INTRODUCTION

Several epidemiological studies have shown that higher serum calcium concentration is associated with increased risk of cardiovascular and cerebrovascular diseases\(^1,2\). Serum calcium is an independent, prospective risk factor for myocardial infarction in middle-aged men\(^3\). The risk of premature death in men less than 50 years of age increases with rising serum calcium concentration, even...
within the normal range, and this increase seems to be largely due to the increased mortality from cardiovascular diseases\textsuperscript{1}. As serum calcium is associated with several conventional risk factors for atherosclerosis, such as blood pressure, total cholesterol, and triglycerides\textsuperscript{2}, increases in serum calcium concentration may be related to a metabolic syndrome that promotes atherogenesis, and may subsequently increase cardiovascular morbidity and mortality.

The correlation between serum calcium concentration and carotid atherosclerosis has been assessed in patients with hyperparathyroidism and dialysis patients\textsuperscript{6-8}: However, little information is available about the relationship between carotid plaque and serum levels of calcium corrected for albumin, or ionized calcium. The present study investigated whether there is any association between serum levels of albumin-corrected calcium and carotid plaque by analyzing data from subjects who had undergone general health-screening tests at our institute.

**METHODS**

**Study subjects**

Between August 1994 and December 2000, 5,732 subjects underwent general health screening tests including high resolution B-mode carotid ultrasound and serum calcium test at the Center for Multiphasic Health Testing and Services, Mitsui Memorial Hospital. Clinical information was obtained by physical examination and chart review of each patient's history, including sex, age, and smoking habits.

**Carotid ultrasound**

The ultrasound protocol involved the scanning of the internal\textsuperscript{6} and common carotid arteries bilaterally using high resolution B-mode carotid ultrasonography and serum calcium test at the Sonolayer SSA270A, Toshiba equipped with a 7.5-MHz transducer (PLF-703ST, Toshiba). The intima-media thickness was measured with computer-assisted methods by experienced sonographers who were unaware of the subjects’ clinical and laboratory characteristics. Plaque was defined as a clearly identified focal thickening of the intima-media layer with a thickness of ≥ 1.3 mm at the common or internal carotid arteries or the carotid bulb\textsuperscript{6,7}.

**Clinical characteristics and laboratory tests**

Body mass index was calculated as weight\(\text{kg}\)/height\(\text{m}\). Blood samples of the subjects were obtained after an overnight fast. Total cholesterol (TC\textsuperscript{9}), high-density lipoprotein cholesterol (HDL-C\textsuperscript{9}), and triglyceride levels were determined enzymatically, and hemoglobin A\textsubscript{1C} was determined by latex agglutination immunoassay. The serum calcium concentrations used for the statistical assessment in the present study were all adjusted for the serum albumin concentration. Based on the same study population, the following formula was empirically obtained using a linear regression model with ordinary least square estimation by the remodeling of the correction formula of Payne et al.\textsuperscript{10}:

\[
\text{Calcium (adjusted)} = \text{Calcium (analyzed)} - \left(\text{albumin} \times 0.5387\right) + 2.2684 - 1.9190
\]

where 0.5387 was the determination coefficient of the regression. 2.2684 was the mean analyzed calcium concentration in the population, and 1.9190 was the y intercept. Pearson correlation coefficients for the relationships between serum calcium and serum albumin before and after the correction were 0.418 and 0.00, respectively.

**Statistical analysis**

Statistical analysis was performed using computer software, Statistica ver. 5J (StatSoft Inc.). Sex and smoking status were included as categorical variables. Other variables were included as continuous variables.

**RESULTS**

**Baseline characteristics of the study population**

Baseline clinical characteristics and laboratory data for the study population are illustrated in Table 1. In 5,732 subjects enrolled in the present study, 3,786 (66%) were male subjects, 1,947 were female subjects, and the age range was 22-88 years (median 57 years). Serum calcium concentrations were 1.95-2.72 mmol/L (7.81-10.90 mg/dL) with a median of 2.26 mmol/L (9.06 mg/dL). Serum calcium concentration was slightly greater in the subjects with carotid plaque (mean ± SE: 2.28 ± 0.08 mmol/L) than those without (2.27 ± 0.07 mmol/L), and the difference was statistically significant by unpaired t-test\(p < 0.001\).

**Relationship between serum calcium and risk factors for atherosclerosis**

At first, we investigated whether there was a sig-
significant association between serum calcium concentration and other variables. Pearson correlation coefficients for the relationships between serum calcium and the variables were as follows: age, 0.045; body mass index, 0.01; systolic blood pressure, 0.072; diastolic blood pressure, 0.058; serum phosphorus, 0.149; TC, 0.18; triglycerides, 0.033; HDL-C, 0.109; hemoglobin A1C, 0.082; serum glucose, 0.007. p values for all these correlations were < 0.001 except body mass index (NS) serum glucose (NS) and triglycerides (p < 0.05; Fig. 1) Although there was a significant association between serum calcium and several conventional risk factors, correlation coefficients were less than 0.2 and therefore the relationship did not seem to be strong (Fig. 1) Serum calcium level in the non-smokers was 2.27 ± 0.07 mmol/l, which was not significantly different from that in the current smokers (2.27 ± 0.07 mmol/l) but was significantly greater than that in the ex-smokers (2.26 ± 0.07 mmol/l, p < 0.001).

