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Renal Insufficiency is Independently Associated with a Distal Distribution Pattern of Symptomatic Lower-limb Atherosclerosis

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Abstract *Objectives:* The purpose of this study was to assess the impact of renal insufficiency (RI) on the distribution pattern of peripheral arterial disease (PAD). We hypothesised that RI is associated with a distally accentuated involvement of the peripheral arterial tree.
Design: This is a retrospective analysis.
Materials and Methods: Analysis was based on a consecutive series of 2709 patients with chronic PAD of atherosclerotic origin undergoing primary endovascular treatment of lower-extremity arteries. Atherosclerotic pattern was grouped into femoropopliteal ($n = 2085$) and infragenicular ($n = 892$) disease according to target lesions treated while using iliac disease ($n = 1133$) as reference. Univariable and multivariable multinomial regression analyses were performed to assess relation with RI. Results are shown as relative risk ratio (RRRs) with 95% confidence intervals (95% CIs). A $p < 0.05$ was considered statistically significant. RI was defined as glomerular filtration rate (GFR) $< 60\ \mathrm{ml\ min^{-1}\ 1.73\ m^{-2}}$.
Results: Presence of RI was an independent risk factor for a centrifugal lesion pattern (RRR 1.48, 95% CI: 1.17–1.86, $p = 0.001$). Moreover, a decrease in GFR by $10\ \mathrm{ml\ min^{-1}\ 1.73\ m^{-2}}$ was associated with an RRR of 1.08 for below-the-knee arterial disease (95% CI: 1.03–1.13, $p = 0.003$).
Conclusion: Presence and severity of RI are independent predictors of a distal obstructive pattern in patients with symptomatic PAD.

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Introduction

Atherosclerosis and its complications are the leading cause of death in Western world.[1,2] Interestingly, while pathophysiological mechanisms are similar throughout the arterial vascular tree, it seems that cardiovascular risk factors induce a differential modulation of the disease progression and clinical phenotype of atherosclerotic disease process.[3–9] Cigarette smoking and hypercholesterolaemia were shown to have a major impact on the incidence of coronary artery disease, while arterial hypertension and diabetes mellitus have an influence on the incidence of cerebrovascular disease;[3,4] and in the lower limb arterial tree, atherosclerotic manifestations were shown to be predominantly related to smoking and diabetes mellitus.[4,5] A high prevalence and incidence of PAD is also known for patients with chronic kidney disease(CKD);[6,7] and cardiovascular events are the leading cause of morbidity and mortality in patients with end-stage renal disease.[8,9] Little is known about the pathophysiological mechanism and its impact on the distribution pattern in PAD. With a substantially increasing prevalence of chronic renal failure[10,11] strongly influenced by the epidemic increase of diabetes mellitus,[12] the treatment of atherosclerosis in this patient group will remain an important challenge for physicians in the future.

To date, despite the frequent coincidence of RI and diabetes mellitus, the impact of renal disease on lower-limb atherosclerosis is limited to anecdotal observation and has not been systematically evaluated.[13–15] The aim of the present study was to scrutinise the association of RI and distribution pattern of atherosclerotic lower-limb lesions in patients with symptomatic PAD. Based on clinical observations, we hypothesised that the presence of RI is associated with distinct below-the-knee arterial disease.

Materials and Methods

A total of 2709 consecutive patients (1048 women, mean age 70.6 ± 11.5 years) with symptomatic chronic PAD and primary angioplasty (±stenting) of lower-limb arteries (3331 limbs and 4110 target lesions) in a tertiary referral centre for peripheral vascular service responsible for a population of about 1 million inhabitants were included in the present analysis between January 1995 and May 2008.

Only patients presenting the first time for endovascular treatment were included in the analysis. Patients with acute limb ischaemia (88 patients during time span of data collection) or redo interventions were excluded. Prior to endovascular revascularisation, all patients had undergone clinical work-up and arterial duplex ultrasound to confirm findings suspected by clinical examination.

