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Impact of Long-term Corticosteroid Therapy on the Distribution Pattern of Lower Limb Atherosclerosis

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Abstract *Objective:* Ectopic calcification and mediacalcinosis can be promoted by corticosteroid use. Aim of the present investigation is to describe macrovascular disease features in patients with long-term corticosteroid therapy and symptomatic lower limb peripheral arterial occlusive disease (PAD).
Methods: A consecutive series of 2783 patients undergoing clinical and angiographic work-up of PAD were screened for long-term (>5 years) corticosteroid use (group A). Comparison was performed to a randomly selected age-, sex- and risk factor-matched PAD control cohort from the same series without corticosteroid use (group B). Patients with diabetes mellitus or severe renal failure were excluded. Arterial calcification was evaluated by qualitative assessment on radiographic images. Severity of atherosclerotic lesions was analysed from angiographic images using a semi-quantitative score (Bollinger score).
Results: In general, 12 patients (5 males, mean age 78.5 ± 9.0 years) with 15 ischaemic limbs qualified to be enrolled in group A and were compared to 23 matching control patients (6 2males, mean age 79.5 ± 6 years) with 32 ischaemic limbs. Incompressibility of ankle arteries determined by measurement of the ankle-brachial index was seen in 12 limbs (80%) in group A compared to 3 limbs (9%) in group B ($p = 0.0009$). No significant difference was found comparing group A and B for segmental calcification, whereas comparison of the atherosclerotic burden using the angiographic severity score showed a significantly higher score at the infragenicular arterial level in group A ($p = 0.001$).
Conclusion: Findings suggest that the long-term corticosteroid therapy is associated with a distally accentuated, calcifying peripheral atherosclerosis inducing arterial incompressibility. This occlusion pattern is comparable to patients with renal failure or diabetes. Further research is required to support our observations.

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Ever since their introduction more than 50 years ago, corticosteroids have played a major role in the management of a wide range of immunological, neoplastic and allergic diseases. However, their use is limited by frequent adverse events, which sometimes may outweigh their beneficial effects. While side effects of corticosteroids such as osteoporosis, cataract and ocular hypertension were reported in various studies,[1–3] there are no clinical data on the macrovascular effects of long-term corticosteroid therapy. Results of some animal and experimental studies suggest that corticosteroids promote arterial calcification.[4,5] The latter is commonly accepted as mediacalcinosis and was found to be associated with advanced age, diabetes mellitus, chronic renal failure and osteoporosis.[6–8] For many years, mediacalcinosis, also known as Mönckeberg sclerosis, was considered a completely benign condition.[9] Currently, it is thought to lead to decreased arterial compliance with increased pulse pressure, left ventricular hypertrophy, peripheral vascular disease and altered coronary perfusion,[7,10,11] and has been associated with a substantially increased risk of cardiovascular morbidity and mortality.[12–14]

Aim of the present study is to describe macrovascular disease features in patients with peripheral arterial occlusive disease (PAD) of the lower limb who have had long-term corticosteroid therapy for the treatment of chronic inflammatory disease. Our hypothesis is that the long-term intake of corticosteroids increases arterial calcification and is associated with a particular distal occlusive pattern as observed in patients with diabetes mellitus or end-stage renal disease.[15]

Patients and Methods

Patients

A consecutive series of 2783 patients presenting to our tertiary vascular referral centre for clinical and angiographic work-up of symptomatic PAD between January 2004 and April 2008 were prospectively screened for long-term corticosteroid use. Inclusion criteria for the present investigation were a documented, symptomatic PAD (Rutherford clinical stage 2–6)[16] and long-term corticosteroid therapy defined as more than 5 years of intake (group A). Exclusion criteria were diagnosis of diabetes mellitus defined as glycosylated haemoglobin >6%, use of hypoglycemic drugs, or renal insufficiency defined as calculated creatinine clearance <30 ml min^{-1}.[17]

A PAD control cohort without corticosteroid therapy at the time of presentation or within their documented medical history was randomly selected from the same 2783 patients presenting to our clinic between January 2004 and April 2008. Control patients were matched in terms of age, sex and risk factor — including smoking, hypertension and hypercholesterolemia — to case patients. The same exclusion criteria as for the patient group were applied to the control group.

