Endothelial dysfunction in uremic patients on continuous ambulatory peritoneal dialysis (CAPD)

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Abstract

Endothelial dysfunction is associated with diabetic micro- and macroangiopathy as well as with the decline in creatinine clearance. It has been suggested that endothelial dysfunction presents in patients (pts) on continuous ambulatory peritoneal dialysis (CAPD). The objective of this study was to examine the plasma biomarkers of endothelial dysfunction and their association with IMT of carotid arteries in diabetic and non-diabetic patients on CAPD. This study included 37 CAPD pts (25 with type II diabetes and 12 non-diabetic pts) mean age 59.2 years ± 2.48. Plasma von Willebrand factor (vWF) activity, serum albumin, glucose, total cholesterol, triglycerides and lipoprotein (a) levels, as well as serum level of homocysteine, parathyroid hormone (PTH) in plasma and microalbuminuria was determined. Ultrasound examination of carotid arteries was performed in all patients by measured bilateral intima-media thickness of carotid artery (CIMT). Mean IMT value was significantly higher in type 2 DM patients (0.86 ± 0.04 mm) compared to non-diabetic patients (0.52 ± 0.06 mm) on peritoneal dialysis (p<0.0001). There was also a significant difference in lipids /triglycerides and Lp (a)/, procoagulation (fibrinogen, von Wilebrand factor, factor VIII) and inflammatory markers (CRP) level between type 2 DM and non-diabetic CAPD patients. A stepwise multiple regression analysis revealed that log triglycerides and factor VIII were independent factors for the IMT. The results of this research impose that diabetic type 2 CAPD patients have developed systemic alteration of endothelial function and higher risk of cardiovascular complications compared to non-diabetic CAPD patients.

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KEY WORDS: CAPD patients, endothelial dysfunction

INTRODUCTION

Due to the significant increase in cardiovascular morbidity and mortality in patients with terminal renal failure, yet more than two decades ago, it was hypothesized about "accelerated atherosclerosis" in such patient population. Non-invasive method of ultrasound examination has found wide application in the general population to identify high-risk patients for cardiovascular incidents and asymptomatic atherosclerosis [1], and ultrasound of the carotid artery has served as a useful predictor of systemic atherosclerosis [2]. In recent years, many studies have confirmed the high prevalence of atherosclerotic lesions in blood vessels of uremic patients [3, 4] with the impossibility of a full explanation of their occurrence by the traditional risk factors, often present in these patients. Factors of atherosclerotic disease in chronic renal disease, primarily in its terminal stage, significantly coexist with other cardiovascular risk factors in the development and progression of vascular complications. Chronic renal disease with creatinine clearance below 90 ml/min for a period longer than three months, regardless of the cause by which it is induced, has been recognized as an important factor that affects the integrity of the endothelium and the occurrence of endothelial dysfunction. Impaired complex endothelial function is manifested by changes in concentration and activity of some vasoactive substances, such as von Willebrand factor (vWF), factor VIII, fibrinogen, homocysteine. Changes in intima-media thickness (IMT) of carotid arteries are a reflection of the morphological changes in the endothelium of blood vessels. Recent studies suggest that measuring the concentration of specific vasoactive substances, or biomarkers in plasma, such as von Willebrand factor, factor VIII, fibrinogen, homocysteine, along with traditional and uremia specific risk factors, can predict the existence of endothelial dysfunction and development of micro and macrovascular changes [5, 6]. Vascular endothelial dysfunction is a significant factor in the pathogenesis of diabetic micro-and macroangiopathy. On the other hand, the decline in creatinine clearance is associated with endothelial dysfunction and development of coronary and generalized atherosclerosis. In the study, Yilmaz et al. [7], which included 400 patients at different stages of chronic kidney disease, endothelial dysfunction was confirmed in all stages of chronic kidney disease, with a strict correlation with the degree of reduction in glomerular filtration rate. It remains

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unclear how present is endothelial dysfunction in uremic patients on continuous ambulatory peritoneal dialysis (CAPD) and whether the prevalence of endothelial dysfunction in this category of patients depends on the presence of diabetes. The aim of this study was to examine the concentration of fibrinogen, von Willebrand factor, factor VIII and homocysteine in plasma as biomarkers of endothelial dysfunction and their association with IMT of carotid arteries in diabetic and nondiabetic patients on CAPD, as well as the correlation of IMT with uremia associated and other traditional risk factors inherent in the presence of vascular endothelial dysfunction, which, with its endocrine and paracrine function, represent an important organ in maintaining cardiovascular homeostasis.

