosis [19]. Therefore, suppression of the increase in ACI is an important theme relating to prevention of cardiovascular complications in hemodialysis patients. Since there are no effective therapies for atherosclerosis in hemodialysis patients, the long-term administration of vitamin E seems to warrant further trials as a useful therapy for prevention of the progress of atherosclerosis.

SUMMARY
The effects of vitamin E on the progress of atherosclerosis in
patients on hemodialysis was investigated clinically using ACI. There was a significant suppression of the increase in ACI in group A, compared to group B, at the time of observation in each year. On the other hand, no significant changes were noted in BWD, CTR, BP and blood chemical examination, except that the level of MDA was significantly decreased in group A as compared with that in group B 4 years later. Since ACI is an index representing atherosclerosis, the results of this study seemed to suggest that the progress of atherosclerosis was suppressed by long-term administration of vitamin E in patients on hemodialysis.

REFERENCES