

Endothelial Function, Subclinical Atherosclerosis and Serum Inflammatory Markers in Chronic Kidney Disease

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Selected Abbreviations and Acronyms

AVD: atherosvascular disease

CKD: Chronic kidney disease

FMD: flow mediated dilation

Hb: haemoglobin

HDL: high density lipoprotein

ICAM- 1: intracellular adhesion molecule 1

IL-6: interleukin 6

IMT: intima-media thickness

LP (a): lipoprotein (a)

Ns: not significant

PDRF: predialysis renal failure

PTH: parathyroid hormone

s-CRP: sensitive C-reactive protein

TG: triglycerides

TNF- α : tumour necrosis factor alpha

U- albumin flow: urine albumin flow

VCAM-1: vascular cellular adhesion molecule 1

Abstract

Background: Chronic kidney disease (CKD) is a major risk factor for developing atherosclerotic vascular disease (AVD), which plays a major role in causing morbidity and mortality in these patients.

Objectives: The aim of this study was to investigate endothelial dysfunction, subclinical atherosclerosis and inflammatory activity in patients with CKD stages 3-4 compared to a population-based control group.

Design: The study groups consisted of 35 controls and 50 predialytic renal failure (PDRF) patients. Flow-mediated dilatation (FMD) and intima-media thickness (IMT) in the brachial artery was measured by B-mode high-resolution ultrasound.

Setting: University hospital.

Results: IMT was significantly increased in the PDRF patients compared to the controls (0.43 ± 0.06 vs. 0.34 ± 0.05 ; $p < 0.001$). However there was no significant difference in FMD between the study groups (0.047 ± 0.04 vs. 0.053 ± 0.05 ; $p: \text{Ns}$). VCAM-1, ICAM-1 and TNF- α were higher in the PDRF group compared to the control group ($p < 0.05$). IMT was significantly associated ($p < 0.05$) with haemoglobin, creatinine, phosphate and IL-6 in the PDRF group and FMD was significantly ($p < 0.05$) negatively associated with fibrinogen, TNF- α and IL-6 and positively associated with triglyceride levels in the PDRF group.

Conclusion: PDRF patients have increased IMT, fibrinogen and inflammatory activity compared to the control group. IL-6 was associated with an increased IMT and a poorer endothelial function.

Key words: atherosclerosis, predialytic kidney failure, endothelial function, flow-mediated dilatation, intima-media thickness, VCAM-1, ICAM-1 TNF- α , IL-6.

Introduction

Cardiovascular mortality and morbidity is significantly increased among patients with chronic kidney disease (CKD). It is estimated that the risk of atherosclerotic vascular disease (AVD) in this group is 10-20-fold higher than in the general population [1-3]. Studies have reported an impairment of endothelium dilatation in CKD patients [4-6]. The endothelium has an important role in the initiation of atherosclerosis. By damage to the endothelial wall, the nitric oxide (NO) production decreases, and consequently the endothelium- dependent vasodilatation is impaired. This is an early key event in atherogenesis [7, 8]. Atherosclerosis is an inflammatory process, and atherogenic factors such as hypertension, hyperlipidemia and hyperglycemia are among the major variables, which can lead to endothelial dysfunction, which again is manifested by overproduction of selective adhesion molecules such as vascular cellular adhesion molecule (VCAM- 1), and intracellular adhesion molecule (ICAM- 1). These factors facilitate leukocyte and monocyte adhesion. Monocytes transform into macrophages and phagocytose oxidized LDLs. Consequently foam cells arise which attract cytokines such as tumor necrosis factor alpha (TNF- α) and interleukin 6 (IL-6). These activate and recruit inflammatory cells. In addition IL-6 stimulates synthesis of acute phase proteins by the liver, especially CRP and fibrinogen [9]. High levels of acute- phase proteins have been recognized as a leading associated factor with mortality in renal failure patient populations [10]. It is possible to measure serum levels of inflammatory markers to detect an inflammation process. By using an ultrasonographic method, it is possible to measure flow mediated dilatation (FMD) and intima- media thickness (IMT) to detect endothelial dysfunction and asymptomatic atherosclerosis [11-13].

Our goal was to compare the endothelial functional and subclinical atherosclerosis in predialytic renal failure disease (PDRF) patients and control subjects, and to consider whether there exist a relationship between serum inflammatory markers and asymptomatic atherosclerosis in the PDRF patient group.

