



Synergism of Malnutrition, Inflammation and Fluid Load in the Development of Atherogenesis in Uremic Patients Undergoing Peritoneal Dialysis

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Authors' contributions

This work was carried out in collaboration between all authors. Author DR designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors SR and VR managed the analyses of the study. Author VH managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Objective: Approximately 50% of end stage renal disease (ESRD) patients lose their lives as a consequence of cardiovascular diseases due to accelerated atherosclerosis. The objectives of this study were to investigate the synergistic effect between nutritional status, inflammation and volume load with atherogenesis estimated using structural and hemodynamic changes in the carotid arteries (CA) in patients on peritoneal dialysis (PD).

Methods: Prospective longitudinal study. The study sample consisted of 50 ESRD patients who were treated with PD and were observed for an 18 months after the commencement of dialysis treatment. All examined patients underwent 4 to 5 dialysis changes with 2 liters of dialysis solution. The laboratory findings were complemented with ultrasound of CA and echocardiography at baseline and at the end of follow-up.

Results: C-reactive protein (CRP), B-type natriuretic peptide and homocysteine significantly were significantly decreased, while normal protein nitrogen appearance (nPNA) and albumin values

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were significantly increased after 18 months on PD. The carotid intima-media thickness (CIMT), left atrium diameter was significantly decreased ($p < 0.001$) at the end of the study. Significant predictors of CIMT and CA diameter were residual renal function (RRF), albumin and CRP whereas significant predictors of presence of atherosclerotic plaques were RRF and CRP.

Conclusion: We have found a close relationship between hemodynamic and structural CA changes with markers of poor nutrition, inflammation and hydration status in PD patients. The synergism of atherogenesis and monitored parameters, especially CA diameter and CIMT, seems to be useful in the management of PD patients and deserves further testing in properly designed clinical validation study.

Keywords: Malnutrition; inflammation; volume load; atherogenesis; peritoneal dialysis.

1. INTRODUCTION

Chronic volume overload is well recognized factor contributing to the high mortality of dialysis patients. The malnutrition, inflammation and atherosclerosis (the so-called MIA syndrome) have also been proposed as the main causes of mortality in the end-stage renal disease patients (ESRD) [1].

Protein-energy malnutrition is a common problem among patients on peritoneal dialysis (PD) [2] and together with inflammation, they make the most potent non-traditional factors of cardiovascular risk in these patients, due to the development of atherosclerosis [3].

In the general population, serum C-reactive protein (CRP) is considered to be a marker of inflammation, and powerful risk factor for ischemic heart disease and peripheral atherosclerosis. Zoccali et al. have found that CRP is also a strong independent predictor of the severity of atherosclerosis in dialysis patients [4].

The risk for myocardial infarction and stroke were increased for each 0.1 mm increase of carotid intima media thickness (CIMT). CIMT was greater in dialysis patients compared to the general population [5,6]. The presence of carotid plaques is also important risk factor for cardiovascular disease (CVD) [7].

The objectives of this study were to investigate the synergistic effect between nutritional status, inflammation and volume load with atherogenesis estimated using structural and hemodynamic changes in the carotid arteries (CA), and to evaluate the usefulness of the vascular system assessment of these patients before renal replacement therapy (RRT) and after 18 months of PD.

2. METHODS

2.1 Patients

This prospective longitudinal study included 50 ESRD patients (diabetic type 2 and nondiabetic) who were treated with continuous ambulatory PD and were observed for an 18 months after the commencement of dialysis treatment. All examined patients underwent 4 to 5 dialysis changes per day with 2 liters of dialysis solution per exchange with the weekly clearance Kt/V urea at least 1.9. Double-chamber bag Stay-Safe® Balance system (Fresenius Medical Care, Germany) was available for all including patients. This system utilizes lactate-buffered PD solution in a two-compartment bag offered in the Stay-Safe® disconnect system. The formation of glucose degradation product (GDP) is greatly reduced by separating the glucose component of the solution (kept at very low pH) from the lactate component of the solution (kept at alkaline pH) during sterilization and storage. Immediately before infusion, the seam between the two chambers is opened, and the contents are mixed. The ready-to-use solution has a near-physiological pH, and a greatly reduced amount of GDP. Laboratory values, CA ultrasound and echocardiography were obtained at the beginning of dialysis treatment and after 18 months. In the methodological approach in this research we used personal, demographic and anamnesis data, physical examination and methods of laboratory diagnosis. The research included determining the following laboratory parameters: serum albumin and C-reactive protein. Serum CRP was analyzed by end-point nephelometry, and the normal range was less than or equal to 5.0 mg/L. Serum albumin was determined by the bromocresol green method.

