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Serum calcium and phosphate concentrations and intracranial atherosclerosis

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ABSTRACT

Objective: Serum calcium and phosphate concentrations are independent risk factors for stroke and positively associated with extracranial carotid atherosclerosis. We evaluated whether higher serum calcium and phosphate concentrations would be associated with intracranial atherosclerosis in a stroke-free Korean population.
Methods: We retrospectively analyzed the records of 361 stroke-free subjects who consecutively visited a general health promotion center. Included subjects had serum calcium, phosphate, and albumin drawn and underwent brain magnetic resonance angiography. The basilar, middle cerebral, intracranial internal carotid, and intracranial vertebral arteries were evaluated. Serum calcium concentration was corrected for serum albumin concentration.
Results: Mean ± SD values were 52 ± 10 years for age, 2.35 ± 0.09 mmol/l for uncorrected serum calcium concentration, 2.24 ± 0.08 mmol/l for corrected serum calcium concentration, and 1.19 ± 0.18 mmol/l for serum phosphate concentration. Seventy-four subjects (21%) had intracranial atherosclerosis. Subjects in the upper three quartiles of corrected serum calcium concentration had a significantly greater risk for intracranial atherosclerosis compared with the lowest quartile with the odds ratios of 3.50 (95% confidence interval 1.50–8.15), 3.11 (95% confidence interval 1.26–7.69), and 3.77 (95% confidence interval 1.58–9.03), respectively. However, serum phosphate and uncorrected serum calcium concentrations were not associated with intracranial atherosclerosis.
Conclusion: Corrected serum calcium concentrations are positively associated with the presence of intracranial atherosclerosis.

1. Introduction

Elevated serum calcium and phosphate concentrations are risk factors for cardiovascular events in patients with chronic kidney disease [1] and a general population [2,3]. In addition, elevated serum phosphate concentrations have been associated with coronary calcification in the chronic kidney disease and general populations [4,5]. Recent data from the Atherosclerosis Risk in Communities Study have shown that serum calcium and phosphate concentrations are independent, prospective risk factors for stroke [6]. Overt hypercalcemia or hyperphosphatemia is not a prerequisite for increased risk of cardiovascular morbidity and mortality. Relatively small elevations in serum calcium and phosphate concentrations in the high normal range have been associated with increased risk of cardiovascular morbidity and mortality [2,7].

Although extracranial carotid atherosclerosis is known to be associated with serum calcium and phosphate concentrations, there are few data on the association of intracranial atherosclerosis with serum calcium and phosphate concentrations. We therefore evaluated whether higher serum calcium and phosphate concentrations would be associated with intracranial atherosclerosis in a stroke-free Korean population.

2. Materials and methods

2.1. Subjects

We retrospectively analyzed the records of 374 subjects who consecutively visited a general health promotion center in a university-affiliated hospital from February 2006 through April 2009. Included subjects had serum calcium, phosphate, and albumin drawn and underwent brain three-dimensional time of flight magnetic

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resonance angiography (MRA) as part of their voluntary health checks. Measurements of serum calcium, phosphate, and albumin concentrations were performed by standard autoanalyzer techniques (Modular DP analyzer, Roche Diagnostics, Mannheim, Germany). Serum calcium concentration was corrected for serum albumin concentration by the formula: corrected calcium (mmol/l)= measured total calcium (mmol/l) − [0.02 × serum albumin (g/l)] + 0.8.

Thirteen subjects were excluded from the analysis due to one of the following criteria: (1) the presence of previous stroke ($n = 7$), (2) the absence of any recorded blood pressure ($n = 3$), and (3) artifacts in the MRA ($n = 3$). Therefore, 361 subjects were analyzed.

This study was approved by an independent ethic committee in the hospital (GNUHIRB-2010-048).

