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Evaluation of Vascular Calcinosis Risk Factors in Patients on Chronic Hemodialysis: Lack of Influence of Calcium Carbonate

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Abstract. Linear calcifications of the abdominal aorta and of the iliac and femoral arteries were measured yearly for 3 years on X rays of 24 patients on chronic hemodialysis taking variable amounts of calcium carbonate and $Al(OH)_3$ but no pharmacological doses of vitamin D or 1α-hydroxylated vitamin D derivatives. The speed of their extension appeared exponential and covariant with the male sex, age only for men and, independently of these two factors, with diastolic blood pressure and blood triglycerides. Plasma concentrations of calcium, phosphate and glucose were covariant with the extension of calcinosis only at a borderline level. The doses of calcium carbonate and the levels of plasma alkaline phosphatase were not at all covariant.

Conclusions: (1) The effect of high doses of calcium carbonate is possibly harmful only when supraphysiological levels of plasma calcium are induced, whereas plasma phosphate is not adequately decreased. The doses of calcium carbonate per se have no deleterious effect (2). Since alkaline phosphatase is not covariant with the extension of calcinosis, the degree of hyperparathyroidism per se does not seem to play a causative role in vascular calcinosis (3). The main risk factors of vascular calcinosis are: age, the male sexe, diastolic blood pressure and blood triglycerides.

Introduction

The administration of high doses of calcium carbonate ($CaCO_3$) in dialyzed patients to control their hypocalcemia and hyperphosphatemia is controversial, since the decrease in plasma phosphate it induces can not only be explained by an increase in fecal phosphate but also by an increased deposition of phosphate in the body, as evidenced by a positive phosphate balance [4]. Although increased bone mineralization and/or good control of hyperparathyroidism has been reported with such a treatment, soft-tissue calcifications and particularly vascular calcifications may also appear. The causal relationship between high doses of $CaCO_3$ and vascular calcifications was not obvious, however, since the incidence of vascular calcifications was not greater than in a control group taking lower doses of $CaCO_3$, aluminium phosphate binders and 1α-hydroxylated vitamin D_3 [6], and the role of other risk factors of vascular calcinosis was not taken into account.

Surprisingly, these factors were the object of only a few studies [1, 7–10]. These studies show that a few factors are common to atherosclerosis, such as the male sex [1], age [1, 10] and duration of hypertension [7]. Other factors are common to nonvascular soft-tissue calcification, as the increase in plasma calcium and plasma phosphate [7, 10]. Conflicting data, however, do exist as regards the effect of lowering the plasma calcium phosphate product since disappearance of vascular calcifications was reported after decreasing this product by $Al(OH)_3$ and vitamin D [15] but not after decreasing it by parathyroidectomy [5].

In these studies, metabolic factors involved in atherosclerosis, like high blood levels of cholesterol, triglycerides, glucose and uric acid, were not systematically evaluated and the arterial calcifications were not considered from the point of view of their speed of extension. Therefore, in this study, the relationship between the speed of extension of vascular calcinosis and all the factors previously mentioned has been evaluated.

Table I. Control of hyperparathyroidism throughout the study

	Normal values	Before dialysis	1 year	2 years	3 years
Plasma calcium, mmol/l	2.2–2.6	2.26	2.30	2.31	2.37
Plasma phosphate, mmol/l	0.8–1.3	1.68	1.64	1.78	1.77
Plasma alkaline phosphatase, IU	70–170	142	139	140	145
Subperiosteal resorption, n		5 (24)	5 (24)	4 (15)	2 (9)
Granular osteoporosis of the skull, n		5 (24)	5 (24)	4 (18)	2 (9)
Plasma PTH[1], ng/ml	4–8		44.4 (7)	37.7 (5)	50.3 (3)
Active resorption surface[1], % of total trabecular surface	<1		5.87 (7)	5.25 (5)	6.75 (3)
Oral $CaCO_3 \pm SD$, g/day		5.6±4.6	5.5±4.7	5.1±3.8	5.2±3.8
Al $(OH)_3 \pm SD$, g/day		3.2±3.1	5.0±5.8	5.7±6.9	6.1±4.2

[1] For these parameters the mean is calculated only on a limited number of patients who are not the same throughout the study. Total number of patients is indicated in parentheses.