The patients with the verified diagnosis of CA stenosis, heart valve diseases, and cerebral

vascular diseases were excluded from the study, based on the criteria of the American Heart Association. At the moment of commencement of observation, all observed patients were without clinical manifestation of heart failure. On the basis of the inclusion and exclusion criteria, 50 ESRD patients were recruited at the dialysis unit, and they represented 69% of the total PD population at the unit. During the monitoring period twelve patients were excluded due to recurrent PD-associated peritonitis, translation on hemodialysis or death. Those twelve patients were excluded in the data analysis.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000.

2.2 Carotid Ultrasound

The severity of carotid artery atherosclerosis was evaluated using the mean common carotid artery (CA) intima-media thickness (mean IMT) and plaque score (PS). Carotid-ultrasonography was used to evaluate the mean IMT and the PS. High-resolution B mode, color Doppler and pulse Doppler ultrasonography of both carotid arteries were performed with an ultrasound scanner (Wall-Track system: W-T, Maastricht, the Netherlands) equipped with a 7.5-MHZ linear array transducer by a same experienced angiologists. Measurement was done by the angiologist who was not familiar with the clinical status of the study patients. Patients were examined in the supine position with the head tilted backwards. After the carotid arteries were located by transverse scans, the probe was rotated 90° to obtain and record a longitudinal image of the anterior and posterior walls. The high-resolution images of the far wall of the bilateral CA, internal carotid arteries (ICA), and carotid bulbs were according to recommendations of the American Society of Echocardiography Carotid Intima-Media Thickness Task Force [8]. The IMT was defined as the distance between the leading edge of the lumen-intima echo and the leading edge of the media-adventitia echo. At least three measurements were taken over a 1-cm length of far wall of each CA segment, and these measurements on both sides were averaged to obtain the mean IMT.

Plaques were sought by using B-mode and color Doppler examinations in both longitudinal and

transverse planes to take into consideration circumferential asymmetry and they were defined, as focal intrusions into the lumen ≥ 1.2 mm thick. Highly echogenic plaques producing bright white echoes with shadowing were considered to be calcifications. The possible carotid plaques were quantified quantitatively as absent or present number of plaques. The PS was computed by adding the maximal thickness in millimetres of plaques in each segment on both sides (A + B + C + thickness of the contralateral carotid artery plaques). Segment A was the region of the internal CA (ICA) that was <15 mm distal to its bifurcation from CA. Segment B was the region of the ICA and the CA that was <15 mm proximal to the bifurcation. Segment C was the region of the CA that was >15 mm and <30 mm proximal to the bifurcation. The length of individual plaques was not considered in determining the PS. The severe stenosis was diagnosed if systolic velocity peak was higher or equal than 125 cm/s.

2.3 Echocardiography

A standard two-dimensional M-mode color Doppler echocardiography was performed on ESRD patients using a 3.75 MHz transducer (Toshiba 270 SSA). The measurement was done by two cardiologists, who were not acquainted with the clinical status of the patients, according to the recommendations of the American Society of Echocardiography. Left ventricular (LV) mass was calculated as follows: $0.8 \times [1.04 \times (PWT + IVST + LVEDD)^3 - LVEDD^3] - 13.6$, where PWT is posterior wall thickness, IVST is interventricular septal thickness and LVEDD is LV end-diastolic diameter. LV mass was normalized to body height as an index in g/m^2 . LV hypertrophy (LVH) was defined according to Framingham's criteria (LV mass/body surface area (BSA) $>110 g/m^2$ in females and LV mass/BSA $>134 g/m^2$ in males) [9].

2.4 Parameters of Peritoneal Dialysis

Adequacy of dialysis (Kt/V_{urea}) was calculated from total weekly removed urea mass by daily volume of dialysate and urine (Kt) and divided with urea distribution volume (V).

During the study period residual renal function (RRF) was estimated as the mean of renal creatinine clearance (mL/min). The patients were not taking diuretic therapy prior to urinary volume measurement and sampling. A simplified peritoneal equilibration test was performed using

4.25% glucose-based solution to obtain the dialysate to plasma creatinine concentration ratio at 4 hours of dwell (D/P Cr). Patients were categorized as high, high-average, and low-average transporters according to criteria of Twardowski and colleagues [10].

