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Relationship between Kidney Disease and Endothelial Function in Peripheral Artery Disease

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Abstract

Objective—We have previously shown that peripheral artery disease (PAD) is associated with marked impairment of endothelial function (EF). Given that poor EF is associated with functional status of PAD patients as well as increased morbidity and mortality in patients undergoing vascular procedures, determining factors associated with poor EF in a PAD cohort is important. We hypothesized that decreased kidney function is associated with impaired endothelial function (EF) in patients with PAD.

Methods—This was a cross-sectional study of PAD patients presenting to a vascular surgery outpatient clinic at the San Francisco Veterans Affairs Medical Center including patients enrolled into the OMEGA-PAD I trial (NCT01310270) and the OMEGA-PAD Cohort. Brachial artery flow-mediated vasodilation (FMD) was performed to assess EF. Kidney function was characterized by eGFR using the abbreviated Modification of Diet in Renal Disease formula. Linear regression was performed to assess the relationship between EF and kidney function in claudicants.

Results—97 patients with intermittent claudication participated in this study. Mean age was 69 ± 8 years, 97% were male, and 77% were Caucasian. Comorbidities included hypertension (91%),

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dyslipidemia (87%), coronary artery disease (42%) and diabetes mellitus (38%). Mean ABI was 0.73 ± 0.14 and mean FMD was $7.0\% \pm 3.8$, indicating impaired EF. Linear regression showed an association between kidney function and EF (by 10 ml/min/1.73m^2, β: 0.12; CI: 0.05, 0.20; P = .001). After multivariable regression adjusting for age, race, log TNF-α, hypertension, dyslipidemia, and diabetes, eGFR remained significantly associated with EF (P = .033).

Conclusions—In patients with PAD, decreased kidney function is associated with endothelial dysfunction. Further longitudinal studies are needed to better understand the impact of kidney function on PAD progression and the role of endothelial dysfunction in this process.

INTRODUCTION

Nearly one-third of patients aged 70 and older will suffer from peripheral artery disease (PAD)[1] which can significantly impact quality of life and longevity. Despite available medical and surgical therapies, patients with PAD continue to have a higher risk of cardiovascular (CV) events, such as stroke or coronary ischemia, compared to patients with coronary artery disease (CAD).[2] Endothelial dysfunction is an early step in the development of atherosclerosis, and several studies have demonstrated that patients with PAD have diminished endothelial function (EF).[3,4] We have previously shown that endothelial dysfunction, as measured by flow-mediated vasodilation (FMD) of the brachial artery, is associated with walking disability in PAD patients.[3] Impaired brachial artery FMD also has been shown to independently predict cardiovascular events in patients undergoing vascular surgery.[5] Given that impaired EF is associated with decreased functional status and increased morbidity and mortality in patients with PAD, determining factors associated with impaired EF in a PAD cohort is important.

PAD patients often have other concomitant manifestations of atherosclerosis. The co-prevalence of chronic kidney disease (CKD) and PAD is high.[6] Impaired kidney function is an accepted risk factor for CV disease (CVD), and even mild stages of CKD have been associated with adverse cardiovascular events.[7,8] For example, patients with stage 3 CKD have a 17% increase in mortality and those with stage 5 CKD have a 600% increase in mortality compared to an age matched population with normal kidney function.[7] Current evidence suggests that decreased kidney function is not only an independent predictor of CV events, it may also be a stronger predictor than traditional risk factors.[9,10] In the setting of PAD, the presence of kidney disease predicts worse outcomes after peripheral revascularization.[11] Kidney disease is known to produce a state of oxidative stress and inflammation,[12] both of which are strong depressors of endothelial function. Whether or not a relationship exists between kidney and endothelial function (EF) in a PAD cohort has not been established. The current study examined the determinants of endothelial dysfunction, including kidney function, in patients with PAD. We hypothesized that kidney function could be an important determinant of EF in patients with PAD.