Target lesions treated defined relevant atherosclerotic disease manifestation. Location of target lesions was grouped as iliac (common and external and internal iliac artery), femoropopliteal (common, superficial and deep femoral arteries and popliteal artery) and infragenicular (tibioperoneal trunk, anterior and posterior tibial arteries and peroneal artery) disease. In case of multi-level disease, every treated lesion accounted once for the corresponding group. According to our institutional policy, patients undergo full revascularisation during the same hospitalisation, that is, no patient undergoes a two-step interventional procedure for iliac and femoropopliteal target lesions.

The present study complied with the Declaration of Helsinki.[16]

Renal insufficiency was defined by glomerular filtration rate (GFR) $<60\ \mathrm{ml\ min^{-1}}$ per $1.73\ \mathrm{m^2}$ estimated by 'four-variable MDRD' (Modification of Diet in Renal Disease) formula according to the National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines.[17] Patients were grouped into chronic kidney disease stage 1 to 5 (stage 1: GFR above $90\ \mathrm{ml\ min^{-1}}$ per $1.73\ \mathrm{m^2}$, stage 2: GFR of $60–89\ \mathrm{ml\ min^{-1}}$ per $1.73\ \mathrm{m^2}$, stage 3: GFR of $30–59\ \mathrm{ml\ min^{-1}}$ per $1.73\ \mathrm{m^2}$, stage 4: GFR of $15–29\ \mathrm{ml\ min^{-1}}$ per $1.73\ \mathrm{m^2}$, stage 5: GFR less than $15\ \mathrm{ml\ min^{-1}}$ per $1.73\ \mathrm{m^2}$).[17] Diagnosis of diabetes mellitus was defined by fasting blood sugar $>120\ \mathrm{mg\ dl^{-1}}$ or glycosylated haemoglobin >6% or if the patient was on hypoglycaemic drugs.[18] Presence of arterial hypertension was defined by systolic blood pressure >140 mmHg and/or diastolic blood pressure >80 mmHg, or if the patient consumed any antihypertensive drug.[18] Presence of hyperlipidaemia was defined by total cholesterol level $>5\ \mathrm{mmol\ l^{-1}}$ or high-density lipoprotein (HDL) cholesterol $<1\ \mathrm{mmol\ l^{-1}}$, or triglycerides $>2\ \mathrm{mmol\ l^{-1}}$, or if the patient consumed any lipid-lowering drug.[18] Furthermore, patients were classified as smokers and non-smokers. A smoking history (current or former smokers) was established in patients who had one pack-year or more of tobacco use based on patient interview or chart documentation.[18]

Statistical analyses were performed at the Institute of Social and Preventive Medicine, University of Bern, Switzerland. Descriptive analyses of socio-demographic characteristics were based on patient characteristics at the time of the first intervention. Demographic and clinical characteristics of study population are reported as mean ± SD for continuous variables and as number (percentage) for categorical variables. Each target lesion was counted once and classified according to its location as iliac, femoropopliteal and infragenicular disease.

Statistical analysis focussed on impaired renal function as a risk factor for distal PAD. RI was defined as GFR $<60\ \mathrm{ml\ min^{-1}}$ per $1.73\ \mathrm{m^2}$.

Data were stratified in a binary (RI yes/no), grouped (normal renal function: GFR $>90\ \mathrm{ml\ min^{-1}}$ per $1.73\ \mathrm{m^2}$; mild RI: GFR $60–89\ \mathrm{ml\ min^{-1}}$ per $1.73\ \mathrm{m^2}$; moderate RI: GFR $30–59\ \mathrm{ml\ min^{-1}}$ per $1.73\ \mathrm{m^2}$; severe RI: GFR $15–29\ \mathrm{ml\ min^{-1}}$ per $1.73\ \mathrm{m^2}$; and kidney failure GFR $<15\ \mathrm{ml\ min^{-1}}$ per $1.73\ \mathrm{m^2}$) and continuous manner.

