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Serum Calcium Concentration and Carotid Artery Plaque: A Population-Based Study

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Abstract

Objectives. Serum calcium level may be associated with the morbidity and mortality of cerebrovascular and cardiovascular diseases. However, only a few large-scale population studies have been performed to investigate the association between serum calcium and carotid plaque.

Methods. A retrospective cross-sectional study was performed on the subjects who underwent general health screening tests including ultrasonographic evaluation of the carotid artery between 1994 and 2000 at our institute. Before the statistical analysis, all serum calcium values were adjusted for the serum albumin concentration.

Results. Of 5,732 subjects enrolled in the present study, 3,785 were male and 1,947 were female, and were aged 22−88 years(median 57 years). Carotid plaque was identified in 1,313(23%)subjects. Serum calcium concentration was slightly greater in the subjects with plaque than in those without(2.28 ± 0.8 vs 2.27 ± 0.7 mmol/*l*, $p < 0.001$; unpaired *t*-test). Multivariate logistic regression analysis including confounding risk factors revealed that serum calcium is an independent positive predictor for carotid plaque with an odds ratio of 1.70[95% confidence interval(CI): 1.50−1.92]for each increase of 1 mg/d*l*. Male and female subjects in the highest quartiles of serum calcium concentrations had a greater risk of carotid plaque with odds ratios of 1.52(95% CI 1.35−1.71, $p < 0.01$)and 1.57(95% CI 1.27−1.92, $p < 0.05$), respectively, compared to the subjects in the lowest quartiles of calcium concentrations.

Conclusions. These findings indicate that serum calcium is an independent risk factor for carotid plaque.

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Key Words

■Carotid arteries ■Atherosclerosis ■Plaque ■Calcium ■Risk factors

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

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RMS = registered medical sonographer

within the normal range, and this increase seems to be largely due to the increased mortality from cardiovascular diseases[1]. As serum calcium is associated with several conventional risk factors for atherosclerosis, such as blood pressure, total cholesterol, and triglycerides[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[4,5]. 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 ultrasonography 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 (bulbous and distal segments) and common carotid arteries bilaterally using high-resolution B-mode carotid ultrasound (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[6].

Clinical characteristics and laboratory tests

Body mass index was calculated as [weight (kg)]/[height (m)]^2. Blood samples of the subjects were obtained after an overnight fast. Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglyceride levels were determined enzymatically, and hemoglobin A_{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.*[7]: Calcium (adjusted) = [calcium (analyzed) − (albumin × 0.5387) + 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's 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, 3,785 (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/d*l*) with a median of 2.26 mmol/*l* (9.06 mg/d*l*). 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-

Table 1 Clinical characteristics and laboratory data of the study population

Variable	All subjects (n=5,732)	No plaque (n=4,419)	Plaque (n=1,313)
Age (yr)	57±10	55±10	64±9†
Male (%)	66	63	77
Height (m)	1.63±0.09	1.63±0.09	1.63±0.08
Weight (kg)	62.1±11.2	61.9±11.5	63.1±10.3†
Body mass index (kg/m^2)	23±3	23±3	24±3†
Blood pressure (mmHg)			
Systolic	128.2±20.6	126.2±19.9	135±21.6†
Diastolic	78.9±12.5	78.2±12.3	81.2±13.0†
Smoking status			
Current smoker (%)	31	30	33
Ex-smoker (%)	18	17	22
Carotid plaque (%)	23	—	—
Corrected calcium (mmol/*l*)	2.27±0.07	2.27±0.07	2.28±0.08†
Phosphorus (mmol/*l*)	1.06±0.15	1.06±0.15	1.04±0.15†
TC (mmol/*l*)	5.38±0.87	5.36±0.86	5.44±0.90
Triglycerides (mmol/*l*)	1.46±1.09	1.44±1.09	1.52±1.10*
HDL-C (mmol/*l*)	1.52±0.45	1.54±0.45	1.46±0.42†
Glucose (mmol/*l*)	5.32±1.10	5.28±1.08	5.46±1.18†
Hemoglobin A_{1C} (%)	5.30±0.71	5.26±0.69	5.46±0.78†

Continuous values are mean±SD. *$p<0.05$, †$p<0.001$ vs no plaque group.
TC=total cholesterol; HDL-C=high-density lipoprotein cholesterol.

nificant association between serum calcium concentration and other variables. Pearson's 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 A_{1C}, 0.082; serum glucose, 0.007. p values for all these correlations were <0.001 except body mass index (NS), serum glucose (NS) and triglyceride ($p<0.05$; **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 nonsmokers 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) 5.06−13.56] per 1 mmol/*l* increase, or 1.70 (95% CI 1.50−1.92) per 1 mg/d*l* 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 (**Table 2**), or 1.16 (95% CI 1.06−1.27) per 1 mg/d*l* increase.