Clinical assessment

Routine assessments consisted of demographic data collection, history of cardiovascular risk factors, blood pressure measurement, lipid status, serum glucose and creatinine. For the assessment of circulatory impairment in the affected limb(s), systolic arterial pressures of the anterior and posterior tibial arteries at the ankle were measured. Measurements were taken by experienced nurses and reported in clinical charts and a database. Of the two pressure readings at the ankle, the higher one was chosen for statistical analysis and for the calculation of the ankle-brachial index (ABI). The ABI was calculated by dividing the highest systolic arterial pressure reading at the ankle by the systolic blood pressure in the arm.[18] Tibial artery incompressibility was assumed when the ABI was >1.15, which was reported to be invariably associated with heavy contiguous calcification in the total length of the tibial vessels.[19] The presence of critical limb ischaemia was defined, according to current consensus, as the presence of ischaemic rest pain for more than 2 weeks or ischaemic tissue loss, associated with an absolute ankle pressure <50 mmHg or first toe pressure <30 mmHg.[20]

The presence of arterial hypertension was defined as systolic blood pressure >140 mmHg and/or diastolic blood pressure >80 mmHg, or if the patient was taking any antihypertensive drugs. The presence of hyperlipidemia was defined by total cholesterol levels >5 mmol l^{-1} or high-density lipoprotein (HDL) cholesterol <1 mmol l^{-1} or low-density lipoprotein (LDL) cholesterol > 2.6 mmol l^{-1}, or if the patient was taking any lipid-lowering drug. Furthermore, patients were classified as smokers and non-smokers. A positive smoking history (current or former smoker) was defined by patients who had 1 pack-year or more of tobacco use based on patient interview or chart documentation.

Qualitative assessment of vascular calcification

Vascular calcification was assessed using a scoring system adapted from Adragao and co-workers,[21] evaluating the presence of linear calcifications on angiographic imaging in each of the main arteries of the pelvis, thigh and calf. The presence of linear calcifications was counted as 1 and their absence as 0. The original score from Adragao was applied for vascular calcifications in pelvic and hand X-rays.

Angiographic atherosclerosis severity score

Angiograms were read in a random order by two experienced readers together (Diehm and Willenberg), blinded to clinical data. Distribution and severity of the obstructive lesions were analysed according to a semi-quantitative angiographic score proposed by Bollinger.[22] In brief, the scoring system consisted of an additive score describing the severity of the lesions visualised within each arterial segment analysed (Table 1). The more severe the stenosis, the higher is the score. A single lesion, multiple alterations in half of the arterial segment or less and lesions in more than half of the arterial segment lengths were given different score numbers. With multiple lesions in one arterial segment the highest severity score was considered for analysis, that is, in the presence of an occlusion, plaques or stenoses were not scored; when both categories of stenoses (>50% and <50%) were present, plaques were not scored; for each type of occlusion only one length category was indicated.

Table 1 Description of occlusive patterns according to the Bollinger scoring system.[23]

Occlusion	Stenosis >50%	Stenosis <50%	Plaque <25%	Location
	4	2	1	Single
13	5	3	2	Multiple < half of vessel
15	6	4	3	Multiple > half of vessel

The vertical columns represent the different atherosclerotic lesions defined, the horizontal ones the extent of the lesions detected in each of the artery segments. The numbers appearing in the single fields correspond to the score numbers. The additive score is obtained by adding the scores for the four different lesions.

The following arteries were evaluated for the qualitative assessment of vascular calcification and angiographic grading: common iliac artery (CIA), external iliac artery (EIA), common femoral artery (CFA), superficial femoral artery (SFA), deep femoral artery (DFA), popliteal artery (PPA), anterior tibial artery (ATA), tibioperoneal trunk (TPT), posterior tibial artery (PTA) and peroneal artery (PA).

The location of target lesions was grouped as iliacofemoral (common, external iliac artery and CFA), femoropopliteal (SFA, DFA and PPA) and infrageniculate or distal (tibiofibular trunk, ATA, PTA and PA). For statistical analysis average scores of these three segments including the latter mentioned arterial vessels were determined.

Statistical analysis

Demographic and clinical characteristics of the study population are reported as mean ± SD for continuous variables, and as numbers and percentages for categorical variables. Comparisons were performed using the Kruskall–Wallis test and the Student *t*-test for continuous variables, and the Fisher exact test for discrete variables. A p-value <0.05 was considered statistically significant. All calculations were performed using SPSS (version 13.0, SPSS, Chicago, IL, USA) and Stata (version 10.1, Stata Corporation, College Station, TX, USA).

Ethics

The study was carried out based on the Declaration of Helsinki[23] and all patients gave informed consent prior to inclusion in the study.

