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C-Reactive Protein is a Significant Predictor of Vascular Calcification of Both Aorta and Hand Arteries

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Although evidence has accumulated indicating a close relationship between inflammation and atherosclerosis, the relationship between inflammation and vascular calcification in patients with chronic renal failure is unclear. In the present study, the relationship between C-reactive protein (CRP) and vascular calcification in dialysis patients was examined. Vascular calcification of the aorta and hand arteries of 512 hemodialysis patients without significant infection (age 58.8 ± 10.1 y; 305 men, 207 women) were examined by roentgenography of the lateral abdomen and hands, respectively. Patients with a mean CRP level greater than 1.0 mg/L (n = 254) were older than those with a CRP level less than or equal to 1.0 mg/L (n = 258) and had a longer duration of dialysis, lower serum albumin level, and higher phosphate level ($P < .01$, $P < .05$, $P < .001$, and $P < .01$, respectively). Prevalence of vascular calcification of aorta and hand arteries in the former group was significantly higher than in the latter (65.0% versus 43.8% for aorta, $P < .0001$; and 25.0% versus 14.7% for hand arteries, $P < .01$). In a multivariate logistic regression analysis adjusted for age, hemodialysis duration, sex, levels of calcium and phosphate, and presence of diabetes, CRP level was a significant predictor for the presence of aortic calcification (odds ratio for highest versus lowest quartile, 2.669; 95% confidence interval, 1.539-5.421, $P = .0010$) and of calcification of hand arteries (odds ratio, 2.243; 95% confidence interval, 1.039-4.841; $P = .0395$). In conclusion, the present study shows that increased levels of CRP are significantly associated with the presence of vascular calcification in both aorta and hand arteries (ie, with both atheromatous and medial forms of calcification), indicating evidence for a relationship between inflammation and vascular calcification in hemodialysis patients.

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Atherosclerosis is a significant predictor of cardiovascular disease and death, not only in the general population[1] but also in hemodialysis patients.[2,3] Atherosclerosis is an inflammatory disease[4] and for this reason the term *atherosclerosis* has been suggested.[5] Blood levels of C-reactive protein (CRP) are related to the degree of atherosclerosis.[6,7] However, the relationship between inflammation and vascular calcification is unclear. This is partly owing to the fact that vascular calcification has been considered a passive or degenerative process, although it is now argued that it is an active process.[8-10] It is also partly owing to the relatively low frequency of vascular calcification detected clinically by conventional methods, such as plain roentgenography, in healthy populations. Vascular calcification is accelerated in hemodialysis patients.[9,11] Because hemodialysis patients have been reported to have high levels of