MATERIALS AND METHODS

Patients

This study included 37 stable uremic patients on CAPD, 25 with type II diabetes and 12 non-diabetic patients (29 M, 16 F, mean age 59.2 years ± 2.48) from Outpatient Department of Clinic for Nephrology, CCU Sarajevo. In the study have not been included patients who were on CAPD shorter than 3 months, patients with congestive heart disease and patients with manifest peripheral blood vessels disease of inflammatory or idiopathic nature, as well as those who have not signed informed consent. The study was performed in period from 1st of January to the 30th of June 2010. The average duration of dialysis treatment in these patients was 30.1 ± 3.6 months of dialysis. Patients were evaluated by standard physical examination, laboratory tests and ultrasound examination of carotid arteries. All patients included in the study signed upon informed consent with careful explanation of the study procedures. Approval for the study was obtained by the local Ethics Committee (Ethical committee approval N° 0305-18501; 24.06.2009). All procedures on human subjects were performed in accordance with the latest version of Helsinki Declaration.

Methods

Design of study and measurements

The study was designed as a cross-sectional comparison between CAPD patients with type II DM and nondiabetic CAPD patients. Blood pressure was measured and venous blood samples were taken in the morning on an empty stomach.

Laboratory procedures

vWF activity was assessed by standard ristocetin-dependent platelet aggregation procedure, using reagents such as BC von Willebrand reagent (Dade Behring, USA). Serum albumin, glucose, total cholesterol, triglycerides and lipoprotein (a) /Lp(a)/ levels were measured by quantitative kinetic spectrophotometric method using a computerized autoanalyzer AXION (Menheim Boehringer, Germany) and reagents from Boehring diagnostics. Level of homocysteine in serum was determined by enzyme immunoassay technique on the appliance Abbott AxSYM, Germany. The level of parathyroid hormone (PTH) in plasma was measured by RIA method. Microalbuminuria was determined by nephelometry.

Ultrasound of carotid artery

In all CAPD patients high-resolution B-mode ultrasound examination of common carotid artery an ATL 7000 ultrasound machine equipped with 12-5 MHz transducer was applied. Intima-media thickness of carotid artery (CIMT) was measured in all patients 1 cm above the carotid bifurcation. IMT diameters were calculated as the average by bilateral IMT measured diameter. Carotid atherosclerosis was defined if a CIMT is greater than 0.8 mm and / or if there is presence of carotid plaque that protrudes more than 1.3 mm in the vascular lumen [8].

Statistical analysis

Each value was expressed as the mean ±SE. Differences between two groups were analyzed by the Mann-Whitney test. Univariate correlation coefficients were determined by Pearson analysis. A stepwise multiple regression analysis was applied to examine the relationship between IMT and a set of clinical parameters including age, glucose, duration of PD treatment, blood pressure (MBP), hemoglobin, cholesterol, log-triglycerides, log-Lp(a), Von wilebrand factor, factor VIII, log-fibrinogen, homocysteine, albumin, microalbuminuria, intact parathyroid hormone (PTH), calcium, phosphate, calcium phosphate, CRP. Since triglycerides, fibrinogen and Lp(a) were non-normally distributed in this study, we normalized these data by log transformation before entering a stepwise multiple regression. The significant independent variables were ordered according to their standardized effect, defined as regression coefficient/standard error of the regression (β). *P* values less than 0.05 were considered statistically significant. All statistical calculations were performed with the SPSS 16 software (version 16.0, SPSS Inc, Chicago, Illinois, USA).

RESULTS

Baseline characteristics of the patients included in the study are shown in Table 1. Mean values of intima media thickness, lipids, procoagulant and inflammatory markers in serum of patients on peritoneal dialysis are shown in Table 2. Type 2 DM was observed in 67.6%, while hypertension was observed in 72.9% of patients on PD. Mean IMT value was significantly higher in type 2 DM patients (0.86±0.04 mm) compared to non-diabetic patients (0.52 ± 0.06 mm) on peritoneal dialysis (p<0.0001) (Figure 1).

TABLE 1. Baseline characteristics of the patients on peritoneal dialysis.

