Different Risk Factors for the Maximum and the Mean Carotid Intima-media Thickness in Hemodialysis Patients

Ayumu NAKASHIMA, Noriaki YORIOKA*, Yukiteru ASAKIMORI*, Takafumi ITO*, Takao MASAKI*, Kenichiro SHIGEMOTO and Satoru HARADA

Abstract

Objective High-resolution B-mode ultrasonography has been widely used for the noninvasive assessment of atherosclerosis in hemodialysis patients. But, there are two major methods of carotid ultrasonography: one including plaque and the other excluding plaque.

Methods The subjects were 112 hemodialysis patients (58 men and 54 women) with a mean age of 55.8±13.0 years. The maximum intima-media thickness (IMT) of the carotid artery (including plaque) was measured as an index of arterial wall thickening and atheroma formation, while the mean IMT (without plaque) was measured as an index of arterial wall thickening. In addition the value of (maximum-mean) IMT was calculated as an index of atheroma formation. Therefore, the independent risk factors associated with the maximum IMT, mean IMT, and (maximum-mean) IMT were investigated by stepwise multiple regression analysis.

Results The independent risk factors associated with the maximum IMT were age, diabetes mellitus, smoking, and intact parathyroid hormone (PTH) (R=0.569, p<0.0001), while factors associated with the mean IMT were age, hypertension, dyslipidemia, intact PTH, and lipoprotein (a) (R=0.602, p<0.0001). The independent risk factors associated with the (maximum-mean) IMT were age, diabetes mellitus, smoking, and intact PTH (R=0.515, p<0.0001).

Conclusion These findings suggest that risk factors for the maximum IMT and mean IMT are somewhat different in hemodialysis patients.

Key words: intima-media thickness, hemodialysis, atherosclerosis, secondary hyperparathyroidism

Introduction

Since cardiovascular complications are a common cause of death in hemodialysis patients (1–3), the early detection of vascular disease would be desirable. High-resolution B-mode ultrasonography has been widely used to make a noninvasive assessment of atherosclerosis affecting the carotid artery in epidemiologic and clinical studies performed on hemodialysis patients (1–3), and it is thought that carotid artery changes mirror the progression of systemic atherosclerosis in dialysis patients as well as in the general population (1–6).

But, there are two major methods of carotid ultrasonography: one measured including plaque and the other excluding plaque (1–6). We considered that the maximum intima-media thickness of the carotid artery including plaque (maximum IMT) could be used as an index of arterial wall thickening and atheroma formation, while the mean intima-media thickness of the carotid artery excluding plaque (mean IMT) could be an index of arterial wall thickening. It is thought that there are different mechanisms between atheroma formation and arterial wall thickening. Accordingly, we investigated each risk factor of the maximum IMT and the mean IMT.

For editorial comment, see p 1061.
Methods

Subjects
We enrolled 112 patients who were on hemodialysis at Harada Hospital (Hiroshima, Japan). All of the patients were clinically stable and had no acute infection. We excluded patients who had undergone parathyroidectomy. There were 58 men and 54 women aged from 23 to 83 years, with a mean age of 55.8±13.0 years. The duration of hemodialysis ranged from 2 to 344 months, with a mean of 80.5±75.1 months. The underlying renal disease was chronic glomerulonephritis in 72 patients, nephrosclerosis in 5 patients, and diabetes mellitus in 35 patients. All patients gave informed consent to participate in this study.

Carotid ultrasonography
Ultrasonography of the carotid artery was performed using a high resolution real-time scanner with a 7.5 MHz transducer (SSA-350, Toshiba, Tokyo, Japan). All subjects were examined by a single trained physician, who was blinded with regard to their clinical characteristics. Examination was performed in the supine position, and the carotid bifurcation as well as the common carotid artery were scanned on both sides.

The maximum IMT value was measured as follows. The carotid artery was scanned in the longitudinal and transverse projections. As defined by Wendelhag et al (6), the site of the most advanced atherosclerotic lesion that showed the greatest distance between the lumen-intima interface and the media-adventitia interface was located in both right and left carotid arteries. When plaque was detected by ultrasonography, it was observed as localized thickening rather than a circumferential change of the vessel wall. The greatest thickness of intima-media complex (including plaque) was used for the maximum IMT value (1, 3).