Results

Out of the 2783 consecutive patients with clinical and angiographic work-up for symptomatic PAD, we identified 38 patients with long-term corticosteroid therapy for at least 5 years. Twenty-three of these 38 patients were excluded due to the presence of diabetes mellitus and renal insufficiency (Fig. 1). Fifteen patients being on long-term steroid therapy fulfilling the inclusion criteria were identified. Age-, sex- and risk factor-matched controls without diabetes mellitus and without severe renal insufficiency and with no use of corticosteroids in their medical history were found for 12 of these 15 patients, so that these 12 patients (5 males, mean age 78.5 ± 9.0 years) with 15 ischaemic legs (group A) entered into the analysis. Indications for long-term corticosteroid therapy in these 12 patients were rheumatoid polyarthritis ($n = 3$), polymyalgia rheumatica ($n = 3$), scleroderma ($n = 1$), Crohn's disease ($n = 1$), lupus erythematosis ($n = 2$), Wegener's disease ($n = 1$) and giant cell arteritis ($n = 1$). The sex-, age- and risk factor-matched PAD control cohort from the same consecutive series of PAD patients consisted of 23 patients (six males, mean age 79.5 ± 6 years) with 32 ischaemic limbs.

Clinical stage of PAD

Case patients showed a statistically significant worst clinical stage at presentation. Eight of 15 legs (53%) of group A were diagnosed with a Rutherford stage 4–6 consistent with the definition of critical limb ischaemia. In the control cohort, 3 of 32 legs (9%) were diagnosed with a Rutherford stage 4–6 and 29 of 32 (91%) legs with a Rutherford stage 2–3 ($p = 0.002$).

Ankle-brachial pressure measurements

Measurement of ankle and brachial pressures revealed arterial incompressibility of lower limb arteries consistent with mediacalcinosis in 12 of 15 (80%) of the affected limbs in group A and in 3 of 32 limbs (9%) in group B, respectively ($p < 0.0001$).

Qualitative assessment of vascular calcification

Substantial arterial calcification of all three vascular segments was more pronounced in patients receiving long-

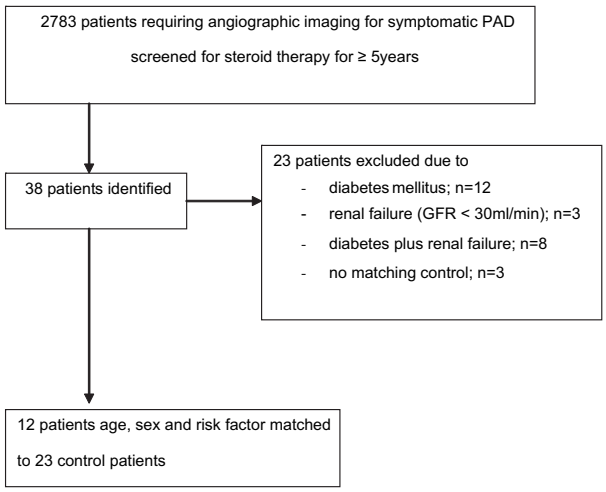

Figure 1 Decision flow chart of screening process.

term steroid therapy, but was also found in the control cohort (Table 2). Of note, 12/12 legs (100%) in the steroid group and 1/12 legs (7%) of control patients exhibiting ankle arterial incompressibility showed linear calcification of infragenicular arteries ($p < 0.001$).

Angiographic severity score

No significant differences were observed in the atherosclerotic burden of iliaco-femoral arteries and femoro-popliteal arteries between both groups (Table 3). By contrast, infragenicular arteries showed a significantly higher atherosclerotic burden in patients from group A as compared with patients from group B ($p < 0.0001$) (Table 3, Fig. 2).

Discussion

The present consecutive series describes macrovascular disease features of PAD patients on long-term glucocorticosteroid therapy for various chronic inflammatory diseases. Findings suggest that long-term corticosteroid therapy is associated with a distally accentuated, calcifying peripheral atherosclerosis inducing arterial incompressibility. An occlusion pattern very comparable to patients with renal failure or diabetes was excluded in this series. The majority of patients with long-term corticosteroid therapy showed mediacalcinosis with incompressibility of ankle arteries, and in all of these patients linear calcification of infragenicular arteries on plain X-ray was observed. Mediacalcinosis is frequently observed in patients with renal insufficiency or diabetes mellitus predefined to be excluded in the present series.[15] Mediacalcinosis with incompressibility of ankle arteries was significantly less in legs of the control group although linear calcification at the infragenicular arteries on plain X-ray was observed in 37% of these legs. This might be simply explained by the qualitative character of our analysis adapted to the scoring of Adragao[21] which does not give any quantitative information. However, qualitative assessment of calcification in group A by means of plain X-ray revealed widespread arterial wall calcification in the peripheral flow path of pelvis and leg with the highest prevalence in the lower limb