2.5 Statistical Analysis

All data were expressed as the mean standard deviation (SD) or as median and interquartile range. The distribution of variables was tested by the Shapiro-Wilk test. Significant change in the variables from baseline to 18 months after treatment was tested by paired-test for the variables that followed normal distribution or by the Wilcoxon signed-rank test for the variables that had skewed distribution. The difference between two groups was analyzed by the Mann-Whitney test. A multiple regression analysis was applied to examine the relationship between ultrasound parameters of CA and a set of clinical and laboratory parameters (indicators of the malnutrition, inflammation and volume load). A P-value of <0.05 (two-sided) was regarded as statistically significant. SPSS (Chicago, IL, USA) for Windows (Version 16.0) was used for statistical analysis.

3. RESULTS

Clinical, demographic and laboratory characteristics of the 50 ESRD patients undergoing PD are summarized in Table 1. Out of all, 52% of patients enrolled in our study were diabetics. The significant reductions of systolic (SBP) and diastolic blood pressure (DBP) were observed after 18 months on PD. Median CRP, B-type natriuretic peptide (BNP) and homocysteine (tHcy) values were significantly decreased, while mean hemoglobin, normalized protein nitrogen appearance (nPNA), and serum albumin values were significantly increased after 18 months on PD (Table 1). The median concentration of serum nitric oxide significantly increased after 18 months on PD treatment. Mean levels of parathyroid hormone and calcium were not significantly different in patients before RRT and after 18 months on PD. At the end of the follow-up period dialysis adequacy, estimated by Kt/V_{urea} , and RRF were satisfactory.

As shown in Table 2, left atrium diameter (LAD) and LVEDD were significantly decreased ($p<0.001$) at the end of the study. In addition, at

the end of follow up significantly smaller number of patients had LVH in comparison to the time prior PD commencement (20 pts vs. 11 pts). The most important finding was a significant reduction in CIMT ($p<0.001$). This decrease in CIMT was accompanied by significant amelioration in the CA diameter ($p<0.05$) and consequently the plaque score and presence of atherosclerotic plaques ($p<0.05$). The baseline average peak systolic velocity (PSV) and end diastolic velocity (EDV) were higher compared to those at the end of follow-up period, but not significantly.

Markers of nutrition, inflammation and volume load were significantly correlated with CA ultrasound parameters (Table 3). Serum albumin was negatively correlated with CIMT and CA diameter. CRP was positively correlated with all the monitored parameters on CA. CIMT and CA diameter were positively correlated with SBP and LAD.

Furthermore, we performed linear regression analysis to examine which of CA parameters were independent predictors of volume, nutrition and inflammation parameters at baseline and at the end of follow-up (Table 4). At the end of the monitoring period, significant predictors of CIMT and CA diameter were RRF, albumin and CRP, while significant predictors of the presence of atherosclerotic plaques were RRF (t: -1.45; $p = 0.01$) and CRP (t: -2.37; $p: 0.05$). Significant predictor of EDV was albumin (t: -2.91; $p < 0.01$).

Median LVEDD was significantly higher in ESRD patients with $CIMT<0.5mm$ compared to the same group of patients after 18 months of PD treatment (51.09 vs. 46.38 mm; $p<0.05$) while no significant difference was found after 12 and 18 months on PD between groups with CA 0.5-1.2 mm and $CIMT>1.2 mm$ (Fig. 3). The solid horizontal lines denote the median value, the box represents the 25% and 75% interquartile ranges and the whiskers represent minimum and maximum values.

4. DISCUSSION

Approximately 50% of ESRD patients lose their lives as a consequence of CVD due to accelerated atherosclerosis [12]. Mark and co-authors noted that even mild deterioration in kidney function might be a risk factor itself for the development of atherogenesis in these patients [13].