2.2. Vascular risk factors

As a part of health checks, standardized questionnaires were used to obtain information about participant demographics, medical history, and medication usage, including current antihypertensive and lipid-lowering medications and aspirin. Blood pressure, height, and weight were measured. Blood samples were obtained (early in the morning after an overnight fast, with the last meal generally 10 h before the blood draw) to measure serum calcium, phosphate, albumin, glucose, total cholesterol, high-density lipoprotein cholesterol, triglyceride, blood urea nitrogen, and creatinine concentrations. The low-density lipoprotein cholesterol was estimated by the method of Friedewald et al. [8]. Hypertension was defined as blood pressure of 140/90 mm Hg or more or a history of physician diagnosis of hypertension [9]. Diabetes was defined as fasting serum glucose concentration ≥7.0 mmol/l (126 mg/dl) or a history of physician diagnosis of diabetes [9]. Hypercholesterolemia was defined as a prior diagnosis of hypercholesterolemia, low-density lipoprotein cholesterol concentration ≥4.1 mmol/l (160 mg/dl), or total cholesterol concentration ≥6.3 mmol/l (240 mg/dl) [10]. Glomerular filtration rate was estimated by using the 6-variable Modification of Diet in Renal Disease formula (in ml/s/1.73 m^2) [11]. Chronic kidney disease was defined as glomerular filtration rate <1 ml/s per 1.73 m^2 [12]. Obesity was defined as a body mass index ≥25 kg/m^2 [13].

2.3. Magnetic resonance angiography

All MRA examinations were performed with a 1.5 T magnetic resonance system (Sonata, Siemens, Erlangen, Germany). Parameters of brain three-dimensional time of flight MRA were a repetition time of 30 ms, an echo time of 4.72 ms, and a flip angle of 20°. The number of excitations was one. A 196 × 384 matrix was used with field of view of 230 mm and a slice thickness of 0.9 mm.

The degree of stenosis was measured at its point of maximal narrowing and compared with the normal section of the vessel proximal to the stenosis ([normal lumen diameter − residual lumen]/normal lumen diameter). Intracranial atherosclerosis (stenosis of more than 50%) eligible for the study had to be located either in the intracranial carotid artery, the horizontal (M1) portion of the middle cerebral artery, the basilar artery, or the intracranial vertebral artery. The extent of intracranial atherosclerosis was determined by the number of intracranial arteries showing stenoocclusion and the degree thereof and was visually graded according to the following criteria: 0 indicating <50% stenosis; 1 indicating 50%–99% stenosis, and 2 indicating occlusion. Stenosis grade was decided by agreement between two neurologists. When there was no agreement, stenosis was graded by consensus after reassessment of MRA images. The total score of the 7 arteries on brain MRA was calculated as the atherosclerosis score [14].

2.4. Statistical methods

Student's *t*-tests and chi-square or Fisher's exact tests were used to assess differences between groups and Spearman's rank correlation coefficients were calculated to identify relationships between variables of interest. After categorization of serum phosphate and uncorrected and corrected serum calcium concentrations according to quartiles of the pooled distribution, univariate analysis was performed for the unadjusted odds ratios and 95% confidence intervals of intracranial atherosclerosis for the upper three quartiles relative to the lowest quartile (uncorrected serum calcium concentration < 2.30 mmol/l [9.20 mg/dl]; corrected serum calcium concentration < 2.19 mmol/l [8.74 mg/dl]; serum phosphate concentration < 1.06 mmol/l [3.30 mg/dl]) as a preliminary analysis (Table 1). In order to compute the statistically adjusted odds ratios, multivariate logistic regression analysis was performed. Variables possibly associated with the intracranial atherosclerosis ($p < 0.2$ after univariate analysis) were included in the multivariate model. Because of their clinical relevance and potential importance, chronic kidney disease [15] and diabetes [16] were retained in the final multivariable model regardless of statistical significance. Corrected serum calcium concentration was not entered as a continuous variable into the multivariate model because the assumption of linearity of the logit has not been met. The interaction term between corrected serum calcium concentration and its log transformation was significant [17]. The level of significance was set at $p < 0.05$ for all statistical analyses. All statistical analyses were performed using SPSS 12.0 for Windows (SPSS Inc., Chicago, Illinois, USA).