Table 2 Vascular calcification as assessed using a scoring system adapted from Adragao and co-workers[22] evaluating the presence of linear calcifications on angiographic imaging in each of the main arteries of the pelvis, thigh and calf. Presence of linear calcifications were counted as 1 and its absence as 0. Group A, glucocorticoid case PAD patients, $n = 12$ (15 limbs); group B, case control PAD patients, $n = 23$ (32 limbs). Iliaco-femoral defines as common femoral artery, common iliac artery, external iliac artery; femoro-politeal defined as superficial femoral artery, deep femoral artery, popliteal artery; infragenicular defined as anterior tibial artery, tibioperoneal trunk, posterior tibial artery, peroneal artery.

Arterial segment	Vascular calcification(%)		p-value[a]
	Group A ($n = 15$ legs) N(%)	Group B ($n = 32$ legs) N(%)	
Iliaco-femoral	8 (53)	12 (37)	0.35
Femoro-popliteal	10 (67)	14 (43)	0.21
Infragenicular	9 (60)	12 (37)	0.21

[a] Fisher's exact test.

Table 3 Average of Bollinger score of the three segments which were evaluated by two independent observers. The average was obtained by adding the score of the single arterial segment divided by the number of single arterial segment of each segment. Group A, glucocorticoid case PAD patients, $n = 12$ (15 limbs); group B, case control PAD patients, $n = 23$ (32 limbs). Iliaco-femoral defines as common femoral artery, common iliac artery, external iliac artery; femoro-politeal defined as superficial femoral artery, deep femoral artery, popliteal artery; infragenicular defined as anterior tibial artery, tibioperoneal trunk, posterior tibial artery, peroneal artery.

Arterial segment	Average of angiographic severity score (mean ± SD)		p-value[a]
	Group A (15 legs)	Group B (32 legs)	
Iliaco-femoral	1.33 (0.5)	1.56 (2.2)	0.12
Femoro-popliteal	3.15 (2.3)	3.79 (3.3)	0.61
Infragenicular	7.85 (2.9)	3.46 (2.8)	0.0001

[a] Kruskal–Wallis rank based comparison.

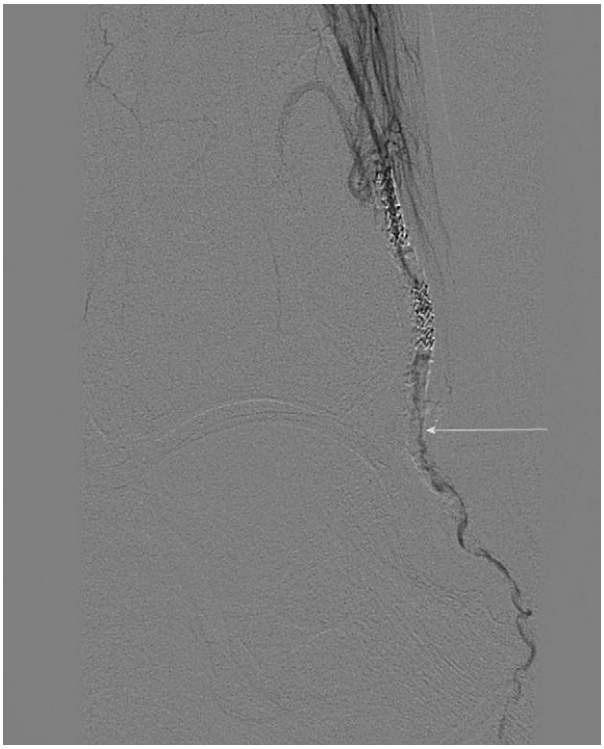

Figure 2 Angiography of a patient on long-term corticosteroid therapy. The anterior tibial artery shows severe calcification and obstruction (arrow). The proximal part of the vessel shows two stents after angioplasty.

distally. These findings were consistent with the clinical presentation and results of ABI measurement. By contrast, the matched control cohort of PAD patients did not show this pattern and mediacalcinosis was only observed in 3/32 legs while arterial wall calcifications were less frequent.