Odds ratios were then calculated against the lowest (*i.e.*, the first) quartile after adjustment for confounding risk factors and serum phosphorus concentration. Mean calcium concentrations in the first, second, third, and fourth quartiles are 2.18, 2.24, 2.29, and 2.36 mmol/*l*, respectively. Subjects in the highest and the second highest quartiles of serum calcium concentrations had a significantly greater risk for carotid plaque with the odds ratios

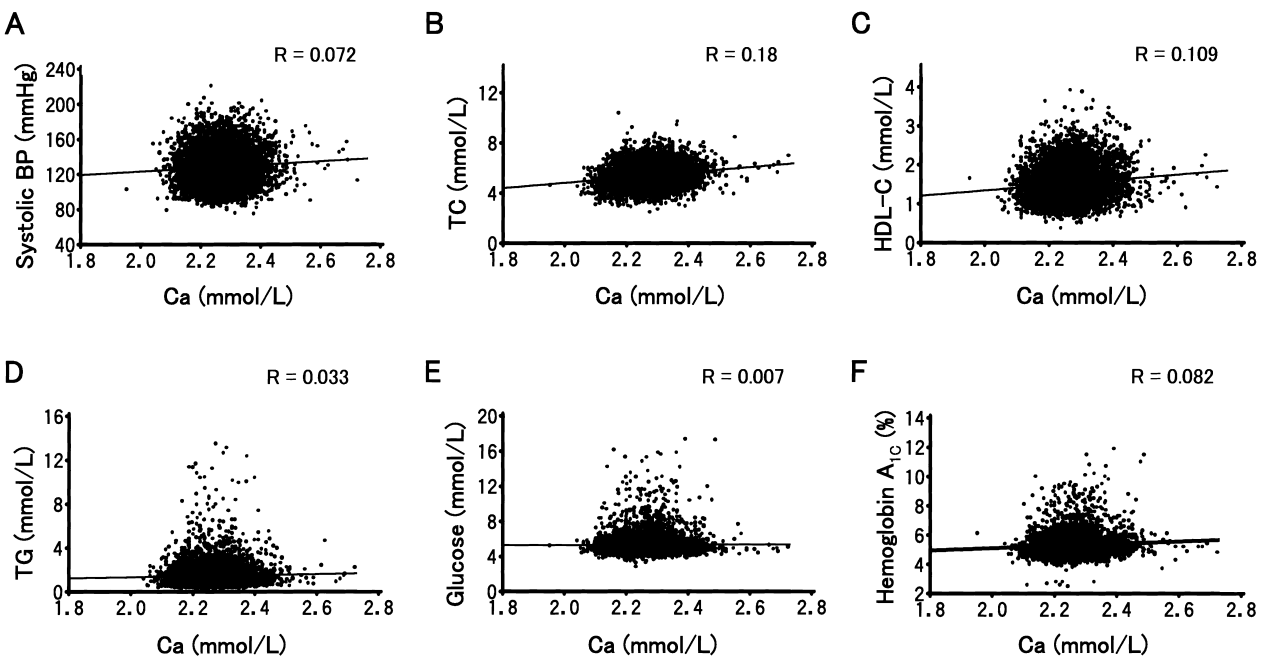

Fig. 1 Relationships between serum calcium and conventional risk factors for atherosclerosis
Relationship between serum calcium and systolic blood pressure(*A*), total cholesterol(*B*), high-density lipoprotein cholesterol(*C*), triglyceride(*D*), serum glucose(*E*), and hemoglobin A_{1C}(*F*). Correlation coefficient is given in each graph. All these correlations were statistically significant except for that between serum calcium and serum glucose.
BP = blood pressure; Ca = calcium; TG = triglyceride. Other abbreviations as in Table 1.

of 1.51(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 the 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[2,8]. Although serum calcium had not been corrected for serum albumin concentration, an association was found between serum calcium and blood pressure, TC/HDL-C, and, in men only, triglycerides[2]. This finding is consistent with the idea that serum calci-