METHODS

Study Population and protocol

This cross-sectional study investigated the relationship between kidney function and EF in PAD patients. The investigator-initiated protocol was approved by the University of California, San Francisco (UCSF), Committee on Human Research, and all patients gave informed consent. Patients referred to the outpatient vascular surgery clinic of the San Francisco Veterans Affairs Medical Center (SFVAMC) for evaluation of PAD were recruited. We included baseline data from patients enrolled into the OMEGA-PAD trial (NCT01310270) and the OMEGA-PAD Cohort.[13] Subjects were enrolled if they had at least one of the following inclusion criteria: intermittent claudication associated with an ankle-brachial index (ABI) < 0.9, toe pressures < 70 mm Hg, or imaging confirming >50% stenosis in the lower extremity arteries. Intermittent claudication was diagnosed based on fatigue, discomfort, or pain that occurs in specific limb muscle groups during effort due to exercise-induced ischemia.[14] Exclusion criteria included: end-stage renal disease (ESRD) initiated on hemodialysis (HD), significant hepatic or inflammatory disease, concurrent severe infections, acute illness or other major surgery within 30 days or taking immunosuppressive medications. We recorded demographic and anthropometric data, cardiovascular history, risk factors, concurrent medications, and pertinent cardiovascular examination findings. EF was measured by brachial artery flow-mediated brachial artery vasodilation (FMD) and kidney function was measured by estimated glomerular filtration rate (eGFR). Other measurements included lipid, metabolic, and inflammatory markers, omega index, blood pressure and bilateral ABIs.

Measurements

Demographic and Anthropometric Data, Hemodynamic Measurements and Walking Distance—Demographic and anthropometric data collected included age, race, gender, hip and waist circumference, body mass index, prior supplement use, exercise frequency. We collected CV history, such as CAD, cerebrovascular disease, and previous lower extremity vascular procedures, as well as risk factors including hypertension (HTN), diabetes mellitus (DM) type I and II, hyperlipidemia (HLD), and tobacco use based on problem list and patient inquiry. Concurrent medications, pertinent cardiovascular examination findings, and blood pressure were also recorded. Walking distance and Rutherford classification was based on the patient's self-report during clinic visit, recorded by the investigator-vascular surgeons.

Vascular Reactivity of Brachial Arteries—Flow-mediated endothelium-dependent vasodilation was performed according to current guidelines and standards previously described by our group.[3,13,15–17] Subjects were asked to fast and abstain from nicotine and caffeine before the exam. A history of recent medications was recorded. Subjects were allowed to rest for ten minutes in a supine position in a darkened room at 23°C. A 5-cm tourniquet blood pressure cuff was placed on the upper arm proximal to the insertion of the deltoid. The brachial artery was surveyed by B-mode ultrasound (Philips HD11) using a broadband linear array transducer with a 3–12 MHz range (Philips L12-3). Prior to cuff inflation, the baseline diameter of the vessel was recorded using EKG-gated image capture

software (Brachial Imager, Medical Imaging Applications LLC, Coralville, IA). Baseline blood-flow velocity was recorded using an insonation angle of 60°. The blood pressure cuff was inflated to the greater of 250 mm Hg or 50 mm Hg above the subject's systolic blood pressure for a period of 5 minutes. Diameter and blood-flow velocity were recorded until 3 minutes post-cuff release.

Analysis of the images was performed using continuous edge-detection software (Brachial Analyzer, Medical Imaging Applications LLC, Coralville, IA). Baseline diameter was recorded as the mean of 60 seconds data. Hyperemia diameter was calculated using a pre-determined time window of 55–65 seconds post-cuff release. FMD% was calculated as (60s Hyperemia diameter-Avg Baseline diameter/Avg Baseline diameter)*100.

Time averaged velocity measurements were obtained using the peak-velocity method. Average velocity at baseline was obtained from 60 seconds of data. Velocity of the hyperemia stimulus was calculated as the mean velocity of the first four heart beats following cuff-release. Both mean velocity and the velocity time integral were recorded. Flow was calculated by multiplying the time averaged velocity by the brachial cross-sectional area.

