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ORIGINAL ARTICLE

Dependance of dispersion of cardiac calcifications on some biochemical markers in hemodialysis patients

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Background. The damage of arteries and heart structures are a major contributory factor to the high cardiovascular morbidity and mortality of patients with chronic renal failure on dialysis. The aim of the study was to find some risk factors for development of cardiac valve calcifications and their relations to myocardial function in patients on hemodialysis treatment.

Material and methods. Conventional M-mode and B-mode echocardiography (Echo) and Pulse-doppler were made, accounting myocardial function and aorta valve calcifications (Ca-Ao), mitral valve calcifications (Ca-M) and total valve calcifications score (Cardiac Ca) of 37 patient with mean age 54.7 ±14.5 years and mean duration of hemodialysis treatment 82.05 ± 27.35 months. Arterial blood presure (ABP) and pulse rate were also registered. Tests of serum levels of Ca++, P, alkaline phosphatase (AP), parathormone (PTH), C-reactive protein (CRP), homocysteine and in 20 patients – fetuin-A and serum Mg were correlated to some myocardial functions (ejection fraction-EF; endsystolic stress – ESS; VpE/VpA), muscle mass index (MMI), and valve calcifications rate.

Results. Some significant correlations were found as follows: Ca++/Cardiac Ca r=0.46, p<0.01; PTH/Cardiac Ca r=0.43, p<0.01; EF/ESS r=0.81, p<0.01; EF/Cardiac Ca r=-0.38, p<0.05; CRP/EF r=-0.4, p<0.01; MMI/MAP r=0.52, p<0.01; VpE/VpA : Cardiac Ca r=-0.38, p<0.05; Age/Cardiac Ca r=0.4, p<0.01; Dur.HD/Cardiac Ca r=0.28, p<0.05; PTH/EF r=-0.22, n.s., Fetuin A/PTH r=-0.33 p<0.05; Fetuin A/CRP r=-0.43 p<0.001; Fetuin A/Cardiac Ca r=-0.71 p<0.001

Conclusion. The results prove the negative influence of increased myocardial burden (ESS, ABP) on the left ventricular function and on MMI. Close relations of disturbed mineral metabolism, PTH, inflamatory status (CRP), fetuin A, age and duration of HD with the rate of valve calcifications show that cardiac calcium deposits have multifactorial origin. The study also suggests that valve calcifications are involved in the complex of risk factors, causing damage of the valve structures and left ventricular dysfunction in HD patients.

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In recent years, increasing interest has been demonstrated to soft-tissue calcifications in patients with chronic renal failure treated by dialysis. Although it has been known for many years as a frequent complication of this condition, its high prevalence and prominent role in cardiovascular morbidity and mortality of uremic patients has only been recognized recently. The damage of arteries and heart structures are a major contributory factor to the high cardiovascular morbidity and mortality of patients with chronic renal failure (CRF)[1-5]. Soft-tissue calcifications in CRF have generally been considered to be a passive event, secondary to the elevation of the extracellular Ca x P product, but recent observations of spontaneous arterial and heart valves calcifications have provided evidence in favour of the participation of active inhibitory processes, involving specific cells and extracellular Ca-regulartory proteins[2, 6-10]. One of them, fetuin-A accounts for more than 50% of precipitation inhibitory effect of the serum. It has been recognized as a negative acute-phase protein that falls during the inflamation or trauma[10-14]. The question whether the levels of serum fetuin-A are predictive for soft tissue calcifications and in a reverse relation to the acute-phase reactants in ESRD and HD pts. stil must be clarified[13-16]. Homocystein also has been accused to be a factor of increased cardiovascular morbidity and mortality in CRF, but no relation between it and calcifications has been described[6,8,15].

The aim of our study was: a) To evaluate the distribution of soft tissue calcifications in: heart valves, in patients on HD without diabetes mellitus; b) To asses the pathological hearth echo-parameters and their relation to calcification rate; and c) To compare the dispersion percentage of the investigated calcifications to some biochemical parameters, especially to bone markers, and to specific proteins which recently were suspected to be responsible for the calcifications.

Subjects and methods

We examined 37 patients more than 3 months on HD; mean duration 82.05 ± 27.35 months; mean age 54.7 ±14.5 years without serious pathology except uremia and its usual complications. Written informed consent was obtained from all subjects.

Echocardiography. Thirty seven patients underwent

M- and B-mode echocardiography with 3.5 MHz transduser. Left ventricular (LV) measurements were made according to the recommendations of American Society of Echocardiography. LV mass (LVM) was calculated as 1.05 x [(PWT+IVST+LVEDD)^3] – 13.6, where PWT is the posterior wall thickness, IVST is the interventricular septal thickness and LVEDD is the LV end-diastolic diameter. LV mean wall thickness (LVMWT) were calculated as (IVST+PWT)/2. The fractional shortening of the LV was calculated as [(LVEDD-LVESD)/LVEDD] x 100, where LVESD is the LV end systolic diameter. LV diastolic filling was evaluated from pulsed Doppler studies obtained from the apical 4-chambers view of the heart. The sample volume was positioned in the inflow area just at the tip of the mitral leaflets. Maximal early diastolic flow velocity (E) and maximal late atrial flow velocity (A) were measured and their ratio (E/A) was calculated.