3. Results

3.1. Baseline characteristics of the study population

A total of 361 subjects were included in this study. The subjects were 183 men and 178 women, and their mean age was 52 ± 10 years. Mean serum calcium concentration was 2.35 ± 0.09 mmmol/l (9.42 ± 0.37 mg/dl); mean corrected serum calcium concentration was 2.24 ± 0.08 mmol/l (8.97 ± 0.33 mg/dl); mean serum phosphate concentration was 1.19 ± 0.18 mmol/l (3.67 ± 0.57 mg/dl, Table 1).

3.2. Serum calcium and phosphate concentrations and intracranial atherosclerosis

The percentage of old subjects (age ≥65) was significantly greater in subjects with intracranial atherosclerosis than in subjects without intracranial atherosclerosis (Table 2). Subjects with

Table 1
Baseline characteristics of the study population.

Variable	
Male sex (%)	183 (51)
Age ≥ 65 years (%)	45 (13)
Smokers (%)	78 (22)
Hypertension (%)	157 (44)
Diabetes (%)	32 (9)
Hyperlipidemia (%)	47 (13)
Cardiac disease (%)	4 (1)
Obesity (%)	137 (38)
Chronic kidney disease (%)	6 (2)
Aspirin (%)	20 (6)
Antihypertensive medications (%)	74 (21)
Lipid-lowering medications (%)	8 (2)
Albumin (g/l)	45.6 ± 2.6
Uncorrected calcium (mmol/l)	2.35 ± 0.09
Corrected calcium (mmol/l)	2.24 ± 0.08
Phosphate (mmol/l)	1.19 ± 0.18

Data are given as the number (percentage) or the mean ± standard deviation.

Table 2
Vascular risk factors by the absence or presence of intracranial atherosclerosis.

Variable	No intracranial atherosclerosis ($n = 287$)	Intracranial atherosclerosis ($n = 74$)	p
Male sex (%)	152 (53)	31 (42)	0.089
Age ≥ 65 years (%)	28 (10)	17 (23)	0.003*
Smokers (%)	62 (22)	16 (22)	0.997
Hypertension (%)	122 (43)	35 (47)	0.459
Diabetes (%)	23 (8)	9 (12)	0.263
Hyperlipidemia (%)	39 (14)	8 (11)	0.527
Cardiac disease (%)	2 (1)	2 (3)	0.188
Chronic kidney disease (%)	5 (2)	1 (1)	1.000
Obesity (%)	108 (38)	29 (39)	0.893
Aspirin (%)	15 (5)	5 (7)	0.575
Antihypertensive medications (%)	54 (19)	20 (27)	0.119
Lipid-lowering medications (%)	8 (3)	0 (0)	0.369
Albumin (g/l)	45.7 ± 2.6	45.3 ± 2.8	0.207
Uncorrected calcium (mmol/l)	2.35 ± 0.10	2.37 ± 0.08	0.229
Corrected calcium (mmol/l)	2.24 ± 0.09	2.26 ± 0.07	0.034*
Phosphate (mmol/l)	1.18 ± 0.19	1.19 ± 0.17	0.721

Data are given as the number (percentage) of each group or the mean ± standard deviation.
*$p < 0.05$.