In addition, measurement of the mean IMT was performed at 0.5, 1, and 2 cm below the carotid bifurcation on each side, and the average value was calculated as the mean IMT (4). These measurements were performed in plaque-free arterial segments. To determine the intraobserver variability of IMT measurement, a total of 30 subjects were examined on two different occasions at an interval of 7 to 14 days. The coefficient of variation was only 2.0% for the maximum IMT value and 2.2% for the mean IMT value.

Blood pressure
After enrollment in the study, 4 predialysis blood pressure readings were obtained from each patient. The mean arterial pressure was calculated as the diastolic blood pressure plus one-third of the difference between the systolic and diastolic blood pressures, and the average of the 4 mean values was determined.

Subjects were classified as hypertensive when their average blood pressure was ≥114 mmHg or when they were receiving antihypertensive drugs (7).

Smoking status
Information on smoking habits was obtained using a self-administered questionnaire. Cigarette smokers were defined as subjects who were current smokers or who had ceased smoking within 3 months before enrollment in this study (8).

Biochemical parameters
Venous blood samples were collected after an overnight fast for measurement of the serum concentrations of intact PTH, calcium, phosphate, total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, and lipoprotein (a). Intact PTH was measured using the Nichols IRMA kit (Nichols Institute, San Juan Capistrano, CA). The adjusted calcium level was calculated using Payne’s formula (adjusted calcium=serum calcium+4-albumin) (9).

According to the criteria of the Japan Atherosclerosis Society, subjects were classified as having dyslipidemia when they were taking lipid-lowering agents and/or when the total cholesterol level was ≥5.72 mmol/l (220 mg/dl), high-density lipoprotein cholesterol was <1.04 mmol/l (40 mg/dl), or triglycerides were 1.70 mmol/l (150 mg/dl).

Statistical analysis
Results are shown as the mean±SD and statistical analysis was performed by the Mann-Whitney U test. We used Pearson’s correlation coefficient analysis to examine the relationship between the maximum IMT and the mean IMT. Multiple regression analysis with a forward elimination procedure was used to assess the combined influence of variables on the maximum IMT, the mean IMT, and the (maximum-mean) IMT. The variables investigated were gender, age, duration of hemodialysis, body mass index, diabetes mellitus, smoking, hypertension, dyslipidemia, and the levels of PTH, adjusted calcium, serum phosphate, and lipoprotein (a). Analysis was performed with StatView 5 software (Abacus Concepts, Inc., CA), and p<0.05 was considered to indicate a significant difference.

Results
Table 1 summarizes the clinical and biochemical parameters of the subjects. A significant difference was observed between men and women with respect to the total cholesterol level (p=0.0183), the HDL cholesterol level (p=0.0375), the lipoprotein (a) level (p=0.0255), and their smoking status (p=0.0003).

The mean IMT showed a positive correlation with the maximum IMT according to Pearson’s correlation coefficient analysis (R=0.553, p=0.0001, Fig. 1). However, the difference between maximum and mean IMT values showed an increase as the mean IMT became larger. Among the 112 hemodialysis patients, 28 patients (25.0%) had carotid plaque.

The results obtained by stepwise multiple regression analysis of predictors of the maximum IMT are summarized in Table 2. The factors associated with the maximum IMT...
Table 1. Clinical Characteristics of the Subjects