**Serum calcium and carotid plaque**

We examined whether higher serum calcium concentration is an independent risk for carotid plaque. Multivariate logistic regression analysis including other confounding risk factors for atherosclerosis demonstrated that serum calcium concentration is an independent risk factor for carotid plaque with an odds ratio of 8.32 (95% confidence interval CI 6.96 - 13.56 per 1 mmol/l increase, or 1.70 (95% CI 1.50 - 1.92) per 1 mg/dl increase (Table 2) Serum phosphorus was also positively associated with carotid plaque after the adjustment of risk factors for atherosclerosis and serum calcium concentration. The odds ratio of serum phosphorus for carotid plaque was 1.59 (95% CI 1.21 - 2.09 per 1 mmol/l increase) in Table 2) or 1.16 (95% CI 1.06 - 1.27) per 1 mg/dl increase.

Odds ratios were then calculated against the lowes

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**Table 1 Clinical characteristics and laboratory data of the study population**

<table>
<thead>
<tr>
<th>Variable</th>
<th>All subjects (n = 5,732)</th>
<th>No plaque (n = 4,419)</th>
<th>Plaque (n = 1,313)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>67.4 ± 10</td>
<td>67.4 ± 10</td>
<td>67.3 ± 10</td>
</tr>
<tr>
<td>Male (%)</td>
<td>66.0 ± 7</td>
<td>63.0 ± 8</td>
<td>69.0 ± 8</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.63 ± 0.09</td>
<td>1.63 ± 0.09</td>
<td>1.63 ± 0.08</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>61.9 ± 11.5</td>
<td>61.9 ± 11.5</td>
<td>62.1 ± 11.5</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>23.1 ± 3</td>
<td>23.1 ± 3</td>
<td>24.3 ± 3</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Systolic</td>
<td>126.2 ± 20.6</td>
<td>126.2 ± 19.9</td>
<td>135.2 ± 21.8</td>
</tr>
<tr>
<td>Diastolic</td>
<td>78.9 ± 12.5</td>
<td>78.2 ± 12.3</td>
<td>81.2 ± 13.0</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>31.0 ± 1</td>
<td>30.0 ± 1</td>
<td>33.0 ± 1</td>
</tr>
<tr>
<td>Ex smoker (%)</td>
<td>18.0 ± 1</td>
<td>17.0 ± 1</td>
<td>19.0 ± 1</td>
</tr>
<tr>
<td>Carotid plaque (%)</td>
<td>23.0 ± 2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Corrected calcium (mmol/l)</td>
<td>2.20 ± 0.07</td>
<td>2.20 ± 0.07</td>
<td>2.28 ± 0.08</td>
</tr>
<tr>
<td>Phosphorus (mmol/l)</td>
<td>1.08 ± 0.15</td>
<td>1.06 ± 0.15</td>
<td>1.04 ± 0.15</td>
</tr>
<tr>
<td>TC (mmol/l)</td>
<td>5.36 ± 0.87</td>
<td>5.36 ± 0.86</td>
<td>5.44 ± 0.90</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.44 ± 1.09</td>
<td>1.44 ± 1.09</td>
<td>1.52 ± 1.10</td>
</tr>
<tr>
<td>HDL-C (mmol/l)</td>
<td>1.52 ± 0.45</td>
<td>1.54 ± 0.45</td>
<td>1.46 ± 0.42</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>5.28 ± 1.10</td>
<td>5.28 ± 1.10</td>
<td>5.46 ± 1.18</td>
</tr>
<tr>
<td>Hemoglobin A1C (%)</td>
<td>5.40 ± 0.74</td>
<td>5.26 ± 0.69</td>
<td>5.46 ± 0.78</td>
</tr>
</tbody>
</table>

Continuous values are mean ± SD. p < 0.05; p < 0.001 vs no plaque group.

TC = total cholesterol; HDL-C = high density lipoprotein cholesterol.
of 1.5 (95% CI 1.37 - 1.67, p < 0.01) and 1.19 (95% CI 1.08 - 1.32, p < 0.05), respectively. The male and female subjects in the highest quartiles of serum calcium levels were at a significantly greater risk for carotid plaque with odds ratios of 1.52 (95% CI 1.35 - 1.71, p < 0.01), 1.57 (95% CI 1.27 - 1.92, p < 0.05), respectively (Fig. 2).

**DISCUSSION**

The present study showed that serum calcium was a predictor of carotid plaque, which was independent of other confounding risk factors. Male and female subjects in the highest quartile of serum calcium had a greater risk of carotid plaque, with odds ratios of 1.52 and 1.57, respectively, than those in the lowest quartiles of serum calcium.