Age (years)	59.2±2.48
Duration PD (months)	30.1±3.6
SBP (mmHg)	149.3±3.1
DBP (mmHg)	86.1±1.54
Hgb (g/L)	112.0±1.9
Albumin (g/L)	34.0±0.5
Microalbuminuria (mg/L)	434.5±89.5
Calcium (mmol/L)	2.27±0.02
Phosphate (mmol/L)	1.54±0.02
CaxP product	3.5±0.08
PTH (pg/mL)	243.1±34.5
Homocysteine (μmol/L)	21.3±1.1

Data are presented as mean ± SE; SBP - systolic blood pressure, DBP - diastolic blood pressure; Hgb -haemoglobin; CaxP - product of calcium and phosphate, PTH - parathyroid hormone

TABLE 2. Mean values of intima media thickness, lipids, procoagulant and inflammatory markers in serum of patients on peritoneal dialysis.

IMT (mm)	0.75 ± 0.04
Cholesterol (mmol/L)	6.34 ± 0.22
Triglycerides (mmol/L)	2.73 ± 0.2
Lp (a) (mmol/L)	0.26 ± 0.04
Fibrinogen (mg/mL)	8.3 ± 0.85
Von Wilebrand factor	154.2 ± 5.5
Factor VIII (ng/mL)	183.4 ± 4.2
CRP (mg/L)	7.85 ± 1.16

Data are presented as mean ± SE; Lp(a) - lipoprotein a, CRP - C-reactive protein

TABLE 3. Comparison of clinical characteristics, intima media thickness (IMT), lipids, procoagulant and inflammatory markers in patients on peritoneal dialysis (PD) with or without diabetes mellitus type 2 (DM2).

	DM2 PD group	non-DM2 PD group	*p*-value
Duration PD (months)	26.0±2.5	38.7±9.5	NS
SBP (mmHg)	153.4±3.1	140.8±6.5	NS
DBP (mmHg)	84.6±1.8	89.2±2.8	NS
Hgb (g/L)	109.3±2.0	117.6±3.7	NS
Albumin (g/L)	34.0±0.6	34.2±0.85	NS
Microalbuminuria (mg/L)	551.7±111.3	112.1±44.9	0.002
Calcium (mmol/L)	2.3±0.03	2.2±0.23	0.022
Phosphate (mmol/L)	1.56±0.03	1.49±0.04	NS
CaxP	3.6±0.1	3.3±0.1	0.015
PTH (pg/mL)	243.9±38.4	241.4±72.7	NS
Homocysteine (μmol/L)	21.6±1.1	20.8±2.5	NS
Cholesterol (mmol/L)	6.4±0.3	6.14±0.45	NS
Triglycerides (mmol/L)	3.1±0.3	1.9±0.1	0.006
Lp(a) (g/L)	0.32±0.05	0.15±0.03	0.014
Fibrinogen (g/L)	9.6±9.2	5.7±0.5	0.004
Von Wilebrand factor (%)	169.0±4.8	124.0±9.0	0.0001
Factor VIII (%)	195.4±3.8	158.5±4.9	0.0001
CRP (mg/L)	9.7±1.6	4.3±1.1	0.017

Data are presented as mean ± SE; SBP - systolic blood pressure, DBP - diastolic blood pressure; Hgb -haemoglobin; Lp(a) - lipoprotein (a), CRP - C-reactive protein, CaxP - product of calcium and phosphate, PTH -parathyroid hormone, NS - not significant

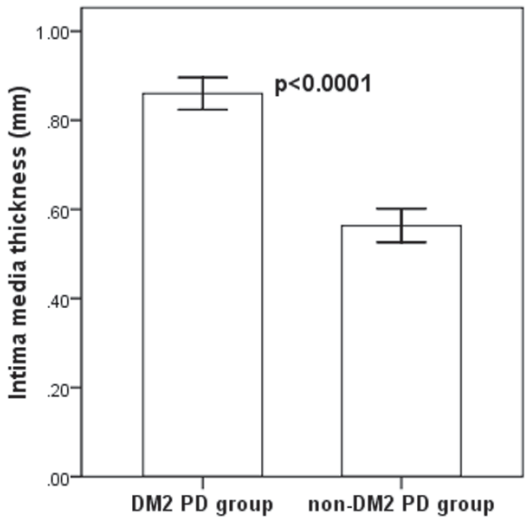

FIGURE 1. Intima media thickness values in patients on peritoneal dialysis (PD) with and without type 2 diabetes mellitus (DM 2). The bars represent mean and error bars represent SE.