A multivariable multinomial logistic regression was used to analyse risk factor associations with the level of lesions. Iliac lesions were chosen as the reference category. Since some patients had more than one target lesion, robust standard errors were used to allow for the multilevel nature of the data. Risk factors included in the statistical model were diabetes mellitus, arterial hypertension, hyperlipidaemia, cigarette smoking, male sex and age.[18]

Results are shown as relative risk ratio (RRR) with 95% confidence intervals (95%- CIs). A $p < 0.05$ was considered statistically significant. All analyses were performed in Stata version 10.1 (Stata Corporation, College Station, TX, USA).

Table 1 Descriptive data of the 2709 patients included in the study additionally classified according to the degree of renal insufficiency (stage 1–5).

Patient characteristics	All	Stage 1[a]	Stage 2[b]	Stage 3[c]	Stage 4[d]	Stage 5[e]
Patients, *n* (%)	2709 (100)	289 (10.7)	1130 (41.7)	1070 (39.5)	147 (5.4)	73 (2.7)
Age (mean ± SD), years	70.6 ± 11.5	62.3 ± 11.7	67.5 ± 11.3	75.4 ± 9.4	76.6 ± 9.3	67.1 ± 10.0
Male gender, *n* (%)	1661 (61.3)	240 (83.0)	800 (70.8)	508 (47.5)	68 (46.3)	45 (61.6)
Diabetes mellitus, *n* (%)	934 (34.5)	81 (28.0)	323 (28.6)	404 (37.8)	83 (56.5)	43 (58.9)
Hypertension, *n* (%)	1771 (65.4)	186 (64.4)	661 (58.5)	752 (70.3)	113 (76.9)	59 (80.8)
Hyperlipidemia, *n* (%)	1405 (51.9)	164 (56.8)	613 (54.3)	516 (48.2)	67 (45.6)	45 (61.6)
Smoking, *n* (%)	1380 (50.9)	217 (75.1)	693 (61.3)	408 (38.1)	37 (25.2)	25 (34.3)
CAD,[f] *n* (%)	749 (28.2)	55 (20.1)	255 (22.9)	360 (34.1)	51 (35.4)	28 (38.4)
CVD,[g] *n* (%)	148 (5.5)	18 (6.3)	39 (3.5)	81 (7.6)	7 (4.8)	3 (4.2)
Bilateral disease, *n* (%)	622 (23.0)	56 (19.4)	287 (25.4)	254 (23.7)	15 (10.2)	10 (13.7)
Multilevel disease, *n* (%)	838 (30.9)	79 (27.3)	308 (27.3)	369 (34.5)	55 (37.4)	27 (37.0)
Mean GFR ± SD	62 ± 24	108 ± 16	73 ± 8	48 ± 8	25 ± 4	9 ± 3

[a] GFR >90 mL/min/1.73 m^2.
[b] GFR 60–89 mL/min/1.73 m^2.
[c] GFR 30–59 mL/min/1.73 m^2.
[d] GFR 15–29 mL/min/1.73 m^2.
[e] GFR <15 mL/min/1.73 m^2.
[f] Coronary artery disease.
[g] Cerebrovascular disease.

Results

Descriptive data of study patients is given in Table 1. Number of treated limbs was 3331 (4110 target lesions). Target lesions were allocated to the three pre-defined anatomic regions as iliac ($n = 1133$), femoropopliteal ($n = 2085$) and infragenicular ($n = 892$).

Results from univariable and multivariable multinominal logistic regression analysis showing the association between RI and distribution pattern of symptomatic lower limb arterial obstructive lesions are given in Tables 2 and 3. RI was an independent predictor for infragenicular disease involvement.

Univariable analysis showed an increased risk for presence of atherosclerotic lesions in the femoropopliteal and more pronounced in the infragenicular as compared with the iliac segment, respectively (Table 2). The grade of RI correlated with an increasing probability for the presence of infragenicular arterial obstructions (all $p < 0.0001$). Continuous analysis of GFR levels demonstrated that a decrease in GFR by 10 ml min^{-1} per 1.73 m^2 was associated with a RRR of 1.30 for distal disease involvement (95% CI: 1.24–1.37, $p < 0.0001$).