<table>
<thead>
<tr>
<th></th>
<th>Normal values</th>
<th>Total (n=112)</th>
<th>Male (n=58)</th>
<th>Female (n=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td>55.8±13.0</td>
<td>54.6±12.5</td>
<td>57.1±13.5</td>
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<tr>
<td>Duration of hemodialysis (months)</td>
<td>80.5±75.1</td>
<td>76.3±72.1</td>
<td>85.0±78.7</td>
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<tr>
<td>Body mass index (kg/m²)</td>
<td>21.1±3.0</td>
<td>21.2±2.1</td>
<td>20.9±3.7</td>
<td></td>
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<tr>
<td>Maximum IMT (mm)</td>
<td>1.121±0.616</td>
<td>1.165±0.678</td>
<td>1.073±0.545</td>
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</tr>
<tr>
<td>Mean IMT (mm)</td>
<td>0.746±0.142</td>
<td>0.750±0.133</td>
<td>0.742±0.152</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>160.5±21.2</td>
<td>163.8±22.0</td>
<td>157.0±20.0</td>
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</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>84.3±13.7</td>
<td>86.7±12.0</td>
<td>81.6±15.0</td>
<td></td>
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<tr>
<td>Average blood pressure (mmHg)</td>
<td>109.7±14.9</td>
<td>112.4±14.0</td>
<td>106.8±15.4</td>
<td></td>
</tr>
<tr>
<td>Intact PTH (pg/ml)</td>
<td>209.8±236.7</td>
<td>192.2±186.2</td>
<td>228.7±281.7</td>
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<tr>
<td>Adjusted calcium (mg/dl)</td>
<td>9.49±0.98</td>
<td>9.44±1.06</td>
<td>9.55±0.90</td>
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</tr>
<tr>
<td>Serum phosphate (mg/dl)</td>
<td>5.53±1.26</td>
<td>5.66±1.31</td>
<td>5.40±1.20</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>178.2±42.3</td>
<td>168.6±39.0</td>
<td>188.4±43.5*</td>
<td></td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>126.5±78.9</td>
<td>130.0±85.0</td>
<td>122.8±72.4</td>
<td></td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dl)</td>
<td>49.3±13.8</td>
<td>47.2±14.5</td>
<td>51.6±12.8*</td>
<td></td>
</tr>
<tr>
<td>Lipoprotein (a) (mg/dl)</td>
<td>20.5±14.5</td>
<td>18.1±15.0</td>
<td>23.0±13.8*</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>n=35 (31.3%)</td>
<td>n=19 (32.8%)</td>
<td>n=16 (29.6%)</td>
<td></td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>n=35 (31.3%)</td>
<td>n=27 (46.6%)</td>
<td>n=8 (14.8%)**</td>
<td></td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.01 (vs. Males).

Figure 1. Correlation between the maximum IMT and the mean IMT (n=112, R=0.553, p<0.0001, Y=-0.7+2.4X). IMT: intima-media thickness.

were age, diabetes mellitus, cigarette smoking, and the intact PTH level (R=0.569, p<0.0001). The results obtained by stepwise multiple regression analysis of predictors of the mean IMT are summarized in Table 3. The factors associated with the mean IMT were age, hypertension, dyslipidemia, the intact PTH level, and the lipoprotein (a) level (R=0.602, p<0.0001).

Table 4 summarizes the outcome of stepwise multiple regression analysis of predictors of the (maximum-mean) IMT. The factors associated with (maximum-mean) IMT were age, diabetes, cigarette smoking, and intact PTH (R=0.515, p<0.0001), which were the same factors as those associated with the maximum IMT.

**Discussion**

In the present study, the risk factors associated with the maximum IMT value were age, diabetes mellitus, smoking status, and the intact PTH level. In addition, the risk factors associated with the mean IMT value were age, hypertension, dyslipidemia, intact PTH, and lipoprotein (a). The risk factors associated with (maximum-mean) IMT were the same as those for the maximum IMT.

The maximum IMT was previously reported to show a positive correlation with age, smoking, serum phosphorus, and serum PTH (1). Although no correlation with serum...
characterized by hypertriglyceridemia, based on an increase in very low density lipoprotein cholesterol and intermediate density lipoprotein cholesterol, along with a decrease of HDL cholesterol (11, 12). Among these parameters, intermediate density lipoprotein cholesterol is the lipoprotein fraction most closely associated with vascular abnormalities in hemodialysis patients (13). Dyslipidemia was previously reported to show a positive correlation with the mean carotid IMT (14) and with the aortic pulse wave velocity (15). In our study, there was no correlation between the maximum IMT value and dyslipidemia, while a positive correlation was found between the mean IMT and dyslipidemia. Accordingly, dyslipidemia might be more closely related to arterial thickening than to atheroma formation in hemodialysis patients.

Lipoprotein (a) has been reported to be elevated in hemodialysis patients (16), and recent evidence has suggested that lipoprotein (a) may aggravate atherosclerosis by inhibiting the activation of transforming growth factor-beta (17). It was also previously reported that a significant positive correlation exists between the lipoprotein (a) level and the mean IMT or plaque score in hemodialysis patients (18). In the present study, there was no correlation between the maximum IMT and the lipoprotein (a) level, but there was a positive correlation between the mean IMT value and lipoprotein (a). This suggests that lipoprotein (a) might also be more involved with arterial thickening than with the formation of atheroma in dialysis patients.