intracranial atherosclerosis had higher corrected serum calcium concentration vs subjects without intracranial atherosclerosis, but no significant differences in the mean phosphate and uncorrected serum calcium concentrations were observed (Table 2). Subjects in the upper three quartiles of corrected serum calcium concentration (>2.30, 2.24–2.30, and 2.19–2.23 mmol/l [>9.19, 8.96–9.19, and 8.74–8.95 mg/dl]) had a significantly greater risk for intracranial atherosclerosis compared with the lowest quartile with the odds ratios of 3.47 (95% confidence interval 1.40–8.59), 2.99 (95% confidence interval 1.19–7.56), and 3.70 (95% confidence interval 1.50–9.01), respectively (Table 3). Adjustment for age, sex, diabetes, cardiac disease, chronic kidney disease, and antihypertensive medications did not change the associations (Table 3). However, no statistically significant differences in prevalence of intracranial atherosclerosis were noted across uncorrected serum calcium concentration quartiles (<2.30, 2.30–2.34, 2.35–2.39, and >2.39 mmol/l [<9.20, 9.20–9.39, 9.40–9.59, and >9.59 mg/dl]) and serum phosphate concentration quartiles (<1.06, 1.06–1.18, 1.19–1.28, and >1.28 mmol/l [<3.30, 3.30–3.69, 3.70–3.99, and >3.99 mg/dl]) (Table 3). No dose–response relationship was demonstrated between corrected serum calcium concentration and prevalence of intracranial atherosclerosis (Table 3).

3.3. Serum calcium and phosphate concentrations and the extent of intracranial atherosclerosis

Next, we analyzed the associations between the serum calcium and phosphate concentrations and the extent of intracranial atherosclerosis. There was a significant relationship between atherosclerosis score and corrected serum calcium concentration, but no correlation was found between atherosclerosis score and uncorrected serum calcium and serum phosphate concentrations (Table 4 and Fig. 1).

4. Discussion

Our data show that changes in serum calcium concentrations even within the “normal reference range” could result in subclinical atherosclerosis in the intracranial arteries, whereas changes in serum phosphate concentrations were not correlated with subclinical atherosclerosis in the intracranial arteries. The prospective, community-based Atherosclerosis Risk in Communities Study had followed 15,732 participants for a mean of 12.6 years and found that baseline serum calcium and phosphate concentrations were predictors of stroke [6]. Considering the relation of serum calcium and phosphate concentrations to stroke, it is not surprising that alterations in serum calcium and phosphate concentrations increase the risk of extracranial carotid atherosclerosis. The Northern Manhattan Study has examined associations between extracranial carotid plaque and corrected serum calcium concentrations within the normal range in community dwelling stroke-free participants [18]. Serum calcium concentrations were positively associated with extracranial carotid plaque thickness in a multi-ethnic American population [18]. Japanese and Italian investigators reached the same conclusion after analyzing data from participants who underwent general health screening in their own country [19,20]. The biracial (black–white) community-based Bogalusa Heart Study has evaluated association between serum phosphate concentrations within the normal range and extracranial carotid intima-media thickness in 1210 young adults without known cardiovascular disease or renal disease [21]. Carotid intima-media thickness was associated with serum phosphate within the normal range in a biracial American population [21]. The aforementioned Atherosclerosis Risk in Communities Study has assessed relation of serum phosphorus concentrations to carotid intima-media thickness in 13,340 subjects without known coronary heart disease, stroke, or renal disease [22]. Serum phosphate concentrations were positively associated with carotid intima-media thickness independent of traditional vascular risk factors in men [22].

Despite the mounting evidence to link serum calcium and phosphate concentrations with extracranial carotid atherosclerosis, the mechanisms whereby elevated serum calcium and phosphate concentrations promote atherosclerosis are still unclear. Alterations in calcium and phosphate concentrations lead to differentiation of vascular smooth muscle cells to an osteogenic phenotype in the vascular wall [15]. These osteogenic vascular smooth muscle cells release calcium-enriched membrane-bound bodies called matrix vesicles that can nucleate hydroxyapatite if there are no mineralization inhibitors [15]. The mineralization inhibitors such as matrix Gla protein, pyrophosphate, and osteopontin prevent the osteogenic conversion of vascular smooth muscle cells and production of calcium-phosphate crystals [15]. High local concentrations of calcium and phosphate are associated with degradation of extracellular matrixes and loss of mineralization inhibitors [15]. In addition, calcium and phosphate promote apoptosis of vascular smooth muscle cells and release of apoptotic bodies that form the nidus for vascular calcification [15].