After adjustment for age, male sex, diabetes mellitus, arterial hypertension, hyperlipidaemia and current smoking by multinominal regression analysis, the observation of a centrifugal lesion pattern in patients with impaired renal function remained statistically significant (Table 3). Presence of RI was associated with an increased risk for relevant infragenicular arterial disease (RRR 1.48, 95% CI: 1.17–1.86, $p = 0.001$). Furthermore, a decrease in GFR levels by 10 ml min^{-1} per 1.73 m^2 was associated with an increased probability for the presence of distal disease involvement (RRR 1.08, 95% CI: 1.03 1.13, $p = 0.003$). Finally, end-stage renal disease was an independent

Table 2 Influence of renal insufficiency on the distribution pattern of atherosclerotic lesions in peripheral arterial disease. Univariable regression analysis for femoropopliteal and infragenicular disease manifestation.

Risk factor	Atherosclerotic lesions						
	Iliac (reference)	Femoropopliteal			Infragenicular		
	RRR	RRR	95%-CI	p	RRR	95%-CI	p
RI[a] (yes/no)	1	2.08	1.77–2.45	<0.0001	3.2	2.61–3.94	<0.0001
Moderate RI[b] (vs. no RI)	1	2.64	2.05–3.39	<0.0001	3.44	2.43–4.86	<0.0001
Severe RI[c] (vs. no RI)	1	3.17	2.06–4.89	<0.0001	5.02	2.94–8.56	<0.0001
Kidney failure[d] (vs. no RI)	1	6.27	2.53–15.53	<0.0001	16.30	6.32–42.06	<0.0001
GFR increment[e]	1	1.18	1.14–1.21	<0.0001	1.30	1.24–1.37	<0.0001

[a] Renal insufficiency (RI): defined as GFR < 60 mL/min/1.73 m^2.
[b] Moderate RI: defined as GFR 30–59 mL/min/1.73 m^2.
[c] Severe RI: defined as GFR 15–29 mL/min/1.73 m^2.
[d] Kidney failure: defined as GFR < 15 mL/min/1.73 m^2.
[e] Estimated for an increase of 10 mL/min/1.73 m^2 of GFR.

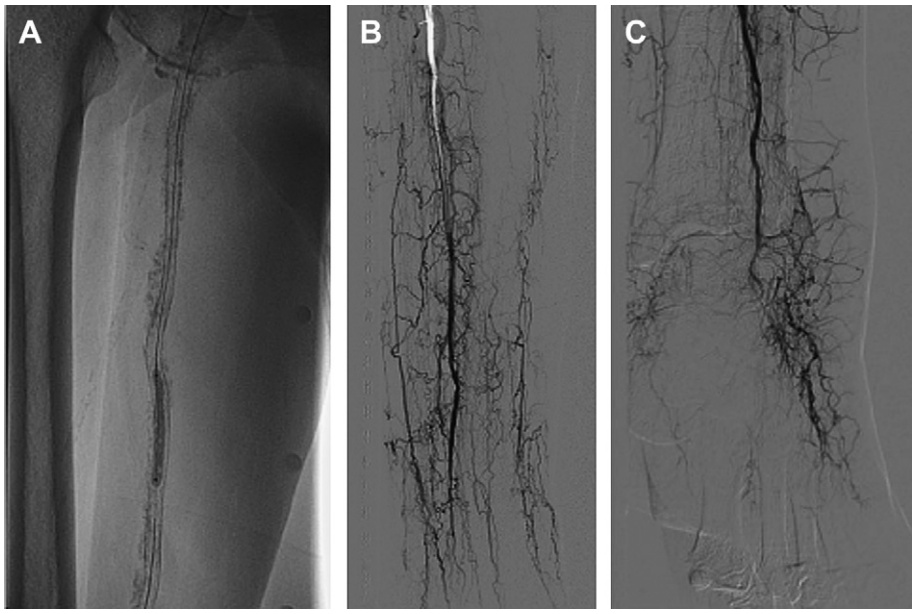

Figure 1 Digital subtraction angiography in a patient with end-stage renal disease and critical limb ischemia. Diffuse severe calcification along the superficial femoral artery (A), occlusion of the distal anterior tibial and proximal peroneal arteries and complete occlusion of the posterior tibial artery (B), occlusion of the plantar and dorsal arterial arches at the foot level (C).