Table 1. Demographic and clinical characteristics of the study patients

Variable	Before RRT	After 12 months on PD	After 18 months on PD	p
Gender (male) (n)	25 (50%)			
Age (years) (range)	60.5 (19-76)			
Diabetes mellitus (n) (%)	26 (52%)			
Smoker (yes)	18 (45%)	16(32%)	16 (32%)	NS
BMI (kg/m ²)	25.9 ± 3.7	25.8±2.6	25.7±2.2	NS
SBP (mm Hg)	147.4±20.1	134.2±14.4	129.4±11.5	<0.001
DBP (mm Hg)	89.2±12.6	96.5±12.0	79.4±9.8	<0.05
Use of antihypertensive drugs				
No drug (n)	2	2	3	
Diuretics (n)	36	30	18	
ACE inhibitors (n)	32	27	24	
Calcium-channel blockers (n)	21	29	29	
β-Blockers (n)	1	1	1	
Hemoglobin (g/L)	101.9±10.3	109.8±8.9	118.6±11.1	<0.001
Urea nitrogen (mmol/L)	25.7±6.7	17.5±2.5	17.5±2.5	<0.001
Serum creatinine (µmol/L)	912.3±223.3	715±204.6	733.9±131.0	<0.001
Total cholesterol (mmol/L)	6.5±1.6	5.9±1.2	5.5±1.3	<0.01
LDL (mmol/L)	4.7±1.4	3.8±0.8	3.6±0.8	<0.05
C-reactive protein (mg/L)	11.1 (6.1-16.4)	5.9(3.5-8.9)	4.5 (2.8-7.7)	<0.01
Fibrinogen (g/L)	6.2±1.9	6.6±1.2	4.4±1.3	<0.01
PTH (pmol/L)	225.5(97.8-387)	205(102-336)	200(100-410)	NS
Calcium (mmol/L)	2.2±0.2	2.2±0.1	2.3±0.1	NS
Phosphorus (mmol/L)	1.8±0.3	1.6±0.7	1.6±0.2	<0.05
Nitric Oxide (µmol/L)	40.72(19.4-56.7)	45.95(33.5-60)	48.0(32.8-60.4)	<0.01
Homocysteine(µmol/L)	26.3(20.3-31.1)	21.0(16.7-23.4)	18 (14.0-20.9)	<0.001
Serum albumin(g/L)	30.9±2.6	31.2±1.9	31.5±3.2	<0.01
TIBC (µmol/L)	47.2±19.3	47.8±21.2	49.7±14.8	NS
nPNA (g/kg/day)	0.98±0.13	1.0±0.2	1.11±0.1	<0.05
PET results				
After 6 months				
High (n)	7	4	3	
High average (n)	9	11	11	
Low average (n)	34	35	36	
Weekly total Kt/V _{urea}	1.94 ± 0.8	2.1± 0.6	2.1 ± 0.6	<0.05
Peritoneal ultrafiltration (ml/ day)	984 ± 327	1094±828	1154 ± 641	<0.05
Peritoneal protein loss (g/day)	6.2±2.4	4.0±2.5	4.0±1.22	<0.05
RRF (mL/min/1.73 m ²)	5.5±3.8	6.5±5.0	7.0 ± 5.0	<0.001
Proteinuria (gr/day)	0.79 ± 0.41	0.71±0.33	0.70 ± 0.39	0.05

Data are expressed as median (range).

Abbreviations are: NS - Not significant; RRT - Renal replacement therapy; BMI - Body Mass Index;

SBP - Systolic blood pressure; DBP- Diastolic blood pressure; ARB-Angiotensin receptor blocker;

ACE-Angiotensin-converting enzyme; LDL-Low-density lipoprotein; PTH-Parathyroid hormone; TIBC- Total iron-binding capacity; nPNA- Protein equivalent of total nitrogen appearance RRF - Residual renal function

Our assumption is that a synergistic effect of volume overload, malnutrition and chronic inflammation may cause increase of CIMT and CA (as indirect indicators of arterial wall rigidity) together with the alteration of hemodynamic factors of blood flow before the RRT initiation.

The mechanisms for arterial stiffness in patients undergoing dialysis are as yet unclear. However,

some probable mechanisms have been considered to be involved in this pathological state, including arterial calcification, chronic volume overload, malnutrition, chronic micro-inflammation, increased mechanical stress by hypertension, sympathetic over-activity, lipid peroxidation and abnormalities of the nitric oxide system [13].

Table 2. Ultrasound measurements of heart and carotid arteries

Parameters	Baseline	12 months on PD	18 months on PD	p	
LAD (mm)	43.3±5.7	42.2±6.3	40.5±6.7	<0.001	
LVEDD	52.9±3.6	51.1±6.5	49.6±6.5	<0.001	
LVH (without/with) (n)	11/39	16/34	20/30	<0.05	
Mean CIMT(mm)	0.76 (0.6-0.9)	0.68 (0.5-0.9)	0.66 (0.5-0.8)	<0.001	
CA diameter (mm)	5.8 (5.2-6.4)	5.53 (5.0-6.0)	5.00 (4.9-5.4)	<0.05	
Plaque score	4.15 (4.2-5.4)	4.05 (3.0-5.2)	3.95 (2.9-5.1)	<0.05	
Plaque estimate (%)	≥50	≥50	≤50		
EDV cm/s	45.0 (35.0-65.0)	40.0 (33.0-50.0)	38.0 (30.0-50.0)	0.053	
PSV cm/s	130.0(110.0-158.0)	125.0(100.0-135.0)	120.0 (98.0-130.0)	0.06	
Presence of atherosclerotic plaques (n)	0 1 2 3 >3	13 14 10 8 5	18 10 7 9 6	22 7 7 8 6	0.003

Data are expressed as median (range).

