Proc EDTA–ERA (1985) Vol 22

EVALUATION OF VASCULAR CALCINOSIS RISK FACTORS IN PATIENTS ON CHRONIC HAEMODIALYSIS. LACK OF INFLUENCE OF THE DOSE OF CALCIUM CARBONATE

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Summary

Linear calcifications of the abdominal aorta and of the iliac and femoral arteries were measured radiologically yearly for three years in 24 patients on chronic haemodialysis taking variable amounts of $CaCO_3$ and $Al(OH)_3$ but no vitamin D. The rate of extension appeared exponential and covariant with the male sex, age (only in males), the diastolic blood pressure, plasma triglyceride, plasma calcium, blood glucose and plasma phosphate but not with the dose of $CaCO_3$. Thus only the eventual effect of high doses of $CaCO_3$ on plasma calcium and phosphate is harmful, not the dose per se of $CaCO_3$.

Introduction

The use of high doses of $CaCO_3$ in haemodialysed patients for controlling their hypocalcaemia and hyper phosphataemia is controversial. The induced decrease in plasma phosphate is not only explained by an increase in faecal phosphate but also by an increased deposition of phosphate in the body as evidenced by a positive phosphate balance [1]. Although increased bone mineralization and/or good control of hyperparathyroidism has been reported with such treatment, eventually soft tissue calcification and particularly vascular calcification can appear [2]. The causal relationship between high doses of $CaCO_3$ and vascular calcification was however not obvious since the incidence of vascular calcification was not greater than in a control group taking lower doses of $CaCO_3$ and $1\alpha(OH)D_3$ and since other risk factors of vascular calcinosis had not been taken into account.

Surprisingly these latter have been the object of only a few studies [3–7] which show that a few factors are common to atherosclerosis such as the male sex [2], age [2–4] and the duration of hypertension [5]. Other factors are common to non-vascular soft tissue calcification as the increase in plasma calcium and plasma phosphate [6,7]. Conflicting data exist, however, as regards the

effect of lowering the plasma calcium phosphate product since disappearance of vascular calcification has been reported after decreasing this product by $Al(OH)_3$ and Vitamin D [8] but not after parathyroidectomy [9]. In these studies, metabolic factors involved in atherosclerosis such as hypercholesterolaemia, hypertriglyceridaemia, hyperglycaemia, hyperuricaemia have not been systematically evaluated, and arterial calcification has been considered from the point of view of its incidence only, and not from the point of view of its rate of extension. In this study, the relationship between the rate of extension of vascular calcinosis and all the factors previously mentioned has been evaluated.

Patients and treatment

Twenty-four patients (8 men, 16 women; age range 24–64 years) were selected because they had been on chronic haemodialysis for at least three years always in the same centre using the same strategy (2–3 dialyses 4 hours weekly with a dialysate calcium of 1.75mmol/L and a dialysate magnesium of 0.75mmol/L) and the same oral treatment for controlling their hyperparathyroidism, i.e. variable doses of $CaCO_3$ (0–20g per day, mean 4.5±4g) but no pharmacological doses of vitamin D or physiological doses of 1α hydroxylated vitamin D (since, experimentally, $1\alpha(OH)D_3$ at doses not inducing hypercalcaemia or hyperphosphataemia increases the calcium content of the aorta in uraemic rabbits [10]. None of the patients was diabetic.

Clinical and biological parameters

At the first dialysis of the week the following were measured: systolic and diastolic blood pressure, plasma calcium and phosphate. At the first dialysis of the month the following were measured: plasma alkaline phosphatase, plasma magnesium, triglycerides, cholesterol, total lipids, blood glucose and plasma uric acid. For each patient, the mean annual value for each year was calculated.

Radiological parameters

Profile radiographs of the abdominal aorta and anterio-posterior radiographs of the pelvis were performed just before starting haemodialysis and then after one, two and three years of dialysis.

The linear calcifications (anterior and posterior for the aorta, lateral for the arteries of the pelvis) were measured in millimetres three times by each of three independent observers. The mean of the nine measurements for each site was calculated.

Statistical methods

The extension of the radiological calcifications has been expressed as a percentage compared to that of the previous year. In the patients who had no radiological calcification at the beginning of the study, the approximation of Henry has been applied [10]. The upper and the lower variations of this increase with a risk of $\alpha=0.05$ have been calculated.

A simple covariance analysis was made to assess the link between the radiological calcification extension and each risk factor. Probability values <0.1 are to be considered as statistically significant because of the better shrewdness of covariance analysis compared to usual statistic methods such as linear regression.

Multiple covariance analysis was made to assess correlations between the radiological calcification extension and different risk factor associations (2, 3 or 4 risk factors). In this case, the multiple covariance coefficient represents the multiplication factor of calcification increase for this subgroup, the risk factors of which have a value greater than the mean value of the whole group, compared to the extension of the subgroup, the risk factors of which have a value lower than the group's mean.