Quality control was assessed at each point of the measurements. Image quality was evaluated by a 2nd person and graded on a 6-point scale that includes: registration structure (landmark), horizontally directed artery, correct longitudinal alignment, clearly visualized near wall intimal medial thickness (IMT) and far wall IMT, and at least 5 mm of clearly visualized artery. The inter-observer variability in our laboratory is $0.05 \pm 0.16\%$ and the intra-observer variability is $0 \pm 0.15\%$.

Kidney Function—Blood samples were collected in a fasting state for measurement of creatinine (Cr) and eGFR was calculated using the abbreviated Modification of Diet in Renal Disease formula based on age, gender, race, and serum creatinine level.[18] Plasma was assayed for these analytes on the same day as collection by the SF VAMC lab per standard methodology (Beckman Coulter Analyzer). Subjects with eGFR > 90 ml/min/1.73m^2 were assumed to be CKD Stage I because of the presence of PAD, although the subjects did not necessarily have the confirmatory kidney damage such as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies as set forth by the KDOQI guidelines from the National Kidney Foundation.[19]

Ankle-Brachial Index—The ABI was measured using current guidelines and standards.[20] Systolic blood pressures of the brachial, posterior tibial and dorsalis pedis arteries were measured bilaterally. For each lower extremity, the highest systolic pressure of the two pedal pulses was divided by the highest systolic pressure of the two brachial arteries.

Lipid, Metabolic, and Inflammatory Measurements—Blood samples were collected in a fasting state for measurement of albumin, total cholesterol, triglycerides, low-density lipoprotein (LDL), high-density lipoprotein (HDL), high sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6), soluble intercellular adhesion molecule-1 (sICAM-1), tumor-necrosis-factor-α (TNF-α), and hemoglobin A1C (Hgb A1C). Plasma was assayed for

albumin, total cholesterol, triglycerides, LDL, HDL, hsCRP, Hgb A1C on the same day as collection by the SF VAMC lab per standard methodology (Beckman Coulter Analyzer). The coefficient of variation for hsCRP using this procedure is 5.1%. Serum was isolated at the same time points for homocysteine and assayed the same day as collection by the SF VAMC lab per standard methodology (Abbott Diagnostics Architect i1000 Analyzer, Lake Forest, IL). Serum was processed per standard protocol and stored at −80°C until assayed for IL-6, sICAM-1, and TNF-α per standard kit protocol (R&D Systems Inc., Minneapolis, MN). The typical coefficients of variation for IL-6, sICAM-1, and TNF-α are 7.4%, 4.6%, and 5.4%, respectively. The lower limits of detection are 0.04pg/ml, 0.1ng/ml, and 0.11pg/ml, respectively.

Statistical Analysis

For descriptive purposes, we categorized participants by FMD tertiles. Inflammatory markers not normally distributed were log-transformed. Differences in characteristics among FMD tertiles were compared using analysis of variance (ANOVA) for continuous variables and Fisher's exact test for dichotomous variables. For the overall regression models, patients were divided into FMD tertiles. We used linear regression models to examine the relationship between all variables listed in Table I, and FMD tertiles. eGFR was treated as a continuous linear variable in the regression models; graphical diagnostics such as spline regression plots supported this decision. Multivariate adjustment was made for demographic characteristics and traditional CV risk factors based on an a-priori determination of $P < 0.1$ in univariate models. An a-priori determination of significance at $P < .05$ was used in the multivariate model. Statistical analyses were performed using Stata/SE 12 (StataCorp, College Station, TX).

RESULTS

A total of 97 patients with intermittent claudication participated in this study. Tables I and II demonstrate the demographics, comorbidities, medications, and PAD risk factors by FMD tertiles. The mean age was 69 ± 8 years, 97% were male, and 79% were Caucasian. Comorbidities included hypertension (91%), dyslipidemia (87%), coronary artery disease (42%) and diabetes mellitus (38%). Mean eGFR was 74 ± 21 ml/min/1.73m^2 and mean index ABI was 0.73 ± 0.14. Mean FMD was $7.0\% \pm 3.8$ (Table III), indicating impaired EF when compared to the normal range of 10–13%.[21] With decreased kidney function, there was a decrease in FMD (I: 65, II: 74, III: 82 ml/min/1.73m^2, $P = .012$) (Figure I).

