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ORIGINAL ARTICLE

Soft tissue calcifications in patients on dialysis treatment

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Background. Patients with end stage renal failure on dialysis treatment may develop several types of soft tissue calcification, including visceral, periarticular and vascular calcifications due to a number of known and unknown factors. The aim of the study was to evaluate the dispersion of vascular and periarticular soft tissue calcifications of a random group of haemodialysis (HDT) patients and their relation to parathyroid hormone (PTH) and some other biochemical markers.

Material and methods. Four middle-range arteries a.a. carotis communis sinistra et dextra and a.a. femoralis sinistra et dextra were investigated by B-mode echography; 4 typical for calcium deposits periarticular regions of the body were checked by x-ray and visible skin calcifications were registered in 40 patients (on HDT more than 3 months) for evaluation of calcification rate, comparing them with some biochemical parameters: PTH, alcaline phosphatase (AP), Ca, Ca^{++}, P and C-reactive protein (CRP).

Results. The study revealed a high percentage (95%) of vascular calcifications (VC), and a low percentage of periarticular and skin calcifications (3.3%). A significant correlation was found between PTH/AP ($r=0.7$, $p<0.001$), PTH/VC ($r=0.51$, $p<0.001$), PTH/Ca^{++} ($r=0.40$, $p<0.01$) and PTH/CRP ($r=0.39$, $p<0.01$) as well as between CRP/VC ($r=0.38$, $p<0.01$)

Conclusion. The study suggests an influence of secondary hyperparathyroidism and existing inflammatory status on vascular calcifications in dialysis patients but no relation of both factors to periarticular and skin calcium deposits, which would require a different way of therapy.

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Increasing interest has been devoted to soft-tissue calcifications in patients with chronic renal failure on conservative or dialysis treatment. Although it has been known many years ago as a frequent complication of this condition, its high prevalence and prominent role in cardiovascular morbidity and mortality of uremic patients have been recognized recently[1-3].

The type, distribution, speed of progression and severity of extraskeletal calcifications vary widely, depending on numerous factors in addition to uremia. Periarticular vascular and valve calcifications, also called non-visceral calcifications, are morphologically and pathogenically distinct from visceral calcifications[1,4-6]. Such distinctions need to be made for the understanding of mechanisms and the identification of appropriate therapeutic and prophylactic measures[6-8]. In the most frequent form, calcium deposits are preferably found in media of arterial walls, in coronary vessels, myocardial structures and heart valves, in skin structures and periarticular regions. The damage of arteries is a major contributory factor to high cardiovascular morbidity and mortality of pts with end stage renal disease (ESRD). Soft-tissue calcifications in chronic renal failure (CRF) have generally been considered to be a passive event, secondary to the elevation of the extracellular Ca x P product. However, recent observations of spontaneous arterial calcifications *in vitro* and *in vivo* in cell culture models have provided evidence in favour of the participation of active inhibitory processes, involving specific cells and extracellular Ca-regulartory proteins, including matrix Gla-protein and human fetuin-A, described as potent inhibitors of Ca x P complex precipitation[9-11]. Inflammation with its acute phase reactants has been accused as another independent factor for appearance and development of these unnatural calcifications[12-14]. Up to now the problem of the pathogenesis and treatment of soft tissue calcifications is not resolved and the attempts to find the answers must continue as the cardiovascular Ca deposits are close related to the morbidity and mortality of the patients with CRF and on HDT.

The aim of our study was:

1. To evaluate the distribution of soft tissue calcifications in: medium arteries, periarticular areas and skin in patients on HD without diabetes mellitus and

2. To compare the dispersion percentage of the investigated calcifications to some biochemical parameters, related to mineral metabolism.

Subjects and methods

We examined 40 patients who were on HD for more than 3 months (mean duration 81.12 ± 23.34 months), with a mean age of 52.9±14.5 years, without diabetes mellitus, sepsis, malignancy or other serious pathology except uremia and its usual complications. Written informed consent was obtained from all subjects.

Arterial calcifications: calcification score. The presence of arterial calcifications was evaluated by sonography with longitudinal and transversal scan (7.5

MHz transducer) in the common carotid artery (a segment of 4 cm length, in the pre-bifurcation), and in the iliofemoral axis.

Periarticular and skin deposits. Conventional x-rays were made on 4 joins with periarticular areas and some other joins if there were symptoms of Ca deposits–tumors, pain etc.; expression of skin calcium eruptions were registered in all investigated subjects.