There was also a significant difference in lipids, procoagulation and inflammatory markers level between type 2 DM and non-diabetic peritoneal dialysis patients. Patients on PD with type 2 DM had significantly higher mean serum concentration of triglycerides (3.1±0.3 mmol/L) and Lp(a) (0.32±0.05 g/L) compared to PD patients without type 2 DM (1.9±0.1 mmol/L and 0.15 ± 0.03 g/L, respectively). Also, mean plasma fibrinogen, von Wilebrand factor, factor VIII and CRP concentrations were significantly higher in type 2 DM patients on PD (9.6 ± 9.2 *vs.* 5.7 ± 0.5 g/L, p=0.004; 169.0 ±4 .8 *vs.* 124.0 ± 9.0 %, p= 0.0001 and 195.4 ± 3.8 *vs.* 158.5 ± 4.9 %, p=0.0001; 9.7 ± 1.6 *vs.* 4.3 ± 1.1 mg/L, p=0.017, respectively) (Table 3). In our study, there was a significant positive relationship between IMT values and age (r=0.49, p=0.002), log-triglycerides (r=0.49; p=0.003)(Figure 2A), log-Lp(a) (r=0.37; p=0.025), factor VIII (r= 0.553; p<0.001)(Figure 2B), Von Willebrand factor (r=0.48; p =0.003)(Figure 2C), glucose (r=0.43; p =0.009) and CaxP product (r=0.34; p =0.048) in patients on peritoneal dialysis. Positive relationship between IMT and microalbuminuria (r=0.327; p =0.083), serum calcium (r=0.3; p =0.08) and CRP concentration (r=0.32, p=0.064) was observed, but it did not reach statistical significance. A stepwise multiple regression analysis revealed that log triglycerides and factor VIII were independent factors for the IMT (Table 4).

TABLE 4. Stepwise multiple regression analysis of the carotid intima-media thickness for the determinants of independent factors

	Unstandardized Coefficients		Standardized Coefficients		*p*-value
	B	SE	Beta	t	
Factor VIII	0.004	0.001	0.437	2.979	0.005
Log-triglycerides	0.385	0.174	0.324	2.211	0.034

Dependant variable-IMT; R^2-0.396

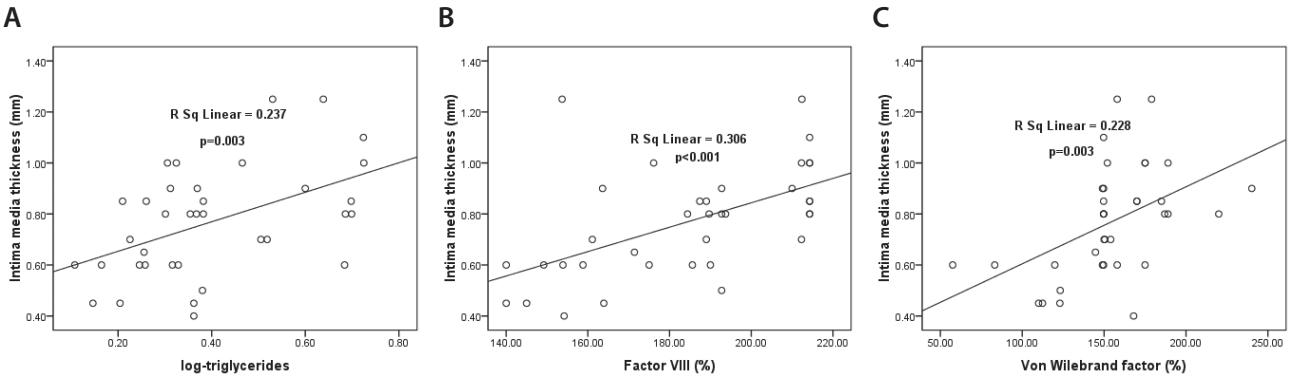

FIGURE 2. Relationship between intima media thickness and logarithmically transformed triglycerides (log-triglycerides) (A), factor VIII (B) and Von Wilebrand factor (C) in patients on peritoneal dialysis