Methods

Subjects

All subjects gave informed consent after written and oral information. The ethics committee of the Karolinska University Hospital Huddinge (Stockholm, Sweden) approved the study. PDRF patients were recruited from the renal outpatient clinic Karolinska University Hospital. PDRF patients (42 men; age 59 ± 14 yr [range 27 to 80 yr]) with stages 3 to 4 CKD (median GFR 30 ml/min per 1.73 m^2 ; range 15 to 52 ml/min per 1.73 m^2). Exclusion criteria for the present study were, in addition to unwillingness/inability to participate in the study procedures, clinical signs of acute infection, active vasculitis and liver disease at the time of evaluation. The causes of CKD were chronic glomerulonephritis in 13 (26 %) patients, diabetic nephropathy in 7 (14 %) patients, polycystic kidney disease in 3 (6 %) patients, interstitial nephritis in 2 (4 %) patients, nephrosclerosis in 10 (20 %) patients, and other or unknown in 15 (30 %) patients.

Presence of clinical CVD was defined by medical history and clinical symptoms and/or findings of cardiac, cerebrovascular (stroke), and/or peripheral vascular disease. A total of 14 (28 %) patients had a clinical history or signs of cardiovascular, cerebrovascular, and/or peripheral vascular disease at the start of the study. Most patients were on antihypertensive medications as well as other commonly used drugs in patients with CKD, such as phosphate and potassium binders; diuretics; erythropoiesis-stimulating agents; iron substitution; lipid-lowering medication; and vitamins B, C, and D supplementation.

A population-based randomly selected group of 35 control subjects (25 men; age 62 ± 13 yr [range 29 to 81 yr] were used for comparative analyses of biochemical and metabolic parameters. The control group comprised individuals who accepted to participate as

volunteers, in response to an invitation sent to randomly selected individuals in the Stockholm region by Statistics Sweden. The control subjects were investigated according to a similar protocol and simultaneously as the patients. No other exclusion criteria than unwillingness to participate in the study were applied in the selection of the healthy controls.

Measurements

After an overnight fast, venous blood samples were drawn and stored at -80°C for biochemical analyses. Serum vascular cellular adhesion molecule-1 VCAM-1 and ICAM concentrations were measured by using commercially available ELISA kits (R&D System, Minneapolis, MN). The serum levels of IL-6 and TNF- α were quantified on an Immulite automatic analyzer (Diagnostic Products Corp., Los Angeles, CA). Serum cholesterol and triglyceride levels were analyzed by means of standard enzymatic procedures (Roche Diagnostics, Mannheim, Germany). HDL cholesterol level was determined after precipitation of apolipoprotein B-containing lipoproteins by using phosphotungstic acid. Serum albumin (bromocresol purple method), hs-CRP, creatinine, urea, and hemoglobin and urinary creatinine and urea were determined by routine procedures at the Department of Clinical Chemistry, Karolinska University Hospital Huddinge. GFR (corrected for body surface area) was estimated using iohexol clearance.

Assessment of FMD and IMT in brachial artery

The ultrasound procedures for assessing endothelium-dependent FMD were performed as described in the international guidelines by Corretti et al. (14). The subjects were examined in the morning after an overnight fast. They were told not to use long-acting nitroglycerin or calcium channel blocking drugs 36 hours before the examination. A high-resolution ultrasound scanner (System Five, GE Vingmed, Horten, Norway) with a 10.0-MHz linear array transducer was used. After 10-minute equilibration period at rest in the recumbent