By univariate analysis (Table IV), age (by decade, β: −0.19; CI: −0.41, −0.02; $P = .082$), hypertension ($P = .009$), diabetes mellitus ($P = .052$), dyslipidemia ($P = .063$), log TNF-α (β: − 0.9; CI: −1.4, −0.4; $P = .001$), diastolic blood pressure (β: 0.019; CI: 0.002, 0.036; $P = .033$), LDL (β: 0.0041; CI: −0.0005, 0.0087; $P = .078$), and eGFR (by 10 ml/min/1.73m^2, β: 0.12; CI: 0.05, 0.20; $P = .001$) were associated with EF.

After multivariate linear regression adjusting for age, race, log TNF-α, and hypertension, only eGFR remained significantly associated with FMD ($P = .033$) (Table IV). A 10 ml/min/1.73m^2 decrease in eGFR was associated with a 0.12% decrease in FMD with a 95% confidence interval of 0.008–0.193.

DISCUSSION

In a cross-sectional cohort study of patients presenting to our outpatient vascular surgery clinic with PAD, we found a significant association between kidney function and EF as measured by brachial artery FMD in patients with PAD. Among PAD patients with claudication, those with CKD have the worst EF. In view of the high risk associated with PAD,[2] a better understanding of the relationship between kidney function and endothelial dysfunction could be clinically relevant.

Factors Influencing Endothelial Function

Traditional risk factors for atherosclerosis including diabetes, hyperhomocysteinemia, hypertension, dyslipidemia and smoking are also known to affect EF.[22–26] Our analysis suggests that kidney disease may be a particularly strong and independent risk factor for endothelial dysfunction in the PAD population.

Several clinical studies have explored the relationship between kidney failure and endothelial dysfunction. Nakamura et al. found that EF assessed by brachial FMD was associated with kidney disease in patients with CAD.[27] They also suggested that systemic EF may precede the development of kidney disease in patients with normal kidney function. In a cohort of patients with essential hypertension, Perticone et al. found an impaired vasodilatory response to acetylcholine associated with moderate kidney disease.[28] Kari et al. found lower brachial FMD, higher eNOS inhibitors, and lower NO metabolites in a small nonatherosclerotic cohort of 23 children with CKD.[29] An ESRD cohort of 44 subjects on HD for at least 3 months was compared to 25 controls, showing that ESRD is associated with lower shear stress, compliance, and brachial FMD using the hand-warming technique.[30] Wever et al. found endothelial dysfunction as assessed by diminished whole body NO production in 7 CKD patients compared to 7 controls.[31] Kidney function and EF have been associated in various CAD and CKD populations with varying techniques of evaluating EF. Nevertheless, this relationship has not been studied in the PAD population.

Mechanisms of Endothelial Dysfunction in Kidney Disease

Endothelial dysfunction is considered to be a systemic issue. In glomerular endothelial cells, albuminuria leads to a reduction in the endothelium-dependent vascular relaxation response in kidney.[32] Whether kidney endothelial dysfunction precedes systemic endothelial function, or vice versa, is controversial.[27] The key markers responsible for this cascade between kidney and systemic endothelial dysfunction are likewise unclear. Potential mediators between kidney function and EF include asymmetrical dimethylarginine (ADMA) and TNF-α.