Patients and Methods

Patients and Treatment

Twenty-four patients (8 men, 16 women; age range 24–64 years) were selected because they had been on chronic hemodialysis for at least 3 years, always in the same center, using the same strategy: 2 or 3 dialyses of 4 or 6 h/week with the following technical conditions: cuprophane membranes of various areas, depending on the patient's weight and wanted weight loss; a dialyzate concentration of calcium of 1.75 mmol/l and a magnesium concentration of 0.75 mmol/l. To control their hyperparathyroidism, the following measures were taken: restricted phosphorus diet, variable doses of $CaCO_3$ (0–20 g/day; mean 5.5 g/day), variable doses of $Al(OH)_3$ (4.8±2 g/day) but no pharmacological doses of native vitamin D or 25-OH vitamin D_3, nor 1α-hydroxylated vitamin D derivatives. No patient was diabetic, or had been parathyroidectomized.

Clinical and Biological Data Collection

Before the first dialysis of the week we noted: systolic and diastolic blood pressure, calcemia, phosphatemia. Before the first dialysis of the month we noted: plasma alkaline phosphatase and magnesium, blood triglycerides, cholesterol, glucose and uric acid. For each patient, mean annual value was calculated each year. The plasma PTH concentrations were available only once in 7 patients after 1 year, in 5 patients after 2 years and in 3 patients after 3 years of dialysis. Bone histomorphometry data were available in 8 patients after 2 years, 4 patients after 2 years, 6 patients after 3 years of dialysis.

Radiological Data Collection

Lateral X-rays of the abdominal aorta and anteroposterior X-rays of the pelvis were performed just before starting hemodialysis and after 1, 2 and 3 years of dialysis. The linear calcifications (anterior and posterior for the aorta, lateral for the arteries of the pelvis) were measured in millimeters 3 times by 3 independent observers and the mean of the 9 measurements for each site was calculated. Bone X-rays of the hands and skull of each patient were taken at the same time as those for soft-tissue calcifications and were evaluated for the presence of subperiosteal resorption of the phalanges and for granular osteoporosis of the skull. The individual data are available in Roussel [12] and Atik [2].

Statistical Methods

Two approaches were used to find out the risk factors of calcinosis. The first consisted in the comparison of the mean of the potential risk factor between the two groups of patients with and without vascular calcification firstly at the beginning of dialysis and finally after 3 years of dialysis. The second consisted, firstly, in the evaluation of the speed of extension of the radiological calcification and then in a covariance analysis assessing the link of a potential risk factor with this speed of extension. The extension of the radiological calcification was expressed in percentages of the calcification measured at the beginning of the study, a correction of the ordinate was made considering the first year as the year during which the first calcification occurred. The upper and the lower variations of this increase with a risk $p = 0.05$ were calculated. A simple covariance analysis was made to assess the link between the different risk factors and the radiological calcification extension. $p < 0.1$ was considered statistically borderline, suggesting only a trend which would be very likely confirmed with a larger number of patients.

The *multiplication coefficient* is the factor multiplying the speed of calcification extension for the subgroup in which the parameter was higher than the mean of the whole group compared with the subgroup in which the parameter was lower than this mean.

Multiple covariance analysis was made to assess the correlations between the radiological calcification extension and an association of risk factors (2, 3 or 4 risk factors). In this analysis, the *multiple covariance coefficient* means a statistical relation between radiological calcification extension and the different associations of 2, 3 or 4 risk factors. *The synergy coefficient* is more precise: it represents the factor multiplying the speed of calcification extension of the subgroup in which 2, 3 or 4 parameters are higher than the mean of the whole group compared with the subgroup in which 2, 3 or 4 parameters are below the mean of the whole group.

Table II. Comparison of clinical, biological and therapeutical parameters between patients with and without vascular calcifications

Vascular cacifications	Beginning of dialysis		After 3 years of dialysis	
	absent	present	absent	present
Systolic blood pressure, mmHg	142	142	142	143
Diastolic blood pressure, mmHg	81	83	81	91*
Plasma calcium, mmol/l	2.36	2.38	2.33	2.43
Plasma phosphate, mmol/l	1.58	1.70	1.74	2.03*
P × Ca product	3.73	4.05	4.05	4.93
Plasma magnesium, mmol/l	1.59	1.71	1.89	1.76
Alkaline phosphatase, IU	149	142	153	143
Triglycerides, mmol/l	1.90	1.95	1.97	2.16*
Cholesterol, mmol/l	4.83	5.01	4.96	5.03
Plasma glucose, mmol/l	5.6	5.7	5.7	6.1*
Uric acid, µmol/l	684	708	678	702
Dose of $CaCO_3$, g/24 h	5.7	5.3	5.4	5.2
Dose of $Al(OH)_3$, g/24 h	2.9	4	6.1	6.2

Significance of the comparison between the presence and absence of calcifications: *$p \leq 0.05$.