Blood chemistry. In all patients tests of serum creatinine, calcium (Ca, Ca++), phosphate (P), hemoglobin (Hb) and hematocrit serum albumins (Alb), alkaline phosphatase (AP), intact PTH, fibrinogen (Fib.), Mg, blood lipids and C-reactive protein (CRP) were made in the beginning of a dialysis procedure.

Statistical analysis. Data were expressed as mean ± SD and analysis of variance (ANOVA) is used for comparison of the different groups.

Results

The mean values of the above mentioned results are shown in **table 1**.

Our study found a quite high expression of vascular calcifications (96%), compared to a relatively low percent of periarticular and skin calcium deposits (3.5%) in the investigated HD patients.

Table 1. *Mean values of the investigated parameters in pts. on HDT*

Studied parameter	Mean Value ± SD	Normal Values
Hb (g/l)	83.02 ± 40.21	120 - 150
Ca (mmol/l)	2.22 ± 0.24	2.02 – 2.6
Ca++ (mmol/l)	1.12 ± 0.10	1.2 – 1.3
P (mmol/l)	2.33 ± 0.69	0.8 – 1.4
AP (U/l)	319.5 ± 427.87	207 - 240
PTH (pg/ml)	352 ± 393	8 - 65
Alb (g/l)	40.11 ± 5.8	35 – 45
Fib (mg/l)	4.53 ± 0.96	3.5 – 4.5
CRP (mg/l))	8.40 ± 7.12	0.3 – 3.0
Vascular calcif. rate	3.14 ± 1.06	0
Mg (mmol/l)	1.03 ± 0.1	0.65 – 1.05
Creat (mmol/l)	878.8 ± 194	63 - 105

Statistical analysis is shown in tables 2 and 3.

Table 2. *Correlations of PTH to some other important parameters*

Parameters	Correlation	p <
PTH/AP	0.74	0.001
PTH/Vasc.Ca	0.52	0.001
PTH/Duration of HD	0.44	0.01
PTH/ Ca++	0.41	0.01
PTH/ CRP	0.38	0.01

Table 3. *Correlations of CRP with some other important parameters*

Related Parameters	Correlation	p <
CRP/Vasc.Ca	0.65	0.001
CRP/PTH	0.38	0.01
CRP/ Duration of HD	0.38	0.01
CRP/Ca++	0.33	0.01
CRP/Ca	0.32	0.05
CRP/HDL	- 0.3	0.05
CRP/Mg	-0.26	n.s.

Discussion

Cardiovascular morbidity and mortality is markedly increased in the dialysis population compared to non-uremic subjects. Vascular and valvular calcifications are most frequently found in dialysis patients and they are predictors of cardiovascular death in this population. The presence of hyperphosphatemia and the increased Ca x P product has been considered as a major pathological mechanism leading to excessive vascular and soft-tissue calcification in uremic subjects. Recent studies however, revealed that deficiencies in calcium-regulatory proteins may also directly contribute to the development of extraosseus calcifications. The α_2-Heremans Schmid glycoprotein (fetuin-A) and matrix Gla protein are important inhibitors of calcification in vivo and there is novel evidence available that a deficiency in such proteins is involved in the pathogenesis of cardiovascular calcifications in dialysis patients[15-17]. Inflammation with its acute phase reactants has been accused as another independent factor for appearance and development of these unnatural calcifications[12-14]. Moreover fetuin-A has been described as a negative inflammatory protein, that significantly decreased during the acute phase inflammatory statuses[12,15-17].

Trying to find out the significant calcification factors and the interactions between them, in our study we could not prove a close relation between higher P levels and investigated soft tissue calcifications in our patients group. Our impression is that the patients are treated with phosphate binders that mask the real picture and, second; the transitory P levels failed to show the influence of the duration of exposition on hyperphosphatemia during the long years of uremia and dialysis treatment, that probably acts as a factor for the Ca x P deposition.

Our study suggests that vascular calcifications may be due to a number of different factors : II HPT ($r=0.58$, $p<0.001$), higher serum Ca^{++} ($r=0.48$, $p<0.01$), chronic inflamatory status (elevated CRP) ($r=0.66$). Some decrease of serum Mg related to the existence of signs of acute inflammation (Mg/CRP $r= - 0.26$) hints about involvement of Mg in inflammatory processes, but did not give any direct evidence that the ion takes part in soft tissue calcifications. And surely some of the reasons for calcifications still must to be discovered.

Although we found only 5 patients with skin or periarticular calcifications, the impression is that this kind of deposits do not directly depend on II HPT, Ca++, P, and CRP. Other unknown factors are probabbly more close related to the problem and that requires a future efforts to be clarified.

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