Kidney failure permits an accumulation of competitive inhibitors of endothelial nitric oxide synthase, namely ADMA.[33] ADMA is raised in ESRD and could contribute to higher CV risk in patients with chronic kidney failure.[33] Studies show that elevated ADMA levels are associated with endothelial function assessed by brachial FMD in patients with PAD,[34] and independently predict arterial stiffness.[26] Elevated ADMA concentrations predict progression of both CKD and PAD.[35] ADMA accumulation leads to increased production of

inflammatory markers such as TNF-α and IL-8, as well as the binding of monocytes to endothelial cells.[33] Furthermore, inflammation inhibits the enzyme that degrades ADMA, contributing to a vicious cycle of ADMA accumulation and increased inflammation.[33]

It is therefore not surprising that our study suggests that TNF-α, a well-known marker of inflammation, may play a role as a link between EF, CKD and PAD. TNF-α is associated with greater incidence of PAD and is known to act independently on human endothelial cells.[2,36] TNF-α also predicts mortality in acute kidney failure and progression to ESRD.[37] The median TNF-α in our cohort was 2.11 pg/ml (IQR 1.68–2.47), which is higher than normal levels around 1.81pg/ml (IQR 1.29–2.33).[38] Our univariate analysis supports endothelial function as an inflammatory process, showing an association with log TNF-α. However, currently it is uncertain whether TNF-α is specifically involved in the pathway for CKD.[37] Further studies need to be done to identify the role of TNF-α in CKD and PAD.

Clinical Implications

Recent studies have shown that decreased kidney function is an independent and significant predictor of outcomes in patients after undergoing peripheral revascularization.[11] Kidney function has increasingly displayed greater predictive value of CV events in patients with atherosclerosis than traditional risk factors.[9,10] Kidney failure patients have extremely low FMD, even more so than those of PAD patients.[29] Once advanced kidney disease is present, it may contribute to the progression of systemic endothelial dysfunction more than traditional cardiovascular risk factors do.

To our knowledge, this report is the first to examine the relationship between kidney function and EF evaluated by brachial artery FMD in a PAD cohort. Several studies have found that impaired vasodilatory response to be associated with loss of kidney function in other cohorts or using techniques other than brachial artery FMD via reactive hyperemia.[27–31] Because several studies have characterized impaired EF in the ESRD population requiring HD, we focused on earlier stages of CKD and were able to detect an association. We therefore confirm through this cross-sectional study that kidney function could serve as a strong risk marker for EF in PAD patients with intermittent claudication. This cohort will continue to be followed longitudinally to determine if there is an association between kidney function and EF over time.

Limitations

The patient population studied was not representative of the wider PAD population as it included only veterans that were mostly male and Caucasian referred to a vascular surgery clinic at the SFVAMC. It is important to state that this study does not address the majority of patients with PAD- those who are asymptomatic. Likewise it also does not examine the most severe end of the PAD spectrum, critical limb ischemia. Although patients were evaluated for peripheral arterial disease, FMD was not assessed in the lower extremity, but in the brachial artery. Nevertheless, Anderson et al. found that brachial FMD modeled FMD in the coronary arteries as well, indicating that brachial FMD is predictive systemic EF.[39] While a history of recent antihypertensive and antiplatelet medications were recorded, cilostazol and nitrates were not included. In addition, walking distance was assessed based

on subjective self-report, rendering a large error within each FMD tertile. We are currently adding the 6-minute walk test to better understand the relationship between walking and EF. Furthermore, the population studied may be skewed compared to the typical PAD patient with regards to the psychological profile of patients, affecting overall stress and inflammation.[40] Although the sample size is modest, it is larger than all but one trial studying the effects of kidney disease on endothelial function as assessed by FMD. Most importantly, this report does not imply causation but rather an association.

CONCLUSIONS

In patients with PAD and claudication, those with CKD have the worst endothelial dysfunction as measured by FMD. As such, kidney function is as important a risk factor as traditional PAD risk factors. Longitudinal studies are needed to explore the relationship between declining kidney function and progression of PAD over time, and whether these are both associated with, or driven by, progressive impairments in endothelial function.