Results

Evaluation of the Control of Hyperparathyroidism

Table I shows that the various parameters assessing the degree of hyperparathyroidism (plasma levels of PTH and alkaline phosphatase, radiological subperiosteal resorption, histological active resorption surface) did not show significant worsening during 3 years of dialysis.

Comparison of Therapeutical and Biological Parameters between Patients with and without Vascular Calcifications

This comparison was made at the beginning of dialysis and 3 years after and is summarized in table II. At the beginning, no significant difference was observed. After 3 years of dialysis, a significant difference was observed as regards diastolic blood pressure, plasma phosphate, triglycerides, total lipids, blood glucose which were all higher in the patients with vascular calcifications.

Radiological Evaluation of the Calcifications

The calcifications were initially present in 3 of the 8 men and in 5 of the 16 women. During the study, vascular calcifications worsened in 4 men and in 4 women; it decreased in none. The increase was 20% during the 1st year, 35% during the 2nd year compared with the 1st year, 60% during the 3rd year compared with the 2nd year. In comparison with the calcification length at the beginning of the study, the increase is exponential (fig. 1): 20% during the 1st year, 65% during the 2nd year and 175% during the 3rd year (range 70–270%).

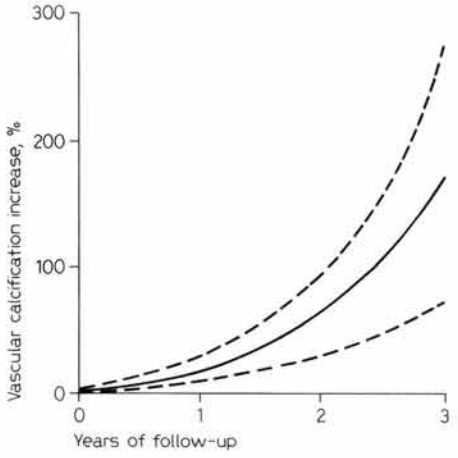

Fig. 1. Radiological evaluation of increases in calcification length.

In the patients who developed vascular calcinosis, a covariance analysis of the annual increase of the radiological calcification was made with the potential risk factors (table III). A significant covariance was found for the male sex, age only for men, diastolic blood pressure and blood triglycerides. Plasma concentrations of cal-

Table III. Covariance analysis of annual increase of vascular calcifications with potential risk factors

Parameter	Simple covariance coefficient	Multiplying coefficient
Male sex	1.97**	
Age in mean	1.99**	
Diastolic blood pressure	1.78*	1.21
Calcemia	1.59 (BL)	1.19
Phosphoremia	1.29 (BL)	1.07
Triglycerides	1.98*	1.37
Blood glucose	1.72 (BL)	1.23

Significance of the differences: BL = borderline ($0.05 < p < 0.1$); *$p < 0.05$; **$p < 0.01$. Female sex, age in women, alkaline phosphatase, blood uric acid, doses of $CaCO_3$ and $Al(OH)_3$ are not significant.

Table IV. Multiple covariance analysis for the association of 2 calcification risk factors

	Multiple covariance coefficient/synergy coefficient		
	calcemia	blood glucose	triglycerides
Diastolic BP	2.24/2.21*	2.05/1.92*	2.39/2.18*
Blood calcium		2.79/2.54**	2.79/2.61**
Blood glucose			2.19/1.97**

Significance of the multiple covariance coefficient: *$p < 0.05$; **$p < 0.01$.

Table V. Multiple covariance analysis for the association of 3 and 4 calcification risk factors in patients with radiological calcifications

Risk factor association	Multiple covariance coefficient	p value	Synergy coefficient
Diastolic BP, Blood calcium Blood triglycerides	3.25	< 0.01	2.87
Diastolic BP Blood calcium Blood glucose	2.90	< 0.02	2.54
Diastolic BP Blood triglycerides Blood calcium	2.54	< 0.04	2.19
Blood calcium Blood triglycerides Blood glucose	1.98	< 0.05	1.90
Diastolic BP Blood calcium Blood triglycerides Blood glucose	4.54	< 0.002	3.79

cium, phosphate and glucose were covariant only at a borderline level ($p < 0.01$). The multiplying coefficient, which would be evaluated only for the parametric factors, is comprised between 1.07 and 1.37. Radiological calcification extension was not covariant with the following parameters: age for women, systolic blood pressure, blood cholesterol, uric acid, plasma alkaline phosphatase, the calcium carbonate and aluminium hydroxide doses. In patients without radiological calcifications, it was impossible to do such a covariance analysis.