Although serum calcium and phosphate concentrations are known to be associated with extracranial carotid atherosclerosis, information concerning the possible association between serum calcium and phosphate concentrations and intracranial atherosclerosis is limited. Previous studies concerning the relationship of serum calcium and phosphate concentrations to intracranial arterial calcification have yielded inconsistent results. Japanese investigators found that corrected serum calcium concentration was higher among the hemodialysis patients with intracranial artery calcification than among those without intracranial artery calcification [23]. However, their analysis was not adjusted for possible confounding variables. Serum phosphate concentrations were not different between the hemodialysis patients with intracranial artery calcification and those without intracranial artery calcification. Chinese researchers studied consecutive patients referred for brain computed tomography and found that serum calcium and phosphate concentrations were not associated with intracranial artery

Table 3
Odds ratios (95% confidence intervals) for intracranial atherosclerosis by quartile of serum calcium and phosphate concentrations.

Model		Quartile			
		1	2	3	4
Uncorrected calcium	Unadjusted	1.00 (ref)	1.58 (0.68–3.66)	2.00 (0.86–4.64)	1.85 (0.84–4.09)
	Adjusted[a]	1.00 (ref)	1.62 (0.69–3.85)	1.96 (0.82–4.65)	1.93 (0.86–4.37)
Corrected calcium	Unadjusted	1.00 (ref)	3.70 (1.50–9.01)	2.99 (1.19–7.56)	3.47 (1.40–8.59)
	Adjusted[a]	1.00 (ref)	3.73 (1.50–9.29)	2.78 (1.09–7.13)	3.09 (1.23–7.76)
Phosphate	Unadjusted	1.00 (ref)	1.55 (0.72–3.33)	1.52 (0.70–3.29)	1.32 (0.61–2.86)
	Adjusted[a]	1.00 (ref)	1.59 (0.72–3.49)	1.25 (0.56–2.79)	0.96 (0.42–2.19)

[a] Adjusted for age, sex, diabetes, cardiac disease, chronic kidney disease, and antihypertensive medications.

Table 4
Spearman rank correlation coefficients (R) between atherosclerosis score and serum calcium and phosphate concentrations in all subjects.

Variable	R	p
Uncorrected calcium	0.081	0.124
Corrected calcium	0.114	0.03*
Phosphate	0.014	0.787

*$p < 0.05$.

calcification after adjustment for possible confounding variables [24]. French investigators found that serum calcium and phosphate concentrations were not different between the ischemic stroke patients with intracranial artery calcification and those without intracranial artery calcification [25]. It should be kept in mind in interpreting the results of these previous studies that intracranial atherosclerosis is not always synonymous with intracranial arterial calcification. Intracranial arterial calcifications are more common in the proximal intracranial arteries (internal carotid and vertebral arteries) compared to the distal intracranial arteries (anterior cerebral, middle cerebral, posterior cerebral and basilar arteries) [24,26]. A majority of stenotic lesions in the distal intracranial arteries are not calcified [26]. Furthermore, high phosphate concentrations can promote atherosclerosis through mechanisms other than vascular calcification [27].

It is intriguing that in our study intracranial atherosclerosis was related to serum calcium concentration, but not serum phosphate concentration. Although the cause of this heterogeneity is uncertain, we can speculate that calcium and phosphate concentrations could exert differential effects, depending on the type and location of the vascular bed. For example, the Multiethnic Study of Atherosclerosis has measured coronary artery calcium scores and aortic arch calcium scores using computed tomography scans in 1974 participants from a multiethnic cohort [5]. There was a strong positive association between serum phosphate concentrations and coronary artery calcium scores, but not aortic arch calcium scores [5]. The heterogeneity observed in our study might be explained by the heterogeneity of mechanisms whereby calcium and phosphate promote vascular calcification. Although elevated calcium and phosphate concentrations have direct effects on vascular smooth muscle cells that promote vascular calcification, the precise mechanisms whereby calcium can promote vascular calcification differ from those of phosphate [15]. Elevated phosphate concentrations have a predominant role in inducing osteogenic conversion of vascular smooth muscle cells while elevated calcium concentrations have a predominant role in nucleating crystalline hydroxyapatite and inducing apoptosis of vascular smooth muscle cells and vesicle release [15].