position, a single dedicated ultrasonographer performed measurements of the left brachial artery FMD proximal to the antecubital fossa. The scans were saved on videotape. Baseline diameter recordings were obtained after which arterial occlusion was performed by inflating a forearm blood pressure cuff (12, 5 cm wide) to 250 mmHg for 4.5 min. After cuff-release, diameter recordings were repeated during the post-occlusive increase in brachial artery blood flow. The complete experimental sequence was performed twice at 30 minutes intervals. Images were digitally acquired from the videotape and measured in random order by a single observer blinded to the conditions under which the ultrasonographic images were obtained. Measurement of the brachial artery diameter was defined as the distance from the leading edge of the near wall intima-lumen echo to the leading edge of the far wall lumen-intima echo along a line perpendicular to the artery's long axis. A computer system (15) with automated tracing of echo interfaces and measurements of distances between the wall echoes within a 5 mm long section of the brachial artery was used. Brachial artery diameter was calculated in diastolic frames taken coincidentally with the R wave on the electrocardiogram twice at rest and then 45, 60 and 75 seconds after cuff deflation. Mean of the diameters after 45, 60 and 75 seconds was calculated. Diameter changes were expressed as the percentage change relative to the mean baseline value. The mean of two FMD examinations was used. The intima-media thickness of the brachial artery was defined as the distance between the leading edge of the lumen-intima echo and the leading edge of the media-adventitia echo in the far wall. The lumen diameter was defined as the distance between the leading edge of the intima-lumen echo of the near wall and the leading edge of the lumen-intima echo of the far wall. The differences between repeated measurements of intima-media thickness, lumen diameter and FMD, by using the automated analysing system, were 3.0 %, 1.4 % and 5.5 % (coefficient of variation), respectively.

Statistical analysis

All data are presented as mean \pm SD or percentage (%). Unpaired student t-test was used to analyze differences among the study groups. Nonparametric Spearman's rank correlation test was used in the correlation analysis. A p value < 0.05 was considered statistically significant.

Results

Table 1 shows the demographic characteristics of the PDRF patients and controls. There were no differences with respect to gender, age, troponin T and I, cholesterol, Apo A, Apo B, LP (a), U- albumin flow, arginin or glucose in these two groups. However, the PDRF patients were significantly heavier and taller. Moreover, they had lower Hb ($p < 0,001$), higher urea ($p < 0,001$), higher creatinine ($p < 0,001$), lower albumin ($p < 0,001$), higher Ca^{2+} ($p < 0,001$), higher phosphate ($p = 0,001$), higher PTH ($p < 0,001$), higher fibrinogen ($p < 0,001$), lower HDL-cholesterol ($p < 0,001$), higher TG ($p < 0,001$) and lower iohexolclearance ($p < 0,001$) compared to the control group (table 1). As expected due to the fact that they had kidney failure, the PDRF patients differed from the control group with respect to several parameters as shown in table 1.

As it is presented in Table 2, PDRF patients have significantly higher VCAM-1 ($p = 0,00$), ICAM-1 ($p = 0,04$) and TNF- α ($p = 0,00$) than controls. However s- CRP and IL-6 were not significantly increased in the patient group compared to the controls.

Differences in FMD and IMT in the brachial artery between PDRF patients and controls are illustrated in Fig.1. IMT in PDRF patients was significantly higher than in controls (0.43 ± 0.06 vs. 0.34 ± 0.05 ; $p < 0.001$). FMD was not significantly higher among controls compared to PDRF ($0,053 \pm 0,05$ vs. $0.047 \pm 0,04$; $p: Ns$, Figure 1).

In patients with PDRF, significant relationships between IMT and Hb ($p = 0.04$), creatinine ($p = 0.04$) and phosphate ($p = 0.04$) were found. FMD was positively associated with TG ($p = 0,01$) and negatively with fibrinogen ($p = 0.04$). In addition IMT was significantly

associated with IL-6 ($p=0.01$). FMD was negatively associated with TNF- α ($p=0.04$) and IL-6($p=0.04$),(Table 3).

Discussion

High-resolution B- mode ultrasonography is a non-invasive, safe and reproducible method to detect endothelial dysfunction by measuring variables such as FMD and IMT, and consequently investigate preclinical atherosclerosis [7, 16-19]. Individuals with impaired endothelial function and thickened IMT carry a major risk for future CVD. Since cardiovascular death rate is much higher among dialysis patients than healthy individuals, CKD is defined as a pro-atherogenic state [20]. The endothelium dependent dilatation is abnormal in CKD patients with asymptomatic vascular disease, and it is suggested that the impaired endothelial function precedes the development of CVD in uremic patients [21]. However, it is unclear during which phase of the disease progression towards dialysis these changes occur. In the present study we have investigated these variables in patients with predialytic RF.