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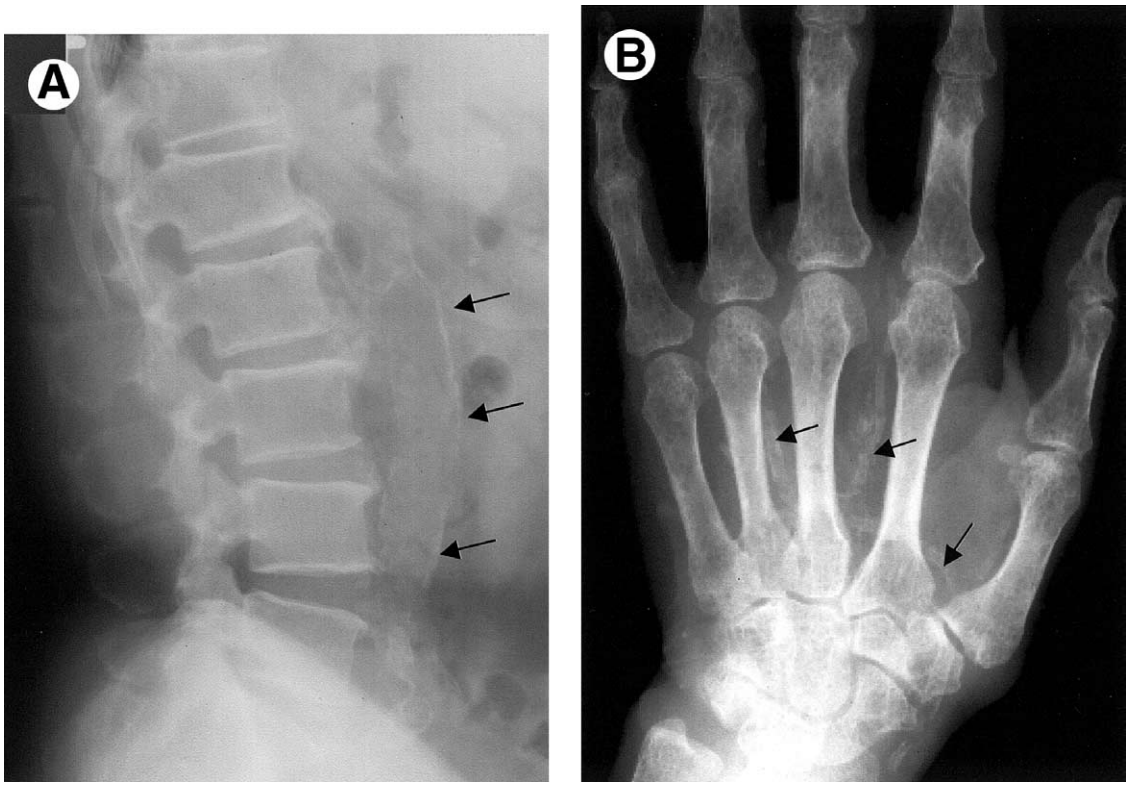

Figure 1 Calcification of aorta and hand arteries in hemodialysis patients. Roentgenographs showing (A) lateral abdominal view and (B) view of both hands (voltage 70 kV and 45 kV, respectively). Presence of vascular calcification (arrows) in aorta and hand arteries distal to the wrist joint was evaluated.

malnutrition, inflammation, and atherosclerosis (MIA syndrome),[3,12,13] we investigated this population to examine the relationship between inflammation and vascular calcification.

Patients and Methods

Patients and Clinical Parameters

There were 594 patients on maintenance hemodialysis (hemodialysis duration >3 mo) at Shirasagi Hospital Kidney Center, Osaka, Japan, at the end of 2000. Of these, patients with significant infection or malignancy were excluded. Patients whose mean CRP value on 3 occasions over 3 months was more than 10 mg/L also were excluded from the present study because of the likelihood of occult infection or malignancy. The remaining 512 patients were investigated in the present study. Mean age (± SD) was 58.8 years (± 10.1 y). Patients consisted of 305 men and 207 women, 123 of whom were diabetic and 389 were nondiabetic. Once a month, blood was drawn in a nonfasting condition before a dialysis session to measure CRP, albumin, urea nitrogen, creatinine, calcium, and phosphate levels. CRP level was evaluated by immunoturbid assay (Wako Junyaku Co. Ltd., Osaka, Japan). Other serum parameters were measured by an autoanalyzer. The mean of 3 measurements over 3 months before roentgenographic examination was used for analysis. Serum intact parathyroid hormone (intact PTH) was measured once by immunoradiometric assay (Allegro Intact PTH; Nichol's Institute, San Juan Capistrano, CA) at the time of roentgenographic examination.

Evaluation of Vascular Calcification of Aorta and Hand Arteries

From October to December 2000, left lateral abdominal views and anteroposterior views of both hands were obtained in each patient at a voltage of 70 kV and 45 kV, respectively. Apparent vascular calcification of the aorta and hand arteries distal to the wrist joint was evaluated by one author (K.K.) who was unaware of other patient data as previously reported (Fig. 1).[11]

Statistical Analysis

Data are expressed as mean ± SD. The χ^2 test was used to compare the prevalence of vascular calcification between patients with higher and lower CRP levels. Unpaired Student's *t* tests were used to compare clinical parameters with CRP levels. Multivariate logistic regression analysis was performed to explore the combined impact of factors affecting vascular calcification. For this analysis, patients were divided into quartiles by CRP level. Binary variables were used for sex (female = 0, male = 1) and diabetes (absence = 0, presence = 1). Statistical significance was defined as $P < .05$. All statistical analyses were performed using Stat-View 5 for Windows (SAS Institute Inc., Cary, NC).