Our study has several limitations. First, it is a retrospective observational study, and we did not have information regarding clinical outcome following the initial investigation. Therefore, causal relationships cannot be inferred. Second, our study sample size was relatively small. In addition, the number of patients with chronic kidney disease was small. The possibility that serum calcium concentrations may be associated with intracranial atherosclerosis also in patients with chronic kidney disease deserves further investigation. Third, MRA is lower in spatial resolution compared with conventional angiography. MRA is also less sensitive to slowly flowing blood and thus can overestimate the degree of stenosis, especially when there is calcification or slow or turbulent flow. Motion, either by the patient or by anatomical structures, can create artifacts [28]. A previous study that compared MRA with conventional angiography demonstrated that MRA has low specificity for diagnosing stenosis in M1 and M2 portions of the middle cerebral artery, A1 and A2 portions of the anterior cerebral artery, and the intracranial internal carotid artery. However, focusing on the intracranial internal carotid artery and the M1 portion of the middle cerebral artery as we did increased the specificity [29]. Forth, intracranial atherosclerosis was defined as intracranial arterial stenosis of more than 50% in our study. Because stroke risk with intracranial atherosclerosis may increase with the degree of stenosis [30], subjects with

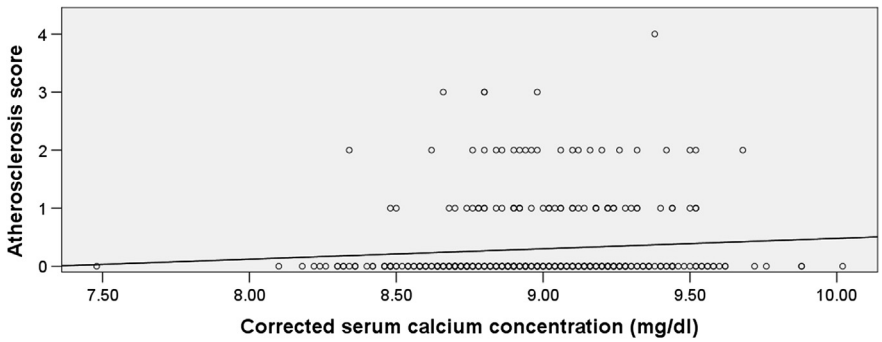

Fig. 1. The relationship between the atherosclerosis score and corrected serum calcium concentration in all subjects. To convert corrected serum calcium concentration to mmol/l, multiply by 0.25.

intracranial arterial stenosis of more than 50% may not have high stroke risk. Finally, we did not measure parathyroid hormone and vitamin D concentrations. The homeostatic regulation of calcium and phosphate occurs via the complex integration of these two hormones [15].

In conclusion, corrected serum calcium concentrations are positively associated with the presence and extent of intracranial atherosclerosis. Intracranial atherosclerosis is believed to be a risk factor for ischemic stroke [31], and examining relation of serum calcium concentrations to intracranial atherosclerosis could help to clarify mechanisms that link serum calcium concentrations and ischemic stroke. The maintenance of calcium concentrations in the normal range is the main goal in patients with chronic kidney disease to reduce the vascular injury [15]. Whether maintenance of calcium concentrations in the lower normal range can minimize the vascular injury in the general population is not clear. However, knowing serum calcium concentrations could help with evaluating risk in the general population, just as they do in patients with chronic kidney disease.

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Conflicts of interest

None.

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