Some other investigators have also reported an impaired FMD in asymptomatic children and young adults with established risk factors for atherosclerotic disease [7]. These trials make the FMD a valuable variable to detect early AVD. We found a slightly higher FMD in the control group compared to the PDRF; however the difference was not significant. The explanation to this conflicting result could be that FMD is influenced by confounding factors such as age [22]. FMD normally decreases with age and therefore one might find no difference in FMD when comparing a diseased group with a healthy group when the subjects are over 60 years old. However, another study, which examined CKD patients with approximately the same age as in our study, observed a significantly impaired FMD among the patients [21]. We observed

a similar tendency and the discrepancy might be explained by a type II error in the present study due to underpowering of the study with respect to FMD. This is supported by the wide confidence intervals of the FMD estimates. On contrary the present study showed that IMT is significantly different between the controls and PDRF group.

Previous studies have demonstrated that classical risk factors for CVD are significantly correlated with FMD% [23]. On the other hand there are other studies suggesting that FMD% is also correlated to the non-traditional risk factors for developing AVD in CKD patients [24]. We found a positive association between TG and FMD, but no associations between FMD and cholesterol and glucose were observed. The present study showed a significant correlation between Hb, creatinine and phosphate and IMT. At the same time no correlations between TG, cholesterol and glucose and IMT were found. These results suggest that IMT impairment in CKD patients is associated not only with the traditional risk factors for AVD. This suggestion is in line with other studies which reported that IMT is not only associated with the classical risk for CVD, but also the untraditional ones [24].

We found no significant correlation between IMT and FMD. This result is also reported in a previous study, which suggested that there is not any association between FMD and IMT in predialysis patients [24]. The authors suggested that FMD and IMT examine different aspects and stages of atherosclerosis. We have previously reported a linear relationship between IMT in the brachial artery and coronary artery disease, as well as a significant correlation between IMT in the brachial artery and carotid IMT, in a group of patients with severe coronary artery disease [22]. These findings underline that brachial artery IMT can be used to detect AVD in a preclinical phase. However, despite a significant correlation between IMT in the brachial artery and coronary artery disease and carotid IMT, it cannot be excluded that increased IMT

in the brachial artery represents muscular medial thickening rather than intimal thickening [22].

It is well known that the inflammatory activity is increased in patients with dialysis [9]. In this study of PDRF patients we observed increased inflammatory activity in the PDRF group compared to the control group. VCAM, ICAM and TNF- α were significantly elevated in the PDRF group whereas the elevations of CRP and IL-6 did not reach significance levels. Thus, the increased inflammatory activity seems to be present even before the disease progresses to dialysis.

Atherosclerosis is an inflammatory disease. We described that increased IL-6 was significantly associated with both IMT and FMD in the PDRF group. The correlations between VCAM-1, ICAM-1 and FMD and IMT did not reach the significance level. A previous study has found that VCAM-1 and IL-2 receptor correlates with IMT in haemodialysis patients [9]. In another study a significant association between ICAM-1 and IMT was found in patients on continuous ambulatory peritoneal dialysis, however they failed to show any correlation between IMT and VCAM-1 [25].

In summary we have shown that brachial IMT is significantly increased in PDRF patients, and it correlates with Hb-, creatinine- and phosphate levels. This proposes that this patient category carry a major risk for developing AVD during the progression of their renal disease, and it might be explained by a combination of the traditional risk factors and some additional coexisting factors. The PDRF group had an increased inflammatory activity, and a positive correlation between IL-6 and preclinical AVD was found in PDRF patients.

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Table 1: Demographic, haemodynamic and biochemical parameters.

Parameters	PDRF (N=50)	Controls (N=35)	p-value
Gender(male/female)	42/8	25/10	Ns
Age(years)	59±14,6	62±12,9	Ns
Weight (Kg)	82±15	75±11	0.01
Length (Cm)	177±8.8	172±7.9	0.03
Body mass index (kg/m ²)	27±4	25±3	0.05
Hb(g/dl)	126±14.6	1418.2	0.00
Systolic blood pressure (mm Hg)	156±22	139±22	0.001
Diastolic blood pressure (mm Hg)	92±11	88±10	0.03
Cholesterol(mmol/L)	5.2±1.2	5.1±0.80	Ns
HDL-cholesterol(mg/L)	1.2±0.4	1.5±0.3	0.00
Apo A-1(g/L)	1.4±0.2	1.5±0.2	Ns
Apo B-1(g/L)	1.1±0.3	0.95±0.2	Ns
TG(mmol/L)	2.3±1.27	1.2±0.5	0.00
LP (a)(mg/L)	248±287	216±251	Ns
S-Creatinine(μmol/L)	300±147	80±17	0,00
S-Albumin(g/L)	37±3.3	39±2.3	0.00
S-Ca ²⁺ (mmol/L)	2.4±0.1	2.3±0.1	0.00
S-Phosphate(mmol/L)	1.4±0.4	1.0±0.2	0.00
PTH	123±82	40±16	0.00
Urea(mmol/L)	19±6.5	5.7±1.3	0.00
U-albumin (mg/24 h)	1215±1351	59±54	0.00
Iohexolclearance (ml/min*1.73 m ²)	27±10	88±14	0.00
Arginin	79±18.6	81±20.9	Ns
Fibrinogen(mmol/L)	3.8±0.8	2.9±0.6	0.00
Glucose(mmol/L)	6.0±1.8	6.4±7.0	Ns
Troponin T (ug/l)	0.02±0.03	0.01±0.01	Ns
Troponin I (ug/l)	0.01±0.02	0.02±0.05	Ns