Abbreviations are: LAD-Left atrium diameter; LVEDD-Left ventricular end diastolic diameter; LVH-Left ventricular hypertrophy; CIMT-Carotid intima-media thickness; CA-Carotid artery; EDV, End-diastolic velocity; PSV, Peak systolic velocity; Plaque estimate (diameter reduction) with gray-scale and color Doppler ultrasound [11]

Table 3. Correlation analysis between nutrition, inflammation, volume load parameters and ultrasound carotid arteries measurements

CA parameters Baseline	Volume parameters			Nutritional parameters			Inflammation
	LAD	SBP	RRF	Albumin	Creatinine	nPNA	CRP
	r			r			r
CIMT(mm)	0.48 ^b	0.47 ^b	-0.02	0.02	0.09	0.12	0.28 ^a
CA diameter (mm)	0.28 ^a	0.2 ^b	-0.18	-0.05	0.14	-0.13	0.51 ^b
Plaque score	0.62 ^b	0.53 ^a	-0.18	-0.05	0.1	-0.41 ^b	0.71 ^b
EDVcm/s	0.54 ^a	0.03	-0.21 ^a	-0.22 ^b	0.33 ^a	0.03	0.3 ^a
PSV cm/s	0.34 ^a	0.15	-0.17	-0.55 ^b	0.27	0.23 ^b	0.44 ^b
Presence ath. plaques	0.52	0.02	-0.29	-0.09	0.02	0.26	0.5 ^a

• ^a Correlation is significant at the 0.05 level

• ^b Correlation is significant at the 0.01 level

Abbreviations are: r- r values; CA-Carotid artery; LAD-Left atrium diameter; SBP-Systolic blood pressure; RRF-Residual renal function; nPNA-Protein equivalent of total nitrogen appearance; CRP-C-reactive protein; CIMT-Carotid artery-intima-media thickness; EDV-End-diastolic velocity; PSV-Peak systolic velocity

Although CIMT typically is seen as a marker of atherosclerosis, it also may reflect hypertrophy of the carotid medial layer. Some have suggested that carotid plaque (i.e., focal wall thickening by at least 50% of the surrounding CIMT) may be a preferable marker of atherosclerotic vascular risk [14]. The reason for the increase of CIMT in ESRD patients is probably multifactorial.

Increased stiffening of large arteries may have important clinical consequences, partly because of its relation to increased SBP and LVH [15]. The characteristics of arterial remodeling depend largely on the nature of hemodynamic stimuli, including elevated blood pressure or increased blood flow applied to the vessel wall and on the present intact endothelium [16].

In this study we confirmed that ESRD patients at the very start of PD treatment had signs of advanced atherosclerosis, which suggests that the uremia itself is an independent risk factor for functional atherosclerotic damage. The increased value of CIMT and the plaque score on CA in ESRD patients, with hemodynamic changes on the flow of blood on CA at the very start of PD, speaks about the significant presence of morphologic and functional macrovascular changes in these patients. The mentioned results agree with the previous reports by other authors and thereby support the presumption about the “accelerated atherogenesis” in ESRD patients [17].

Table 4. Multivariate linear regression analysis for independent predictors of atherogenesis and volume, nutrition and inflammation markers in PD patients

		Volume parameters			Nutritional parameters			Inflammation
		LAD	SBP	RRF	Albumin	Creatinine	nPNA	CRP
		t						
CIMT	Baseline	2.097 ^a	1.55	0.632	-4.154 ^a	7.89 ^b	-4.47 ^a	4.615 ^b
	PD (18 months)	-4.17 ^b	1.29	0.43	-2.872 ^a	4.43 ^a	-1.33	4.002 ^b
CA diameter	Baseline	1.29	0.78	0.89	7.81 ^b	-0.29	-0.89	-2.38 ^a
	PD (18 months)	2.097 ^a	2.24 ^a	0.81	3.66 ^a	0.168	0.19	-1.9 ^a
Ath.plaq.	Baseline	-2.91 ^b	0.38	0.94	-1.52	5.35 ^b	-2.37 ^a	-2.91 ^b
	PD (18 months)	-1.45 ^b	0.31	1.99	-1.80	1.07	-2.91 ^a	-2.37 ^a
EDV	Baseline	0.94	2.81 ^b	0.19	-0.89	-0.816	-0.03	-0.62
	PD (18 months)	1.21	3.13 ^a	0.29	-2.91 ^b	-0.008	0.19	-0.24
PSV	Baseline	-0.29	1.76	4.15	-0.62	0.53	-0.52 ^a	-0.89
	PD (18 months)	-0.43	1.35	3.25 ^a	-0.77	0.44	-0.82	0.163

- ^a Significant differences, p<0.05.
- ^b Significant differences p<0.01.