Table 1 Predictors for Vascular Calcification of Aorta and Hand Arteries (Multivariate Logistic Regression Analysis).

	Odds Ratio	95% Confidence Interval	P
Aortic calcification			
Age (per year)	1.096	1.070-1.123	<.0001
Sex (male versus female)	2.339	1.466-3.732	.0004
Diabetes (presence versus absence)	3.927	2.250-6.854	<.0001
Duration of hemodialysis (per year)	1.064	1.024-1.106	.0015
Serum calcium (per 1 mg/dL)	1.094	0.730-1.642	.6629
Serum phosphate (per 1 mg/dL)	1.179	0.967-1.437	.1044
Parathyroid hormone (per 1 pg/mL)	1.002	1.000-1.003	.0677
CRP (versus lowest quartile)			
Lower quartile	1.430	0.603-2.544	.2244
Higher quartile	1.701	0.918-3.152	.0915
Highest quartile	2.669	1.539-5.421	.0010
		R^2 = .219	<.0001
Calcification of hand arteries			
Age (per year)	1.030	1.002-1.060	.0345
Sex (male versus female)	1.857	1.043-3.306	.0355
Diabetes (presence versus absence)	14.501	7.542-27.883	<.0001
Duration of hemodialysis (per year)	1.117	1.066-1.171	<.0001
Serum calcium (per 1 mg/dL)	0.875	0.551-1.390	.5713
Serum phosphate (per 1 mg/dL)	1.406	1.115-1.773	.0039
Parathyroid hormone (per 1 pg/mL)	1.000	0.999-1.002	.6553
CRP (versus lowest quartile)			
Lower quartile	1.042	0.475-2.283	.9186
Higher quartile	1.587	0.728-3.463	.2455
Highest quartile	2.243	1.039-4.841	.0395
		R^2 = .227	<.0001

R^2, regression coefficient.

Results

CRP levels ranged from 0.0 mg/L to 10.0 mg/L, with a median value of 1.0 mg/L. In patients with CRP levels greater than 1.0 mg/L (n = 254) compared with those with CRP levels equal to or less than 1.0 mg/L (n = 258), age was greater (mean ± SD) (62 ± 12 versus 58 ± 12 y, $P < .01$), hemodialysis duration was longer (7.8 ± 6.5 versus 6.6 ± 6.2 y, $P < .05$), serum albumin level was lower (39 ± 3 versus 41 ± 3 g/L, $P < .01$), and serum phosphate level was higher (5.9 ± 1.3 versus 5.6 ± 1.3 mg/dL, $P < .01$). A significant male preponderance was seen in the former group (male/female ratio, 164/90 versus 141/117; $P < .05$, χ^2 test). There were no significant differences between the groups in body weight, height, blood urea nitrogen level, serum creatinine level, calcium level, intact PTH level, or prevalence of diabetes.

Of 254 patients with CRP levels greater than 1.0 mg/L, vascular calcification of the aorta or hand arteries was seen in 165 (65.0%) and 58 (22.8%), respectively. Of 258 patients with CRP levels equal to or less than 1.0 mg/L, vascular calcification of the aorta and hand arteries was seen in 113 (43.8%) and 35 (13.6%), respectively. For both aorta and hand arteries, vascular calcification in the CRP group with higher levels was significantly more common ($P < .0001$ for aorta, $P < .01$ for hand arteries, χ^2 test).