Table 2 Multivariate logistic regression analysis

Variable	Odds ratio(95% CI)
Age(per yr)	1.11(1.11−1.12)†
Male	2.12(1.93−2.33)†
Blood pressure(per 10 mmHg)	1.12(1.10−1.14)†
Current smoker	1.39(1.29−1.50)†
Ex-smoker	1.10(1.00−1.20)*
Calcium	
Per 1 mmol/*l*	8.32(5.06−13.69)†
Per 1 mg/d*l*	1.70(1.50−1.92)†
Phosphorus	
Per 1 mmol/*l*	1.59(1.21−2.09)*
Per 1 mg/d*l*	1.16(1.06−1.27)*
TC(per 1 mmol/*l*)	1.17(1.12−1.22)†
Triglycerides(per 1 mmol/*l*)	1.00(0.97−1.03)
HDL-C(per 1 mmol/*l*)	0.73(0.65−0.80)†
Hemoglobin A_{1C} (per 1%)	1.12(1.07−1.18)*

All listed variables were considered as co-variables in the multivariate logistic regression analysis.
*$p<0.05$, †$p<0.001$.
CI=confidence interval.

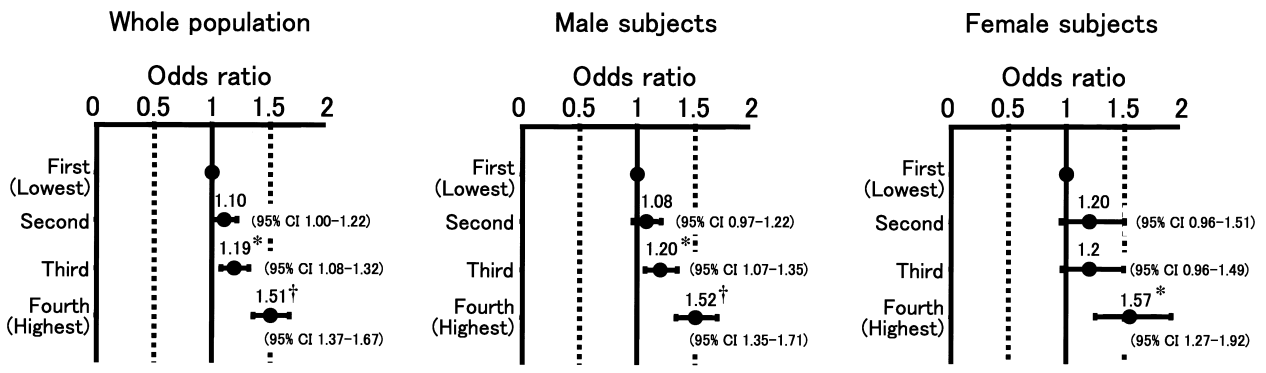

Fig. 2 Odds ratios for carotid plaque according to the serum calcium concentrations
Subjects were divided into four subgroups according to their serum calcium concentrations.
$^{*}p < 0.05$ and $^{\dagger}p < 0.01$ compared with the subjects in the first (*i.e.*, lowest) quartile of serum calcium concentration.
Abbreviation as in Table 2.

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 A_{1C}. However, correlation coefficients between serum calcium and these risk factors were rather small (< 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 aortosclerosis 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.

要　　約

血清カルシウム値と頸動脈プラークの関連: 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，健診受診者のデータを分析し，アルブミン値で補正した血清Ca値が，頸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1994−2000年に三井記念病院総合健診センターに健康評価のために訪れた症例のうち，血中のCa，アルブミン値を含む採血を受け，かつ頸動脈心エコー図法を施行されている症例を対象とした．統計学的検討は，すべてアルブミンで補正した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57歳）であった．血清Ca値は7.8−10.9 mg/dl（1.95−2.72 mmol/l）で，中央値が9.1 mg/dl（2.26 mmol/l）であった．頸動脈プラークは1,313例（23%）に認められた．Ca値はプラーク群，非プラーク群でそれぞれ2.28，2.27 mmol/lと，若干プラーク群で高かった（$p < 0.001$，t検定）．多変量のロジスティック回帰分析では，血清Ca値は独立した，有意なプラーク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1.70，95% 信頼区間1.50−1.92）．また，症例を血清Ca値により，4分割し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1.52（95% 信頼区間1.35−1.71，$p < 0.01$），女性で1.57（95% 信頼区間1.27−1.92，$p < 0.05$）と，有意にプラーク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値は頸動脈プラークの独立した危険因子であることが示唆された．