Included variable: Body mass index, calcium, phosphorous; total Kt/V; Peritoneal protein loss, proteinuria, CRP, albumin, creatinine, nPNA, LAD, RRF, systolic and diastolic blood pressure.

Abbreviations are: CIMT-Carotid intima-media thickness; CA-Carotid artery; EDV, End-diastolic velocity; PSV, Peak systolic velocity; LAD-Left atrium diameter, RRF-Residual renal function; SBP-Systolic blood pressure; nPNA- Protein equivalent of total nitrogen appearance; CRP-C-Reactive protein

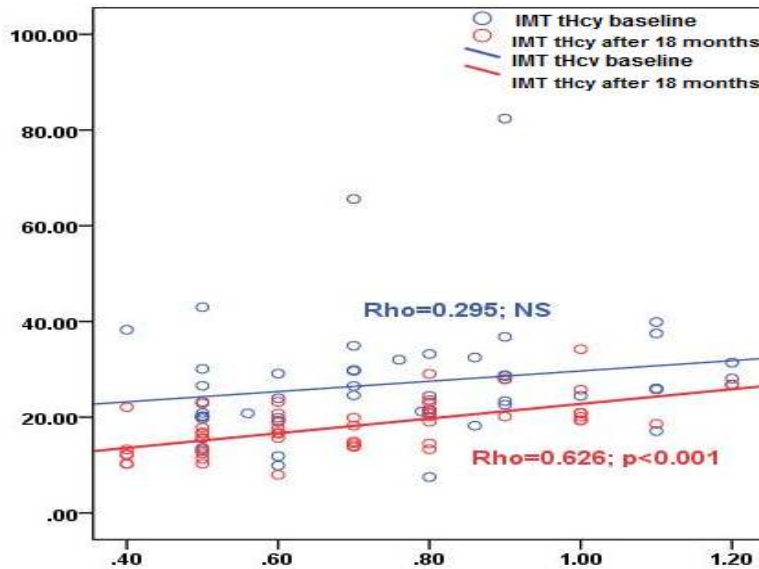


Fig. 1. Scatter chart is showing CIMT (x-axis) vs. tHcy (y-axis). Linear line of best fit is shown

Although some studies indicate that arterial structure and function became worse with time on dialysis in most patients, a few studies [18,19] report results of the regression of changes to CA. These results are consistent with our findings.

Nutritional status is evaluated by various techniques such as anthropometric and laboratory measurements. Some of these measures like serum albumin are affected by many non-nutritional factors such as increased

dialysate protein loss, an accompanying systemic illness or inflammatory disorder and hypervolemia [20].

It is generally accepted that the serum albumin level is associated with atherosclerosis, and that hypoalbuminemia is a predictor of vascular

events and cardiovascular mortality in ESRD patients. Traditionally, many authors have believed that hypoalbuminemia in ESRD patients was due to inflammation or malnutrition. In addition, there has been a tendency to link poor nutrition, albumin levels and atherosclerosis with processes causing inflammation [20].