DISCUSSION

Epidemic increase in the incidence of chronic kidney disease in the world is the result of the global pandemic of type 2 diabetes, associated with a high prevalence of metabolic syndrome, and diabetic kidney disease. In diabetic patients endothelial dysfunction is the earliest event that precedes the alteration of endothelial integrity and the appearance of micro- and macrovascular complications [9, 10]. Previous studies have shown that the arterial vascular disease and hypertrophy of the left ventricle are the main causes of high cardiovascular mortality in dialysis patients [11]. Atherosclerosis is the most common pathological process leading to cardiovascular disease. It is a disease of intima of blood vessels, for which has been proven that it starts with endothelial dysfunction, progression of plaque formation and accumulation of macrophages, the formation of fibrous caps and the presence of necrotic core. Recent studies indicate a link between endothelial dysfunction and hypertension, on the one hand [12, 13] and loss of renal function, on the other hand [14]. In patients on peritoneal dialysis arterial diseases are characterized by a high level of calcification in the arterial wall, in response to hemodynamic humoral abnormality in chronic uremia, which leads to the increased stiffness of large arteries like the aorta and common carotid arteries (CCA), especially loosing elasticity of arteries [15]. Results of our study have shown that mean IMT value was significantly higher in type 2 DM patients compared to non-diabetic patients on peritoneal dialysis, with significantly higher levels of microalbuminuria, calcium, Ca x P product, as well as a significant difference in lipids / triglyceride, Lp (a)/, procoagulation markers (von Willebrand factor, factor VIII) and inflammatory markers (CRP) in type 2 DM patients compared to non-diabetic patients on peritoneal dialysis, which supports the concept of malnutrition-inflammation-atherosclerosis syndrome [16]. The development of endothelial dysfunction in type 2 diabetes mellitus involved hyperglycemia, insulin resistance, impaired lipid metabolism and metabolism of lipoproteins, and oxidative stress [17]. Hyperglycaemic recurrent episodes, with the accumulation of advanced glycation end products (AGEs) and the induction of plasminogen activator inhibitor type-1, lead to a chronic endothelial dysfunction [18]. Elevated glucose level stimulates the synthesis of growth factors and vasoactive substances, contributing to increased permeability of endothelial cells and indirect disruption of their functions. It has been shown that endothelial function in diabetics is being disturbed by components of the metabolic syndrome [19], particularly pronounced in patients on CAPD. Therefore, the search for biomarkers of endothelial dysfunction is an important step in improving the diagnostic and therapeutic approach in these patients. Numerous studies indicate that the von Willebrand factor is a biomarker of endothelial dysfunction. Von Willebrand factor is primarily synthesized in endothelial cells and released into circulation when endothelial integrity is compromised by harmful same agents. This factor, inducted from endothelial cells, rapidly binds to collagen fibres at the site of vascular damage. Action of shear stress is a subject of conformational change, by which it becomes a substrate for adhesion and aggregation of platelets. Bongers et al. [20], were examining a number of biological markers, and have found that vWF is also an indicator of risk for coronary heart disease and stroke. Chronic renal failure is recognized as a clinical situation which imposes the greatest risk for endothelial integrity. Systemic endothelial dysfunction appears in the early stages of chronic kidney disease, increasing the risk of cardiovascular morbidity and mortality in patients with chronic kidney disease [21]. In patients with chronic renal insufficiency elevated levels of vWF were found [22]. Our results indicate that the von Willebrand factor is increased in CAPD patients with type 2 DM, as well as intima-media thickness. Triglycerides and factor VIII were independent predictors of carotid intima-media thickness, presenting a strong surrogate of endothelial dysfunction and atherosclerosis in these patients. Dyslipidemia with hyperglycaemia contributes to endothelial dysfunction, the earliest stage of atherosclerosis, as well as the

inflammatory process in the atherosclerosis, by presenting higher concentration of fibrinogen and CRP value in CAPD patients with type 2 DM in our study. We found a statistically significant correlation between microalbuminuria and intima-media thickness which indicates the close relationship between microalbuminuria and endothelial dysfunction. Previous studies suggest that endothelial dysfunction may be a link between microalbuminuria and cardiovascular disease [23]. Many peritoneal dialysis patients already have significant vascular lesions before initiating dialysis in response to humoral abnormality in chronic ureamia. This study has confirmed that carotid ultrasonography is one of the useful non-invasive imaging techniques for the assessment of intima-media thickness, which is in strong relationship with values of biomarkers of endothelial dysfunction. Endothelial dysfunction in CAPD patients is especially expressed in patients with type 2 diabetes. Existent endothelial dysfunction in diabetic kidney disease may have additive effects on cardiovascular risk and therefore the endothelial function tests must be accepted as a valid parameter of cardiovascular pathology assessment in these patients.

CONCLUSION

In conclusion, the results of this research impose that factor VIII and triglycerides are independent predictors of intima-media thickness. IMT is significantly higher in DM type 2 patients on CAPD in comparison to non-diabetic patients on CAPD. Significantly higher values of von Willebrand factor and triglycerides in CAPD patients with DM type 2 compared to the same in non-diabetic patients impose that diabetic patients have developed systemic alteration of endothelial function and higher risk of cardiovascular complications compared to non-diabetic CAPD patients.

DECLARATION OF INTEREST

The authors declare no conflict of interest for this study.

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