Acknowledgments

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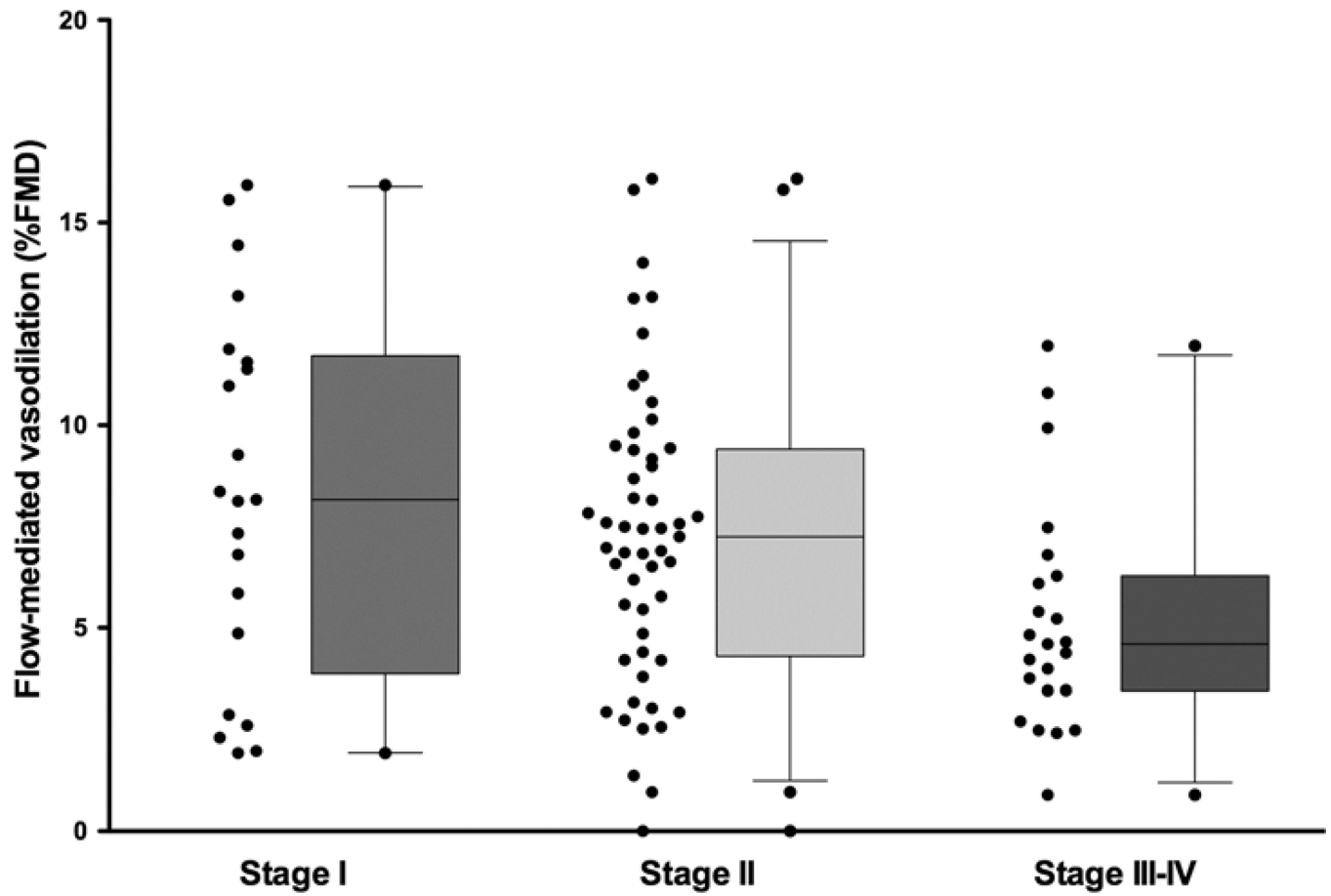
Figure 1.
Relationship between chronic kidney disease (CKD) and endothelial function in a cohort of
PAD patients. CKD stages are defined according to the KDOQI guidelines.[19]