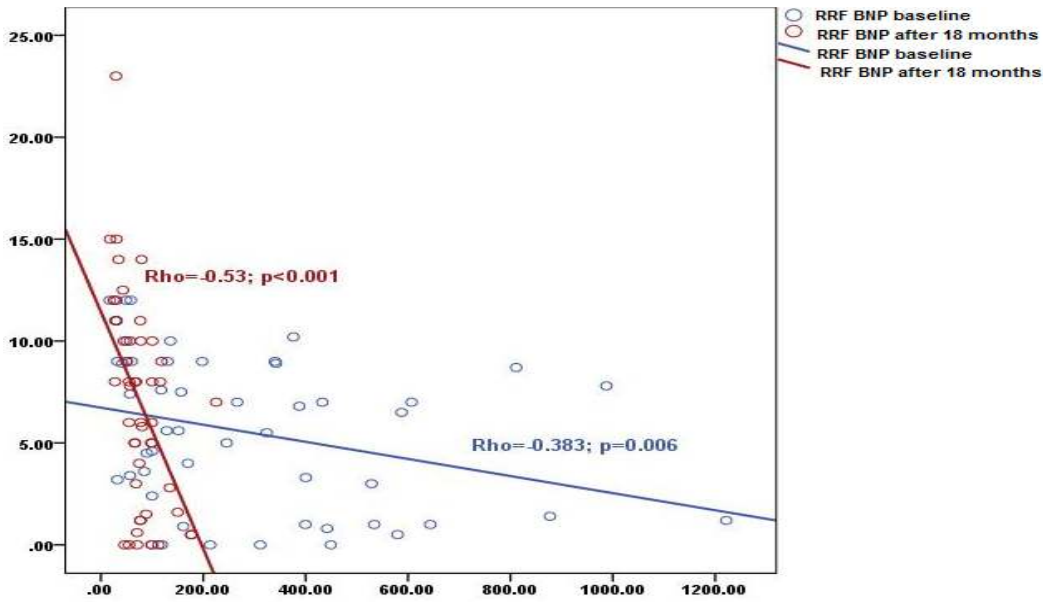


Fig. 2. Scatter chart is showing BNP (x-axis) vs. RRF (y-axis). Linear line of best fit is shown

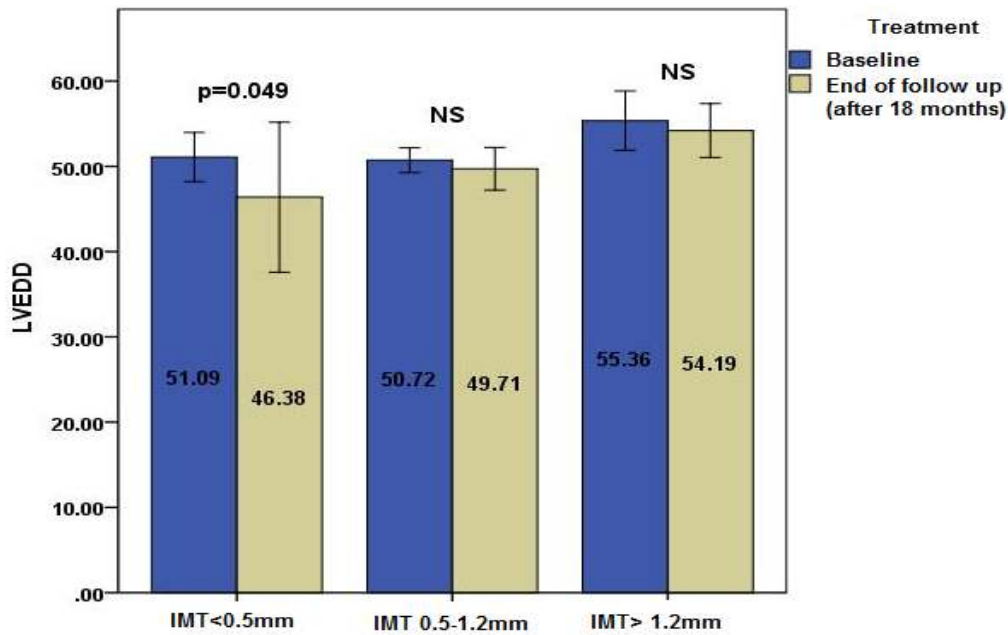


Fig. 3. LVEDD in patients with a different CIMT in 18 months follow-up

Hyperhomocysteinemia is frequently found in uremic subjects and has demonstrated as a potent indicator of mortality in the previous studies [21,22]. However, we haven't found independent association between plasma homocysteine (Hcy) and CA diameter and presence of atherosclerotic plaques on CA, neither is proven an independent prediction of Hcy on CIMT in this study. The reasons for this relative „minor“ role of Hcy are unknown, but they can partly be caused by good nutritional status in our patients. In this study median serum albumin before RRT initiation was 30.9 ± 2.6 g/L, while after 18 months of PD treatment it amounted 31.5 ± 3.2 g. Serum albumin is the main carrier of circulating tHcy. Blood tHcy is strongly related to albumin, nutritional status, and dietary protein intake in dialysis patients, indicating that well-preserved nutritional status may influence the impact of tHcy on vascular system [23]. In addition, our study may not have enough population to demonstrate the complete effect of tHcy on CA remodeling.

The results which show significantly better nutritional status of patients after 18 months of PD, estimated using nPNA and serum albumin as well as significantly lower protein loss by the urine and dialysis effluent, deserve special attention. At the end of the follow-up period dialysis adequacy, estimated by Kt/V_{urea} , was satisfactory, compared to Kt/V_{urea} after 6 months of PD treatment.