predictor for a centrifugal arterial lesion pattern (RRR 7.72, 95% CI: 3.0—19.88, $p < 0.0001$). In the grouped analysis, a tendency for distal disease involvement was observed for moderate RI (RRR 1.05, 95% CI: 0.72—1.54, $p = 0.804$), but these findings did not reach statistical significance. For patients with severe RI, no correlation with a distal distribution pattern of PAD could be demonstrated.

A similar centrifugal obstructive lesion pattern in multivariable multinominal regression analysis was observed in patients with diabetes mellitus (RRR 3.26, 95% CI 2.59—3.11, $p < 0.0001$) and increased age (RRR per 1-year increment 1.06, 95% CI: 1.05—1.07, $p < 0.0001$), both independent from the presence of RI. Current or former smoking was inversely associated with distal disease involvement (RRR 0.23, 95% CI: 0.17—0.29, $p < 0.0001$).

Prevalence of multilevel PAD and cardiovascular disease was higher in patients with RI, whereas cerebrovascular disease did not show this association (Table 1).

Discussion

This large cohort of patients with symptomatic PAD highlights a significant independent association between RI and below-the-knee arterial disease (Fig. 1). A very similar atherosclerotic phenotype has been described in association with diabetes mellitus and advanced age.[18—21]

Current hypotheses potentially explaining the site selectivity of atherosclerotic lesions include shear stress related to arterial geometry and anatomic, cellular or

Table 3 Influence of renal insufficiency on the distribution pattern of atherosclerotic lesions in peripheral arterial disease. Multivariable multinominal regression analysis for femoropopliteal and infragenicular disease manifestation (data adjusted for diabetes mellitus, arterial hypertension, hyperlipidemia, cigarette smoking, male gender and age).

Risk factor	Atherosclerotic lesions						
	Iliac (reference)	Femoropopliteal			Infragenicular		
	RRR	RRR	95%-CI	p	RRR	95%-CI	p
RI[a] (yes/no)	1	1.11	0.93—1.34	0.252	1.48	1.17—1.86	0.001
Moderate RI[b] (vs. no RI)	1	1.04	0.78—1.38	0.775	1.05	0.72—1.54	0.804
Severe RI[c] (vs. no RI)	1	0.92	0.57—1.48	0.727	0.94	0.52—1.71	0.840
Kidney failure[d] (vs. no RI)	1	3.64	1.51—8.81	0.004	7.72	3.0—19.88	<0.0001
GFR increment[e]	1	1.02	0.98—1.05	0.327	1.08	1.03—1.13	0.003

[a] Renal insufficiency (RI): defined as GFR < 60 mL/min/1.73 m^2.
[b] Moderate RI: defined as GFR 30—59 mL/min/1.73 m^2.
[c] Severe RI: defined as GFR 15—29 mL/min/1.73 m^2.
[d] Kidney failure: defined as GFR < 15 mL/min/1.73 m^2.
[e] Estimated for an increase of 10 mL/min/1.73 m^2 of GFR.

biochemical characteristics of the arterial wall.[19,22,23] Histological structure of lower extremity arteries changes from proximal to distal. Whereas iliac arteries consist of more elastic elements, femoral and infragenicular arteries are characterised by an increased amount of muscular components. Moreover, the relation of arterial lumen to wall thickness decreases from proximal to distal, both generating an alteration in arterial flow, oscillation and shear stress associated with endothelial dysfunction and early atherosclerotic lesions at sites with low shear rate and disturbed flow.[18]