Comparison of the iliaco-femoral, femoro-popliteal and infragenicular arterial segments between both groups revealed a significant augmentation of atherosclerotic burden in infragenicular arteries in patients of group A. This centrifugal pattern of atherosclerosis is also typical for patients with diabetes mellitus or end-stage renal disease.[15] Of note, we did not observe any augmented atherosclerotic involvement of the DFA in patients on long-term steroid therapy as often seen in patients with diabetes mellitus.[15] Consistent with the more distal disease burden in steroid case patients, clinical stage was clearly more advanced as compared with the case control cohort with case and control PAD patients selected from the same consecutive patient series using identical inclusion and exclusion criteria.

Mechanisms of vascular calcification promoted by corticosteroids are not entirely understood yet. Recently, it has been shown that corticosteroids mediate osteoblastic differentiation.[8] The cells — which may be derived from stem cells or differentiation of existing cells like pericytes or smooth muscle cells — have been identified to promote calcification of the extracelluar matrix in the absence of a cartilage template.[4] It has also been shown that dexamethasone enhances the differentiation of pericytes which reside in the vascular wall, exhibiting decreased expression of osteopontin and matrix G1a protein as well as vascular calcification associated factor mRNA, which results in increased alkaline phosphatase activity and calcium deposition.[4]

Hypotheses explaining site selectivity of atherosclerotic lesions include hemodynamic stress related to arterial geometry, and cellular anatomic or biochemical variations in the arterial wall.[24] Iliac arteries are characterised by elastic fibres, whereas femoral and infragenicular arteries contain progressively more muscular elements. Moreover, the relation of arterial lumen to wall thickness decreases from proximal to distal, generating both, an alteration in arterial flow and shear stress associated with endothelial dysfunction, and an early type of atherosclerotic lesions at sites with low shear rate and disturbed flow.[15]

Several authors reported on the cardiovascular risk of patients requiring corticosteroid therapy.[25–27] Results are heterogeneous, and the overall effect of corticosteroid on the cardiovascular system and risk of cardiovascular events remains unclear. Wei and co-workers[26] reported a three-fold increased risk for cardiovascular events in high-dose corticosteroid users (>7.5 mg day^{-1}). Davis et al.[28] found a three-fold elevated risk for cardiovascular events in rheumatoid factor-positive patients with rheumatoid arthritis, whereas Kremers and colleagues[25] did not find an association between corticosteroids and elevation of risk for cardiovascular events in patients with polymyalgia rheumatica. Corticosteroids may indirectly increase the risk of cardiovascular disease through their adverse effects on traditional cardiovascular risk factors.[29] This may be one of the components increasing the risk of cardiovascular disease, which was found to be independent of traditional cardiovascular risk factors in patients with rheumatoid arthritis.[30] Due to the complex mechanisms of vascular calcification and plaque formation, clinical data including mainly heterogeneous settings of cardiovascular risk factors will always be limited in their significance. A mechanism that may be independently associated with cardiovascular risk and macrovascular disease features is the inflammatory activity related to the disease entity treated with corticosteroids, and this might influence atherosclerotic progression.[31]

This study has several limitations. First, the limited number of patients hampers our ability to draw definitive conclusions. This is, however, contra-balanced by meeting strict inclusion and exclusion criteria of the patient population analysed in the present series. Second, as the present study is descriptive it cannot be excluded that the inflammatory activity of the disease entity being treated with corticosteroids influenced atherosclerotic progression,[31–33] whereby the extraordinary trend for calcification is consistent with mechanisms related to corticosteroids.[4,5] Even if the mechanism remains unclear, our findings should be recognised by various specialists treating patients particularly underlining the risk of severe distally accentuated arterial disease. Third, the advanced age of the study population may have contributed to the presence of vascular calcification and mediacalcinosis.[8] However, the latter is hardly possible considering the data of the age-, sex- and risk factor-matched control group, which shows significantly less mediacalcinosis.

Conclusion

Results of this consecutive series suggest that long-term corticosteroid therapy for the treatment of chronic inflammatory disease might be associated with a distally dominated calcifying peripheral atherosclerosis. The distribution pattern of lower limb atherosclerosis is comparable to that of patients with severe renal failure or long-standing diabetes, suggesting that similar pathogenic mechanisms may play a role. Further investigations are necessary to confirm our findings, explain the effects and define consequences of corticosteroid use on peripheral vascular vessels.

Conflicts of interest

The authors have declared no conflicts of interest.

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