Table I

Baseline characteristics of the population categorized by FMD Tertiles

Descriptive Characteristics	All patients (N= 97)	FMD Tertile I (N= 33)	FMD Tertile II (N= 32)	FMD Tertile III (N= 32)	p-value[a]
Age, y	69 ± 8	71 ± 8	68 ± 8	68 ± 7	0.13
Male sex, %	94 (97)	31 (94)	31 (97)	32 (100)	0.77
Caucasian race, %	77 (79)	26 (79)	24 (75)	27 (84)	0.67
BMI, kg/m^2	28 ± 5	30 ± 6	28 ± 5	28 ± 5	0.21
Waist-to-hip ratio, %	1.02 ± 0.06	1.02 ± 0.07	1.04 ± 0.06	1.01 ± 0.04	0.28
Blood pressure, mm Hg					
Systolic	138 ± 18	139 ± 17	143 ± 18	134 ± 19	0.14
Diastolic	76 ± 10	72 ± 10	78 ± 10	77 ± 8	0.011
Index ABI	0.73 ± 0.14	0.71 ± 0.17	0.73 ± 0.14	0.74 ± 0.11	0.67
WIQ Walking	33 ± 31	36 ± 35	25 ± 25	36 ± 32	0.29
Distance					
WIQ Walking Speed	29 ± 27	28 ± 28	25 ± 23	34 ± 31	0.42
WIQ Stairs	35 ± 30	31 ± 30	35 ± 26	41 ± 35	0.46

[a]P-value calculated from ANOVA for continuous variables or Fisher's exact test for categorical variables

Mean ± SD presented for continuous variables; Number of patients with relative % of cohort presented for categorical variables.

Table II

Baseline comorbidities, medications, and PAD risk factors of the population categorized by FMD Tertiles

Characteristics	All patients (N= 97)	FMD Tertile I (N=33)	FMD Tertile II (N= 32)	FMD Tertile III (N= 32)	p-value[a]
Hypertension	88 (91)	33 (100)	29 (91)	26 (81)	0.024
Dyslipidemia	84 (87)	30 (91)	30 (94)	24 (75)	0.10
History of CAD	41 (42)	19 (58)	8 (25)	14 (44)	0.023
Diabetes mellitus	37 (38)	17 (52)	11 (34)	9 (28)	0.14
Aspirin	69 (71)	26 (79)	20 (63)	23 (72)	0.36
ACE-inhibitor	44 (45)	19 (58)	13 (41)	12 (38)	0.22
β-blocker	59 (61)	21 (64)	21 (66)	17 (53)	0.61
Statin	79 (81)	27 (82)	26 (81)	26 (81)	1.00
Hx of smoking, %	91 (94)	29 (88)	31 (97)	31 (97)	0.36
Pack-years, if applicable	48 ± 34	51 ± 37	49 ± 37	45 ± 26	0.76
Cholesterol, mg/dL					
Total	160 ± 42	150 ± 32	169 ± 41	163 ± 49	0.16
LDL	86 ± 36	75 ± 28	94 ± 38	91 ± 40	0.086
HDL	45 ± 13	45 ± 15	44 ± 12	46 ± 12	0.94
Triglycerides, mg/dL	149 ± 92	151 ± 97	162 ± 103	134 ± 73	0.47

[a]P-value calculated from ANOVA for continuous variables or Fisher's exact test for categorical variables

Mean ± SD presented for continuous variables; Number of patients with relative % of cohort presented for categorical variables.

Table III

Baseline biomarkers and brachial artery FMD study values of the population categorized by FMD Tertiles