Given the novel concepts regarding the pathogenesis of atherosclerosis,[24–26] it is suggestive that the comparable distribution pattern of lower limb arterial obstructions in diabetic and renally impaired patients may be attributable to a similar pathophysiology of arterial calcification in these two patient groups. Pathogenesis of atherosclerosis is today no longer simply looked upon as passive precipitation of calcium and phosphate in supersaturated plasma. In fact, the aetiology of vascular calcification is mainly dependent on complex molecular and cellular interactions leading to atypical mineralisation resulting from an imbalance of promotion and inhibition of mineralisation.[26] Several studies indicate that a phenotypic change of vascular smooth muscle cells (VSMCs) to osteoblastic cells is a key factor of arterial calcification.[24–28]

In diabetic patients, hyperglycaemia, free fatty acid release and insulin resistance can cause endothelial changes that lead to augmented vasoconstriction, increased inflammation and a hypercoaguable state promoting thrombosis. Within this cascade, VSMC dysfunction is known to have an integral influence on the development of atherosclerosis due to extracellular matrix deposition in intimal lipid-rich lesions and a general cell growth contributing to increased vasoconstriction.[24] Moreover, hyperglycaemia stimulates VSMCs to produce reactive oxygen species contributing to the oxidant-rich milieu in atherosclerotic lesions.[29]

To date, the precise pathophysiology of vascular calcification in RI remains unclear. However, several studies have linked vascular calcification in RI to the induction of VSMC calcification due to elevated serum calcium and phosphate levels or uraemic toxins.[25,30–32]

Inflammation has also been linked to the promotion of VSMC calcification[33] and a higher burden of chronic inflammation is known for both patients with chronic RI and diabetes mellitus. VSMC dysfunction seems to be a key factor in the development of atherosclerosis in patients with chronic kidney disease or diabetes mellitus. Given that VSMCs are abundant in smaller vessels such as the infragenicular arteries, we assume that both histological prerequisites and pathophysiological similarities might explain the similar distribution pattern of PAD in those two patient groups.

Studies on vascular calcification in patients with RI have mostly been performed in end-stage renal disease but growing evidence indicates that already moderate RI promotes vascular calcification.[8,34] Consistent with these findings, an increase in arterial stiffness predominantly in small vessels associated with early kidney dysfunction has been described.[35] Interestingly, a correlation of small-vessel atherosclerosis with moderate renal insufficiency was confirmed by our study, thereby corroborating the above-mentioned associations.

The following limitations of our study have to be addressed. First, obstructive lesion pattern in the present study was defined by endovascular target lesions treated. Consequently, the entire atherosclerotic burden was not considered for analysis and patients undergoing surgical revascularisation were not represented in the present study. However, considering that our institutional protocol stipulates an endovascular-first strategy in both claudicants and patients with critical limb ischaemia[36] we feel that the data set represents a clinical real-life scenario. Moreover, PTA target lesions represent clinically relevant atherosclerosis, although information about early atherosclerotic lesions is missing. Second, we are aware that grouping the treated vessels into three categories might be an oversimplification. We feel, however, that a more differentiated analysis of vascular territories would not have changed our basic message. The present study does not contain information on clinical and angiographic recurrence rates comparing patients with renal impairment to those without renal impairment. Third, as it is known that GFR is regularly underestimated in healthy patients when using the MDRD formula to estimate GFR,[37] we might have overestimated the number of patients with RI and thereby weakened the statistical significance of our results. Finally, we cannot rule out a bias created by only including patients selected for endovascular therapy.

In conclusion, we demonstrated that presence of RI is an independent predictor of a distal obstructive pattern in patients with symptomatic PAD and that the probability of distal disease manifestation increases with its severity. Site selectivity of atherosclerosis in this patient group might be related to given anatomical and histological structures and complex pathophysiological molecular mechanisms. Further studies on the similarities and differences in the pathogenesis of atherosclerosis in patients with diabetes mellitus and RI are warranted. Due to the rapidly increasing number of patients with diabetes mellitus and RI an improved understanding of the pathophysiological mechanisms in these patient subgroups is mandatory and might lead to more specific treatment options in the future.

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