This study showed no dependence of CA changes on transport characteristics of peritoneum, proteinuria and dialysis effluent protein loss which is in accordance with the research of Rodrigues and associates [24], who ascertained that the increased mortality of PD patients did not depend of peritoneal permeability but was probably the result of associated comorbidity, basic atherosclerosis, volume overload, chronic inflammation, and humoral abnormalities in uremia. The same authors have concluded that peritoneal transport characteristics are primarily dependent of the vasoactive intermediate compounds concentration, produced by mesothelium [25].

The role of the RRF is especially important in PD patients. The decrease in RRF is closely related to the volume overload, anemia, inflammation, malnutrition, and eventually increased morbidity. The reduction of creatinine clearance is very much associated with endothelial dysfunction and arterial rigidity [26] in patients with CKD,

which indicates that that the kidney function plays an important role in the protection of blood vessels. Due to the results of our study, we have concluded that RRF is an independent predictor of CA diameter, CIMT and presence of atherosclerotic plaques but not the predictor of other functional parameters of CA in patients after 18 months of PD treatment.

Furthermore, RRF plays an important role in maintaining the nutritional status of patients on chronic dialysis. In an international study, loss of RRF correlated with muscle wasting and contributed to anorexia and the symptoms of severe malnutrition [27]. Likewise, a progressive decrease of nutritional parameters with declining RRF was observed 6 months after PD initiation in the CANUSA multicenter study [28]. Hence, preserving RRF should be an important goal.

The criteria for clinical volume overload are somewhat arbitrary. The extension of cardiac cavities can be caused not only by overhydration but it can also be the manifestation of the cardiac failure. This is especially true of related to LAD because diastolic dysfunction (left ventricular stiffness) may impair atrial emptying during diastole. Our study has shown a significant difference in the LAD and LVEDD before and 18 months after PD treatment commencement. This result could be explained not only by adequate dialysis with preserved RRF and maintained nutritional status but also by the fact that study did not include anuric patients.

It is also necessary to point out significant negative correlation between BNP and RRF over the study period. This indicates that BNP has an important role in the assessment of volume overload in PD patients, together with well-known role in the prediction of subsequent cardiac events and mortality in the dialysis population. Similar findings were shown in the study of Papakrivopoulou et al. [29].

Many studies have confirmed a close association between cardiovascular disease and inflammation in dialysis patients [30-32]. In accordance with previous reports, the present study demonstrated a significant association between CA changes and CRP values. C-reactive protein is a valuable independent surrogate marker for atherosclerotic vascular damage.

Our results have shown that PD treatment contributes to the correction of traditional and uremia-related cardiovascular risk factors, in

comparison to the period prior PD commencement. In this study, CA structural and hemodynamic changes are well correlated with markers of nutrition (serum albumin, nPNA), inflammation (serum CRP) and volume load (LAD, RRF, SBP) in PD patients and they confirm the results of previous studies [17,33].

Although our findings look intriguing, one should consider several limitations of this study. The number of patients studied was relatively small, which did not permit firm conclusions about differences between monitored parameters prior and 18 months after PD commencement. Furthermore, patients with diabetes mellitus were not separately observed. Since modern methods were unavailable to us (bioimpedance as markers for body composition and hydration status) and were not monitored skin-fold thickness, we used clinical criteria, including echocardiography, to assess the volume status which might be another study limitation. Thirdly, longer period of monitoring is needed in order to estimate a clear effect of PD and there is also a need for observation of PD patients after kidney transplantation.

Finally, our findings suggest that we can perform assessment of different parameters with different forms of measurement. Evaluation of vascular changes should be performed globally by the criteria that combine different measurements, using the changes in monitored parameters in a dynamic way. Further studies will be needed to establish a new definition or clinical scoring system for atherogenesis risk stratification of PD patients.

Furthermore, CA remodeling is related to LVEDD and LAD which suggests that some cardiac and vascular changes in PD patients may occur in parallel. Large prospective studies are further required to establish the link between these parameters and the complexity of coronary artery disease in PD patients.

5. CONCLUSIONS

We have found a close relationship between hemodynamic and structural CA changes and markers of poor nutrition, inflammation and hydration status in PD patients.

Monitoring of markers of inflammation, malnutrition, volume load in the last stages of CKD provides important information about changes in the vascular tree, which enables

timely starting RRT. PD is a good choice of modality in the first year of dialysis treatment and it can slow down the accelerated atherogenesis process on potentially reversible risk factors as well as make the optimal conditions for the most important goal-kidney transplantation.

CONSENT

All authors declare that 'written informed consent was obtained from the patient (or other approved parties) for publication of this paper and accompanying images.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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