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References

1) Leifsson BG, Ahren B: Serum calcium and survival in a large health screening program. J Clin Endocrinol Metab 1996; **81**: 2149−2153
2) Jorde R, Sundsfjord J, Fitzgerald P, Bonaa KH: Serum calcium and cardiovascular risk factors and diseases: The Tromso study. Hypertension 1999; **34**: 484−490
3) Lind L, Skarfors E, Berglund L, Lithell H, Ljunghall S: Serum calcium: A new, independent, prospective risk factor for myocardial infarction in middle-aged men followed for 18 years. J Clin Epidemiol 1997; **50**: 967−973
4) Malatino LS, Benedetto FA, Mallamaci F, Tripepi G, Zoccali C, Parlongo S, Cutrupi S, Marino C, Panuccio V, Garozzo M, Candela V, Bellanuova I, Cataliotti A, Rapisarda F, Fatuzzo P, Bonanno G, Seminara G, Stancanelli B, Tassone F, Labate C, for the CREED Investigators: Smoking, blood pressure and serum albumin are major determinants of carotid atherosclerosis in dialysis patients: Cardiovascular Risk Extended Evaluation in Dialysis patients. J Nephrol 1999; **12**: 256−260
5) Kosch M, Hausberg M, Vormbrock K, Kisters K, Rahn KH, Barenbrock M: Studies on flow-mediated vasodilation and intima-media thickness of the brachial artery in patients with primary hyperparathyroidism. Am J Hypertens 2000; **13**: 759−764
6) Ishizaka N, Ishizaka Y, Takahashi E, Yamakado M, Hashimoto H: High serum bilirubin level is inversely associated with the presence of carotid plaque. Stroke 2001; **32**: 580−583
7) Payne RB, Little AJ, Williams RB, Milner JR: Interpretation of serum calcium in patients with abnormal serum proteins. Br Med J 1973; **4**: 643−646
8) Lind L, Jakobsson S, Lithell H, Wengle B, Ljunghall S: Relation of serum calcium concentration to metabolic risk factors for cardiovascular disease. BMJ 1988; **297**: 960−963
9) Vincenzi FF, Morris CD, Kinsel LB, Kenny M, McCarron DA: Decreased calcium pump adenosine triphosphatase in red blood cells of hypertensive subjects. Hypertension 1986; **8**: 1058−1066
10) Hvarfner A, Larsson R, Morlin C, Rastad J, Wide L, Akerstrom G, Ljunghall S: Cytosolic free calcium in platelets: Relationships to blood pressure and indices of systemic calcium metabolism. J Hypertens 1988; **6**: 71−77
11) Tsuchihashi K, Takizawa H, Torii T, Ikeda R, Nakahara N, Yuda S, Kobayashi N, Nakata T, Ura N, Shimamoto K: Hypoparathyroidism potentiates cardiovascular complications through disturbed calcium metabolism: Possible risk

of vitamin D(3)analog administration in dialysis patients with end-stage renal disease. Nephron 2000; **84**: 13−20
12) Bommer J, Strohbeck E, Goerich J, Bahner M, Zuna I: Arteriosclerosis in dialysis patients. Int J Artif Organs 1996; **19**: 638−644
13) Amann K, Tornig J, Flechtenmacher C, Nabokov A, Mall G, Ritz E: Blood-pressure-independent wall thickening of intramyocardial arterioles in experimental uraemia: Evidence for a permissive action of PTH. Nephrol Dial Transplant 1995; **10**: 2043−2048
14) Narang R, Ridout D, Nonis C, Kooner JS: Serum calcium, phosphorus and albumin levels in relation to the angiographic severity of coronary artery disease. Int J Cardiol 1997; **60**: 73−79
15) Kawagishi T, Nishizawa Y, Konishi T, Kawasaki K, Emoto M, Shoji T, Tabata T, Inoue T, Morii H: High-resolution B-mode ultrasonography in evaluation of atherosclerosis in uremia. Kidney Int 1995; **48**: 820−826
16) Clase CM, Norman GL, Beecroft ML, Churchill DN: Albumin-corrected calcium and ionized calcium in stable haemodialysis patients. Nephrol Dial Transplant 2000; **15**: 1841−1846

J Cardiol 2002 Mar; 39(3): 151–157