Radiological Calcification Extension and Combined Risk Factors

Table IV summarizes the result of multiple covariance analysis for the association of 2 risk factors by giving the multiple covariance coefficient as well as the synergy coefficient. For this association, the synergy coefficient is comprised between 1.9 and 2.8. The results for 3 and 4 risk factors are noted in table V. The synergy coefficient is the highest with the association of 4 factors: 3.79.

Discussion

(1) Linear measurement of the arterial calcifications seen on a lateral X-ray of the aorta and an anteroposterior x-ray of the pelvis showed that the speed of extension of the calcifications was exponential. This phenomenon suggests two mechanisms:

– an interrupted calcinosis with a predisposition phase followed by a calcium deposition phase;

– an uninterrupted calcinosis with an autoaggravation phenomenon: the more important the existing calcinosis, the faster the calcic accretion.

(2) Covariance analysis has shown that the radiological vascular calcifications of the hemodialyzed patients are favored independently and therefore cumulatively in both sexes by the diastolic blood pressure and the blood triglycerides, and at a borderline level of significance by the plasma concentrations of calcium, glucose and phosphate. The male sex per se represents a risk factor. In the 8 men, vascular calcifications were present in 3 at the beginning of the study and in 7 at the end. Age is only a risk factor in the male sex. This study points out for the first time the role of hypertriglyceridemia as well as the role of the level of diastolic blood pressure and not only the duration of hypertension, as in the study of Ibels et al. [8]. It suggests the harmful effect of high concentrations of plasma calcium and phosphate and therefore that high doses of calcium carbonate may be harmful inasmuch as

they induce hypercalcemia without decreasing hyperphosphatemia. This hazard of increasing the calcium × phosphate product is the same when pharmacological doses of vitamin D or 1α-hydroxylated vitamin D derivatives are used in association with $Al(OH)_3$ to control hyperparathyroidism [6]. Furthermore, this hazard of vascular calcification may be even greater with 1α-hydroxylated vitamin D derivatives since this 1α-hydroxylated vitamin D_3 has been shown to increase the calcium content of the aorta in uremic rabbits, while plasma calcium and phosphate remained in the normal range [14].

(3) The high prevalence of hypertension, hypertriglyceridemia, hyperglycemia and hyperphosphatemia in hemodialyzed patients may thus account for the high prevalence of radiological vascular calcifications in this population (25–50%) [1, 7, 8, 10]. This prevalence is probably much higher than in the nonuremic patients although we could not find a comparative study with an age- and sex-matched control group. The only controlled study based on histological findings is the study of Ibels et al. [8], who found that 46% of the hemodialyzed patients exhibited calcinosis versus only 17% of age- and sex-matched nonuremic patients. The incidence of increased calcifications of the large vessels is 30% in our population, i.e. an incidence intermediate between that reported in CAPD patients by Meema et al. [10] (45% after 28 months) and that reported in CAPD patients by Cassidy et al. [3] (21.7% after 24 months).

(4) The important point of the study is to show that the doses of $CaCO_3$ are not covariant with the extension of the calcifications, i.e. they cannot be attributed to the doses of calcium carbonate per se. As suggested in the Introduction, the lowering effect of $CaCO_3$ on plasma phosphate could be explained by an increased deposition of calcium phosphate, not only in the bone but also in the soft tissues. If this latter hypothesis was true, one would expect that the higher the doses of $CaCO_3$ the severer these metastatic calcifications would be, even in the absence of an elevation of the calcium × phosphate product. This study demonstrates that this hypothesis is unwarranted.

(5) In order to assess the role of hyperparathyroidism per se on the speed of calcification extension we studied only the covariance of this speed with the plasma alkaline phosphatase levels since plasma PTH levels were not available in all the patients. The lack of covariance found suggests that the degree of hyperparathyroidism per se does not play a direct role in the extension of vascular calcinosis.

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