Results

Radiological calcification

Calcifications were initially present in seven of the eight men and in seven of the 16 women. The increase percentage is: 20 per cent during the first year, 35 per cent during the second year compared to the first year and 60 per cent during the third year compared to the second year. In comparison with the length of calcification at the beginning of the study, the increase is (Figure 1): 20 per cent in the first year, 65 per cent in the second year and 175 per cent in the third year.

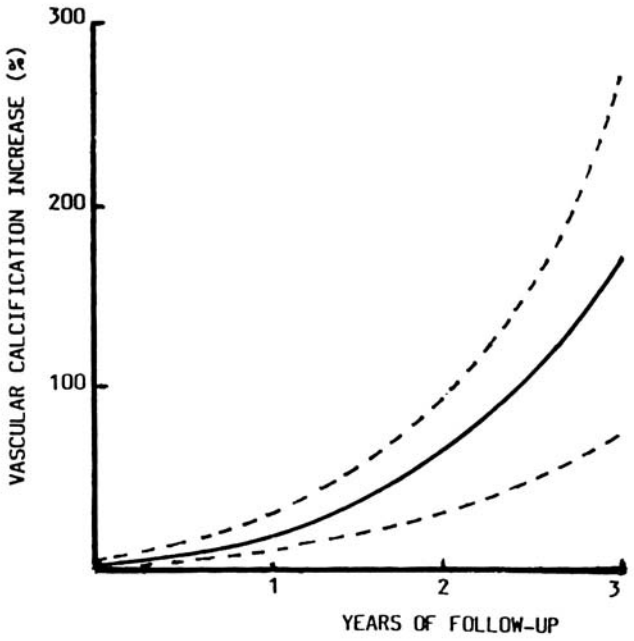

Figure 1. Radiological calcification length increase

Radiological calcification extension and risk factors

The following parameters are covariant with radiological calcification extension: male sex: $c=1.97$; $p<0.01$, age (only for men): $c=1.99$; $p<0.01$, diastolic blood pressure: $c=1.78$; $p<0.05$, triglycerides: $c=1.98$; $p<0.05$, plasma calcium: $c=1.59$; $p<0.08$, blood glucose: $c=1.72$; $p<0.10$ and plasma phosphate: $c=1.29$; $p<0.12$ (borderline). The following are not covariant with radiological calcification extension: age (for women); systolic blood pressure; plasma cholesterol; total lipids; plasma uric acid; plasma alkaline phosphatase and the doses of calcium carbonate and aluminium hydroxide.

Radiological calcification extension and combined risk factors

For the double association of the most important risk factors, the multiple covariance coefficient ranges between 2 and 3 were: diastolic blood pressure and plasma calcium: $Cc=2.24$; $p<0.05$, diastolic blood pressure and blood glucose: $Cc=2.05$; $p<0.05$, diastolic blood pressure and triglycerides: $Cc=2.39$; $p<0.05$, plasma calcium and blood glucose: $Cc=2.79$; $p<0.01$, plasma calcium and triglycerides: $Cc=2.79$; $p<0.01$ and blood glucose and triglycerides: $Cc=2.19$; $p<0.05$.

For the triple association, the coefficient ranges between 2 and 3.5: diastolic blood pressure, plasma calcium and triglycerides: $Cc=3.25$; $p<0.01$, diastolic blood pressure, plasma calcium and blood glucose: $Cc=2.9$; $p<0.02$, diastolic blood pressure, triglycerides and blood glucose: $Cc=2.54$; $p<0.04$ and plasma calcium, triglycerides and blood glucose: $Cc=1.98$; $p<0.05$. It is maximal with the quadruple association of the main risk factors ($Cc=4.54$; $p<0.002$).

Conclusions

Radiological calcification increase is exponential which suggests two mechanisms: (1) interrupted formation with predisposition phases followed by formation phases or (2) uninterrupted formation with a phenomenon of auto-aggravation, the calcium accretion being faster than the pre-existing calcinosis.

Arterial calcinosis of haemodialysed patients is favoured in both sexes, independently and therefore cumulatively by: diastolic blood pressure, triglycerides, plasma calcium, blood glucose and plasma phosphate. The male sex is an independent factor and age is a risk factor only in this sex. This study points out for the first time the importance of hypertriglyceridaemia and diastolic blood pressure.

The fact that both plasma calcium and phosphate are risk factors emphasizes the importance of the control of these parameters in their physiological ranges. Therefore high doses of $CaCO_3$ may be harmful when they induce hypercalcaemia without decreasing hyperphosphataemia. However, calcium carbonate per se is not a risk factor, since its dose is not covariant with calcinosis. Thus the hypothesis that high doses of calcium carbonate per se are responsible for vascular calcinosis seems unwarranted.

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