Blood chemistry. In all 37 patients the levels of serum creatinine, calcium (Ca, Ca++), phosphate (P), hemoglobin (Hb) and hematocrit serum albumins (Alb), alkaline phosphatase (AP), intact PTH, fibrinogen (Fib.), C-reactive protein (CRP), homocystein (Hcy), Mg, and fetuin-A (– in 20 patients), were estimated at the beginning of dialysis procedure.

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

Results

The mean values of the results are presented in table 1.

Our study found a quite high expression of cardiac calcifications (76%). Statistical analysis showed a high correlation or a tendency of relations between a number of important biochemical parameters, echocardiography parameters and cardiac calcifications score (Tables 2-5).

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

STUDYED PARAMETER	MEAN VALUE ± SD	NORMAL VALUES
Hb (g/l)	82.02 ± 40.19	120 - 150
Ca (mmol/l)	2.21 ± 0.22	2.2 – 2.6
Ca++ (mmol/l)	1.13 ± 0.1	1.2 – 1.3
P (mmol/l)	2.38 ± 0.69	0.8 - 1.4
Cardiac Calcif. Rate	1.86 ± 0.55	0
AP (U/l)	319 ± 423	207 - 240
PTH (pg/ml)	397 ± 393	8 - 65
Hcy (mcmol/l)	35.7 ± 9.78	4 - 17
Alb (g/l)	41 ± 5.9	35 – 45
Fib (mg/l)	4.59 ± 0.93	3.5 - 4.5
CRP (mg/l)	8.44 ± 7.11	0.3 - 3.0
Creat (mcmol/l)	905 ± 194	53 - 106
Fetuin (n=20)	0.39 ± 0.12	0.4 – 0.95
Mg (mmol/l) (n=20)	1.02 ± 0.1	0.65 – 1.05

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

Parameters	Correlation	p <
PTH/AP	0.72	0.001
PTH/ Cardiac Ca	0.43	0.01
PTH/Dur.HD	0.46	0.01
PTH/ Ca++	0.40	0.01
PTH/ CRP	0.39	0.01
PTH/Fetuin-A	-0.33	0.05
PTH/ESS	0.24	n.s.
PTH/EF	- 0.22	n.s.

Table 3. *Correlations of myocardial function to some other important parameters*

Related Parameters	Correlation	P<
EF/CRP	-0.4	0.01
Cardiac Ca/Age	0.4	0.01
EF/Cardiac Ca	-0.38	0.01
VpE:VpA/Cardiac Ca	-0.38	0.01
Cardiac Ca/HD duration	0.28	n.s.
EF/PTH	-0.22	n.s.

Table 4. *Correlations of CRP with some other important parameters*

Related Parameters	Correlation	p <
CRP/Cardiac Ca	0.66	0.001
CRP/Ca++	0.34	0.01
CRP/Fetuin-A	-0.43	0.01
CRP/EF	- 0.40	0.01
CRP/PTH	0.39	0.01
CRP/HD duration	0.38	0.01
CRP/Ca	0.30	0.05
CRP/Mg	-0.26	n.s.

Table 5. *Correlations of Fetuin-A with some important parameters*

Related Parameters	Correlation	P <
Fetuin-A/Card.Ca	- 0.71	0.001
Fetuin-A/CRP	- 0.43	0.01
Fetuin-A/PTH	- 0.33	0.05

The correlations of cardiac calcifications to serum Ca++, PTH and myocardial functions are shown in the figures 1-4.

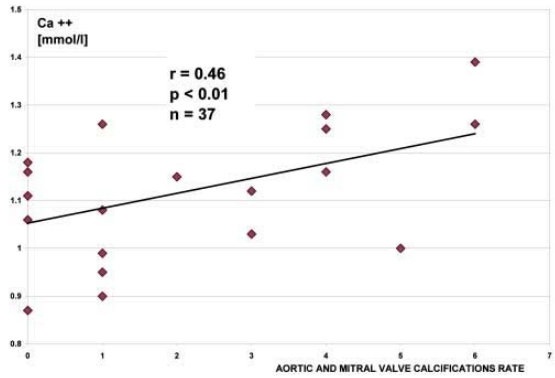

Fig 1. *Correlation of aortic and mitral valve calcifications rate to serum Ca^{++} (mmol/l).*

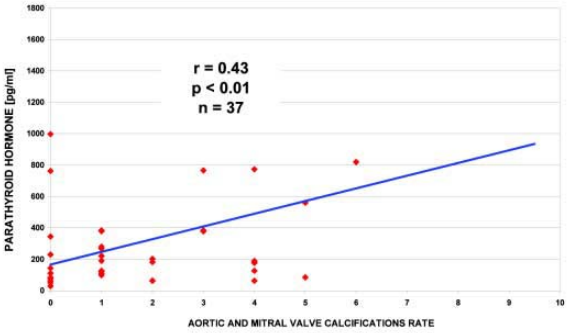

Fig 2. *Correlation of aortic and mitral valve calcifications rate to iPTH (pg/ml).*