A multivariate logistic regression analysis was performed to explore the combined impact of factors affecting vascular calcification. The various independent variables that have been shown to affect vascular calcification in hemodialysis patients[9,11] were examined. Even after adjustment for age, hemodialysis duration, sex, presence of diabetes, calcium level, phosphate level, and intact PTH level, the CRP level remained a significant predictor of vascular calcification for both aorta and hand arteries (Table 1). Patients with the highest quartile of CRP values had an odds ratio for aortic calcification of 2.699 (95% confidence interval, 1.539-5.421, $P = .0010$), and for calcification of hand arteries of 2.243 (95% confidence interval, 1.039-4.841, $P = .0395$) compared with those in the lowest quartile of CRP values.

Discussion

Vascular calcification, which significantly increases mortality from cardiovascular and other causes,[14,15] has a high prevalence in dialysis patients. Factors affecting vascular calcification in dialysis patients include advanced age, derangement of calcium-phosphate metabolism,[15-17] use of calcium-based phosphate binder,[18,19] and diabetes,[20-22] although there has been some variability in the reported strength of these associations. An MIA syndrome has been described in hemodialysis patients.[3,12,13] However, few studies have examined di-

rectly the relationship between inflammation and vascular calcification. Recently, Nitta et al[19] reported a significant association between CRP levels and progression of aortic calcification in hemodialysis patients, although their study included a relatively small number of patients (n = 26). In the present study, we show that the association between CRP levels and the presence of vascular calcification in a large number of hemodialysis patients (n = 512) remains significant even after adjustment for age, duration of hemodialysis, and calcium-phosphate metabolism. This association is significant for vascular calcification, both of the aorta and of hand arteries. Calcification of the aorta and of hand arteries represent different aspects of vascular calcification. Atheromatous calcification, as occurs in the aorta, affects the intimal layer of the vessel wall and is associated with atherosclerosis, whereas the calcification seen in hand arteries affects the medial layer and is of the type found in Moenckeberg's sclerosis.[14,23] The present study shows a relationship between inflammation and vascular calcification of both types.

A large body of evidence has accumulated concerning the relationship between the risk for atherosclerosis and of cardiovascular disease and increased CRP levels.[1,24,25] In these studies, CRP level has been considered a marker of chronic inflammation. Recently, however, Pasceri et al[26] showed that recombinant CRP up-regulates the expression of adhesion molecules, such as intracellular adhesion molecules, vascular cell adhesion molecules, and E-selectin in human endothelial cells. CRP is reported to be deposited in the arterial wall during atherogenesis.[27,28] Further, CRP has been shown to mediate low-density lipoprotein uptake by macrophages.[29] These studies showed specific roles for CRP in the development of atherosclerosis. Thus, the high prevalence of vascular calcification seen in hemodialysis patients in the present study in association with increased levels of CRP may be caused by an inflammatory process for which CRP is both a participant and a marker for arteriosclerosis; when the latter is advanced severely it will be associated with calcification.

Recently, Wang et al[30] showed a significant association between CRP level and cardiac valve calcification in patients undergoing continuous ambulatory peritoneal dialysis, even after adjustment for age, duration of dialysis, calcium-phosphate product, and presence of diabetes. Nitta et al[19] showed that, in addition to osteoprotegerin, CRP level was a significant predictor of the progression of aortic calcification in hemodialysis patients. By using vascular smooth muscle cells in vitro, Tintut et al[31] induced alkaline phosphatase production and matrix-calcium incorporation by coculture with macrophages, showing that macrophages regulate vascular calcification. In vivo, macrophages are reported to surround arterial calcium deposits.[32] Because vascular calcification is thus an active process, associated with inflammation involving macrophages,[9] rather than a passive or degenerative one, these studies, together with the present study, may indicate that chronic inflammation itself is a significant factor for the emergence and progression of vascular calcification in hemodialysis patients.

In conclusion, the present study adds new clinical evidence based on data concerning both atheromatous and medial arterial wall calcification on the significant relationship between inflammation and vascular calcification, in addition to the well-established relationship between atherosclerosis and inflammation.[4]

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