Characteristics	All patients (N= 97)	FMD Tertile I (N= 33)	FMD Tertile II (N= 32)	FMD Tertile III (N= 32)	p-value[a]
CRP[b] (mg/dL)	0.8 (0.4, 1.7)	0.8 (0.5, 1.4)	0.9 (0.6, 1.8)	0.8 (0.3, 1.7)	0.97
IL-6[b] (pg/ml)	0.1 (−0.2, 0.5)	0.2 (−0.2, 0.2)	0.2 (−0.1, 0.42)	0.04 (−0.02, .06)	0.75
ICAM[b] (ng/ml)	5.5 (5.4, 5.7)	5.5 (5.4, 5.8)	5.5 (5.4, 5.8)	5.5 (5.3, 5.7)	0.78
TNF-α[b] (pg/ml)	0.7 (0.5, 0.9)	0.8 (0.6, 1.1)	0.8 (0.5, 1.0)	0.6 (0.4, 0.8)	0.004
Homocysteine (μmol/L)	14 ± 4	14 ± 4	14 ± 5	13 ± 6	0.97
Albumin (g/dL)	4.0 ± 0.3	4.0 ± 0.4	4.1 ± 0.3	4.0 ± 0.3	0.92
Hemoglobin A1C	6.2 ± 1.2	6.5 ± 1.2	6.2 ± 1.5	6 ± 0.9	0.30
Creatinine (mg/dL)	1.16 ± 0.67	1.41 ± 1.06	1.08 ± 0.29	0.98 ± 0.23	0.026
eGFR (mL/min/1.73 m^2)	74 ± 21	65 ± 23	74 ± 19	82 ± 19	0.005
Baseline brachial diameter (cm)	0.39 ± 0.07	0.42 ± 0.06	0.38 ± 0.08	0.36 ± 0.05	0.0002
Baseline velocity (m/s)	0.2 ± 0.1	0.2 ± 0.1	0.1 ± 0.1	0.2 ± 0.1	0.36
Baseline flow (ml/min)	122 ± 73	150 ± 86	104 ± 62	109 ± 62	0.018
Baseline shear stress (dynes/cm^2)	12 ± 6	12 ± 5	12 ± 8	13 ± 5	0.52
Hyperemia diameter (cm)	0.41 ± 0.07	0.44 ± 0.06	0.40 ± 0.08	.40 ± 0.06	0.044
Hyperemia velocity (m/s)	0.7 ± 0.3	0.6 ± 0.2	0.7 ± 0.3	0.8 ± 0.2	0.0001
Hyperemia flow (ml/min)	576 ± 307	531 ± 318	554 ± 327	645 ± 273	0.29
Hyperemia shear stress (dynes/cm^2)	48 ± 20	36 ± 15	48 ± 19	59 ± 18	<0.0001
Brachial FMD (%)	7.0 ± 3.8	3.0 ± 1.2	6.7 ± 0.9	11.4 ± 2.4	-

[a]P-value calculated from ANOVA and Mean ± SD presented for continuous variables

[b]Inflammatory marker levels not normally distributed were log-transformed and presented as median (interquartile range)

Table IV

Determinants of endothelial function in univariate and multivariate linear regression analysis

Independent variable	Univariate Analysis; N=97			Multivariate Analysis; N=84		
	aβ-Coefficient	95% Confidence-interval	p-value	aβ-Coefficient	95% Confidence-interval	p-value
Age, by decade	−0.19	−0.41, −0.02	0.082	−0.009	−0.230, 0.211	0.93
Race			0.33			0.52
Caucasian (ref)						
African American	0.2	−0.4, 0.7		−0.04	−0.53, 0.46	
Hispanic	−0.5	−1.2, 0.2		−0.39	−1.03, 0.25	
Asian/PI	−0.5	−1.7, 0.7		−0.50	−1.58, 0.57	
Hypertension	−0.7	−1.3, −0.2	0.009	−0.5	−1.1, 0.1	0.085
Diabetes mellitus	−0.333	−0.669, 0.004	0.052	−0.04	−0.39, 0.31	0.81
Dyslipidemia	−0.46	−0.94, 0.02	0.063	−0.45	−0.96, 0.06	0.082
TNF-α[b], pg/ml	−0.9	−1.4, −0.4	0.001	−2.07	−5.10, 0.97	0.18
10 ml/min/1.73m² eGFR	0.12	0.05, 0.20	0.001	0.101	0.008, 0.193	0.033

[a] The β-coefficients of the multivariable model represent the change in % FMD due to the presence of a variable (race, hypertension, or 10 ml/min/1.73m² change in eGFR)

[b] Inflammatory marker levels not normally distributed were log-transformed.