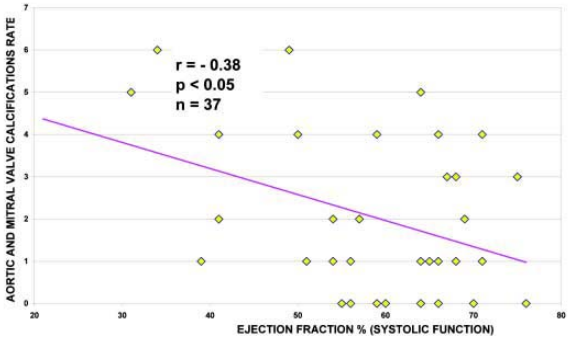

Fig 3. *Correlation of aortic and mitral valve calcifications rate to ejection fraction rate.*

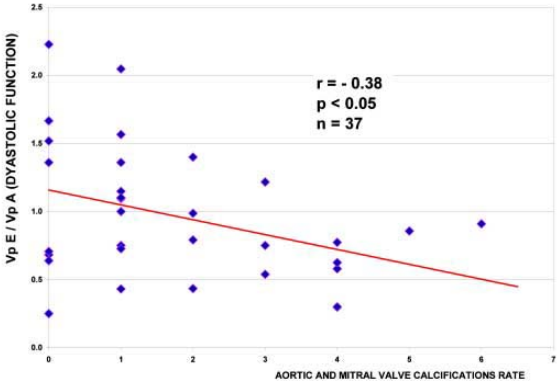

Fig 4. *Correlation of aortic and mitral valve calcifications rate to VpE/VpA.*

Discussion

The reasons for the high incidence of cardiovascular disease in hemodialysis patients are multiple. There are a number of traditional risk factors such as hypertension, diabetes, dyslipidaemia, sodium overload, elevated homocysteine levels, and water overload that are commonly seen in the end stage renal disease (ESRD) population[8-10, 17]. In addition, there are factors specific to ESRD that contribute to the high incidence of cardiovascular calcification in the dialysis population, such as disturbances in mineral metabolism, and specifically abnormalities in phosphorus, calcium and protein homeostasis [8-10,17,18]. Calcifications of the myocardium, coronary arteries, and cardiac valves are frequently observed in patients with ESRD[1-3,15,18]. Vascular calcification is also associated with increased aortic stiffness, which is predictive of cardiovascular mortality in these patients. Cardiovascular calcification lesions can lead to the development of a number of clinically significant complications, including myocardial ischaemia, myocardial infarction, impaired myocardial function, congestive heart failure, cardiac valve insufficiency, and cardiac arrhythmias[10, 17,18]. Thus, cardiovascular lesions in the ESRD patient are associated with substantial morbidity and mortality risks[16,17]. Myocardial calcification can impair left ventricular function[13,14,18] and calcification of the cardiac conduction system can cause death[6,8,12,17]. Thus, these studies clearly demonstrate that the development of cardiovascular complications is relatively frequent in patients treated with long-term dialysis therapy. Our study found a remarkable prevalence and extent of valvular calcifications - 76% of the patients had calcifications of the mitral or aortic valve, compared with an expected prevalence of 15% to 20% in the general population, age- and gender mached individuals. The results also showed that poor left ventricular function (systolic and diastolic) was signifficantly related to the high score of cardiac calcifications ($r = - 0.38$, $p < 0.05$). Cardiac and vascular calcifications evidently are due to a number of factors : II HPT ($r=0.58$, $p<0.001$), higher serum Ca++, ($r=0.48$, $p<0.01$), chronic inflamatory status (elevated CRP) ($r=0.66$), lower inhibitory proteins of Ca x P precipitation (fetuin-A) ($r= - 83$, $p<0.001$). Decreasing of fetuin-A obviously is greatly associated to the higher rate of cardiovascular calcifications and some more investigations are obligatory to clarify the reasons for its lower serum level in HD pts. The found reverse correlation of this protein with CRP ($r= -0.43$, $p<0.01$) suggests the possible role of the inflamatory state on this event. Moreover some authors recognized fetuin-A as a negative acute-phase protein, and CRP is one of the reactants[1,4,13]. The relation of fetuin to PTH-levels is not too strong ($r=-33$, $p<0.05$), but interference between them exists in negative form. Homocystein was not related to cardiac calcification score that means it has another mechanism of affection on heart structures.

A general conclusion can be made, as follows: the

factors affecting heart structures and functions in patients on dialysis treatment are multiple in origin and they act in different ways. One of the most important causes of them is the disturbed bone metabolism and the prevention of its development would be of great protection and help, overcoming the high rate of cardiovascular morbidity and mortality in patients with ESRD on dialysis treatment.

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