An association between serum calcium and some of the cardiovascular risk factors has been demonstrated in several previous studies. Although serum calcium had not been corrected for serum albumin concentration, an association was found between serum calcium and blood pressure, TCHDL-C, and in men only, triglycerides. This finding is consistent with the idea that serum calcium...
um is related to a metabolic syndrome that may be involved in atherogenesis. It is possible that changes in membrane Ca\(^{2+}\) binding and transport\(^9,10\) that are observed in patients with hypertension may be involved in abnormal calcium handling in some metabolic disorders. Indeed, the present study also found significant and positive correlations between serum calcium and several conventional risk factors for atherosclerosis, including age, blood pressure, TC, triglycerides, HDL-C, and hemoglobin A1C. However, correlation coefficients between serum calcium and these risk factors were rather small (\(r < 0.2\)) in our study population.

Multivariate logistic regression analysis indicated that serum calcium is independently associated with carotid plaque. The reason for this association was not evident in the present study, though there are some possible mechanisms. Parathyroid hormone may be important in cardiovascular complications\(^11\), and progression of atherosclerosis is reduced in parathyroidectomized patients\(^12\). In addition, animal studies have suggested that parathyroid hormone is involved in the hypertrophy of the vascular wall\(^13\). Therefore, parathyroid hormone, which will modify the calcium homeostasis, may have a role in the development of vascular lesions. This possibility should be investigated by measuring parathyroid hormone levels in future studies.

Multivariate analysis of our data suggested a possible link between serum phosphorus and carotid plaque. Only a little information about the association between serum phosphorus and the atherosclerotic diseases is available. A retrospective study analyzing patients who had undergone routine coronary angiography showed that serum phosphorus concentration was associated with the angiographic severity of coronary artery disease and was independent of other coronary risk factors\(^14\). Serum phosphorus levels are associated with the intima-media thickness of the carotid artery in patients with uremia after adjustment for confounding risk factors\(^15\). As serum phosphorus level is regulated by mechanisms that may also affect serum calcium level, we have to be careful in interpreting the data.

The present study showed a significant relationship between serum calcium and carotid plaque. However, it should be kept in mind that only ionized calcium is physiologically active and under homeostatic control. Reported correction formulae may not agree well with the ionized calcium level in some cases\(^16\). However, measurement of ionized calcium is relatively difficult and is not available in standard laboratories, such as ours. To demonstrate an independent correlation between serum calcium and carotid plaque more definitively, ionized calcium should be measured in future studies.

**CONCLUSIONS**

Serum calcium, which has been adjusted for serum albumin level, is associated with formation of carotid plaque, which is independent of confounding risk factors for atherosclerosis. The pathophysiologic mechanisms involved in this relationship should be assessed in future studies.
血清カルシウム値と頸動脈プラクの関連: 健診データに基づいた検討

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目的: 血清Ca値は高いほど、心血管系の罹病率や、死亡率を上昇させると考えられている。これは、血清Ca値が、血圧や血清コレステロール値など、動脈硬化の危険因子と正相関を有することに関係している可能性がある。今回我々は、検診受診者のデータを分析し、アルプミン値で補正した血清Ca値が、動脈硬化の危険因子となっているか否かについて検討した。

方法: 症例は1994年-2000年に三井記念病院総合健診センターに健康診断のために訪れた症例のうち、血中のCa、アルプミン値を含む採血を受け、かつ検診結果を基にデータを対象とした。統計学的検討は、すべてアルプミンで補正したCa値を用いた。

結果: エントリーされた5,732症例のうち、3,785例が男性、1,947例が女性で、年齢範囲は22-88歳、中央値77歳であった。血清Ca値は7.8-10.9 mg/dl、中央値が9.1 mg/dl（2.26 mmol/l）であった。動脈硬化プラクは1,313例（23%）に認められ、Ca値はプラクラ群で非プラクラ群それぞれ2.28、2.27 mmol/lと、若干プラクラ群で高かった（p<0.001、検定）。他、多变量のロジスティック回帰分析では、血清Ca値は独立した、有意なプラクラの危険因子であることがわかった（1 mg/dlの上昇につきオッズ比は1.70、95%信頼間1.50-1.92）。また、症例を血清Ca値により、4群に分けて同様の多変量解析を行った場合、最もCa値の低い第1の4分位数と比較して、最も高い第4の4分位数でのオッズ比は、男性で1.32（95%信頼間1.15-1.51、p<0.01）、女性で1.37（95%信頼間1.27-1.92、p<0.05）と、有意にプラクラのリスクが高かった。

結論: 健診受診症例における検討で、血清Ca値は動脈硬化プラクラの独立した危険因子であることが示唆された。

References
1) Leifsson BG, Ahren B: Serum calcium and survival in a large health screening program. J Clin Endocrinol Metab 1996; 81: 2149-2153
of vitamin D analog administration in dialysis patients with end-stage renal disease. Nephron 2000; 84: 13 - 20