A relationship between vascular disease and cigarette smoking has been shown in the general population (19), as well as in hemodialysis patients (1). In the present study, there was no correlation between the mean IMT and smoking, while a positive correlation was found between the maximum IMT and smoking. This suggests that cigarette smoking might contribute to atheroma formation in hemodialysis patients.

It has already been shown that diabetes mellitus is a major independent risk factor for atherosclerosis (4, 20). There was no correlation between the mean IMT and diabetes in the present study, but there was a positive correlation between diabetes and the maximum IMT. Accordingly, the presence of diabetes might contribute to atheroma formation in hemodialysis patients.

The present study showed that the intact PTH level was associated with both the maximum and the mean IMT values. It has already been reported that hyperparathyroidism is a major independent risk factor for atherosclerosis in hemodialysis patients (1, 15). Uremic patients have markedly reduced levels of hepatic triglyceride lipase, the key enzyme that catabolizes intermediate density lipoprotein to form low-density lipoprotein (21). This abnormality of lipoprotein metabolism may contribute to the acceleration of atherosclerosis. Shoji et al (22) reported that serum level of this enzyme was independently associated with hyperparathyroidism in hemodialysis patients. In addition, the phosphate level is increased by hyperparathyroidism and hyperphosphatemia directly accelerates aortic smooth muscle cell calcification.

Table 3. Risk Factors Affecting Mean IMT in Hemodialysis Patients

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>β</th>
<th>F value</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.382</td>
<td>21.475</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.233</td>
<td>8.555</td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>0.165</td>
<td>4.427</td>
<td></td>
</tr>
<tr>
<td>Intact PTH</td>
<td>0.237</td>
<td>9.115</td>
<td></td>
</tr>
<tr>
<td>Lipoprotein (a)</td>
<td>0.185</td>
<td>5.158</td>
<td></td>
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</tbody>
</table>

0.602 (p<0.0001)

Significant predictors of the mean IMT were identified among the following parameters: gender (male=1, female=0), age, duration of hemodialysis, body mass index, diabetes (absent=0, present=1), smoking (absent=0, present=1), hypertension (absent=0, present=1), dyslipidemia (absent=0, present=1), intact PTH, adjusted calcium, serum phosphate, and lipoprotein (a). The F value to enter was set at 4.0 in each step. β: standard regression coefficient. R: multiple coefficient of determination.

Table 4. Risk Factors Affecting (Maximum-Mean) IMT in Hemodialysis Patients

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>β</th>
<th>F value</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.243</td>
<td>8.17</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.309</td>
<td>12.931</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>0.181</td>
<td>4.635</td>
<td></td>
</tr>
<tr>
<td>Intact PTH</td>
<td>0.235</td>
<td>7.86</td>
<td></td>
</tr>
</tbody>
</table>

0.515 (p<0.0001)

These significant predictors of the (maximum-mean) IMT were identified among the following parameters: gender (male=1, female=0), age, duration of hemodialysis, body mass index, diabetes (absent=0, present=1), smoking (absent=0, present=1), hypertension (absent=0, present=1), dyslipidemia (absent=0, present=1), intact PTH, adjusted calcium, serum phosphate, and lipoprotein (a). The F value to enter was set at 4.0 in each step. β: standard regression coefficient. R: multiple coefficient of determination.
(23). These conditions suggest that hyperparathyroidism would promote both atherosclerosis and arterial calcification. However, hyperphosphatemia showed no association with IMT in the present study; the serum phosphorus level is unstable in hemodialysis patients because of the effects of food intake and treatment with calcium-containing binders, so these factors may make it difficult to evaluate the influence of phosphorus on carotid vascular disease. In young hemodialysis patients, however, a strong association between coronary artery calcification and a high calcium-phosphate product was detected by a study using electron-beam computed tomography (24), suggesting that treatment of secondary hyperparathyroidism as well as hyperphosphatemia is necessary to prevent atherosclerosis and Mönckeberg’s medial calcific sclerosis.

The present study found no significant correlation between the IMT and the duration of hemodialysis. In this context, some previous studies have suggested that carotid atherosclerosis might be accelerated by the uremic state per se rather than by hemodialysis (1).

In conclusion, our findings suggest that age and hyperparathyroidism are common risk factors for the development of atheroma and arterial wall thickening in hemodialysis patients. However, the other risk factors for atheroma and arterial wall thickening seem to differ, with hypertension, dyslipidemia, and lipoprotein (a) being risk factors for arterial wall thickening, while diabetes and smoking are risk factors for atheroma.

References