Data are expressed as mean ±standard deviation (SD) or percentage (%).

Hb: haemoglobin, PTH: parathyroid hormone, HDL: high-density lipoprotein, TG:

triglycerides, LP (a): lipoprotein (a), U- albumin flow: urine albumin flow, Ns: not significant,

Na: not available.

Table 2: Serum levels of inflammatory markers in CKD patients and controls.

Parameters	PDRF (N=50)	Control (N=35)	p-value
s- CRP (mg/L)	5.0±7.6	2.7±5.6	Ns
VCAM- 1 (ng/mL)	984±282	722±162	<0.001
ICAM- 1 (ng/mL)	253±47.8	232±47.1	0.04
TNF- α (pg/mL)	9.1±4.3	4.3±2.1	<0.001
IL-6 (pg/mL)	2.8±1.2	2.0±2.1	Ns

Data are expressed as mean \pm standard deviation (SD) or percentage (%).

s-CRP: sensitive C-reactive protein, VCAM-1: vascular cellular adhesion molecule 1, ICAM-

1: intracellular adhesion molecule 1, TNF- α : tumour necrosis factor alpha, IL-6: interleukin 6.

Table 3: Correlations of IMT and FMD in the brachial artery and the inflammatory parameters in PDCKD patients (n=50).

Parameters	r-value	p-value	r-value	p-value
	IMT	IMT	FMD	FMD
s-CRP(mg/dL)	0.18	Ns	-0.11	Ns
VCAM- 1(ng/mL)	0.13	Ns	-0.20	Ns
ICAM- 1(ng/mL)	-0.18	Ns	0.17	Ns
TNF- α (pg/mL)	0.14	Ns	-0.31	0.04*
IL-6 (pg/mL)	0.37	0.01*	-0.28	0.04*

s-CRP: sensitive C-reactive protein, VCAM-1: vascular cellular adhesion molecule 1, ICAM-1: intracellular adhesion molecule 1, TNF- α : tumour necrosis factor alpha, IL-6: interleukin 6.

r: Spearman's correlation coefficient, p: p value for correlation.

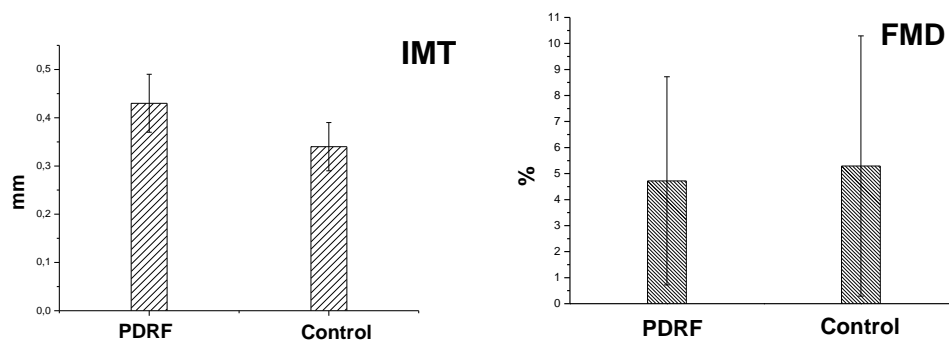


Figure 1: Comparison of flow- mediated dilatation (FMD), and intima- media thickness (IMT) between predialysis renal failure (PDRF) patients and controls.

