Review Article

Medial Sclerosis—Epidemiology and Clinical Significance

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Summary

Background: Medial sclerosis (MeS) is a chronic systemic vascular disease that mainly affects the arteries of the lower limb. Its prevalence in the general population is approximately 2.5% (range: 1.6% to 10.0%). It is more common in men than in women.

Methods: This review is based on pertinent publications retrieved by a selective search in PubMed.

Results: MeS is the final common pathway of a wide variety of diseases; its pathogenesis is not fully understood. It often remains clinically silent for decades and is usually diagnosed as an incidental finding or in a late stage. MeS with or without atherosclerosis is the most common histologic finding after limb amputation. MeS of the below-the-knee arteries is a major risk factor for chronic critical leg ischemia (OR:13.25, 95% confidence interval: [1.69; 104.16]) and amputation (RR 2.27, [1.89; 2.74]). Patients with peripheral arterial occlusive disease and marked calcification have a much higher risk of amputation (OR 2.88, [1.18; 12.72]) and a higher mortality (OR 5.16, [1.13; 21.61]). MeS is a risk factor for the failure of endovascular treatment of the pedal arteries (OR 4.0, [1.1; 16.6]). The more marked the calcification, the higher the risk of major amputation (HR 10.6 [1.4; 80.7] to HR 15.5 [2.0; 119]). Patients with vascular calcifications have been found to have lower patency rates and higher treatment failure rates two years after open surgical revascularization of the below-the-knee arteries. No pharmacotherapy for MeS is available to date.

Conclusion: MeS is an important risk factor for chronic critical lower limb ischemia, amputation, morbidity, and complications, particularly after endovascular and surgical procedures.

Cite this as:
Lanzer P, Ferraresi R: Medial Sclerosis—epidemiology and clinical significance.
Dtsch Arztebl Int 2023; 120: 365–72. DOI: 10.3238/arztebl.m2023.0066

Medial sclerosis (MeS) was first described by Johann Georg Mönckeberg in 1903 (1). However, it was not until the 1990s that MeS was identified as an independent risk factor for cardiovascular disease (2). Today, MeS has been recognized as an important cause of chronic critical leg ischemia and a major risk factor for complications, especially of endovascular treatment (3).

The disease is characterized by increasing deposition of hydroxyapatite crystals, leading to progressive medial destruction. The pathogenesis of MeS is not fully understood; most likely, it is a final common pathway of several different conditions. No pharmacotherapy for MeS is available to date.

In this review article, we provide information on the epidemiology and clinical significance of this disease whose importance has so far been rather underestimated in everyday clinical practice.

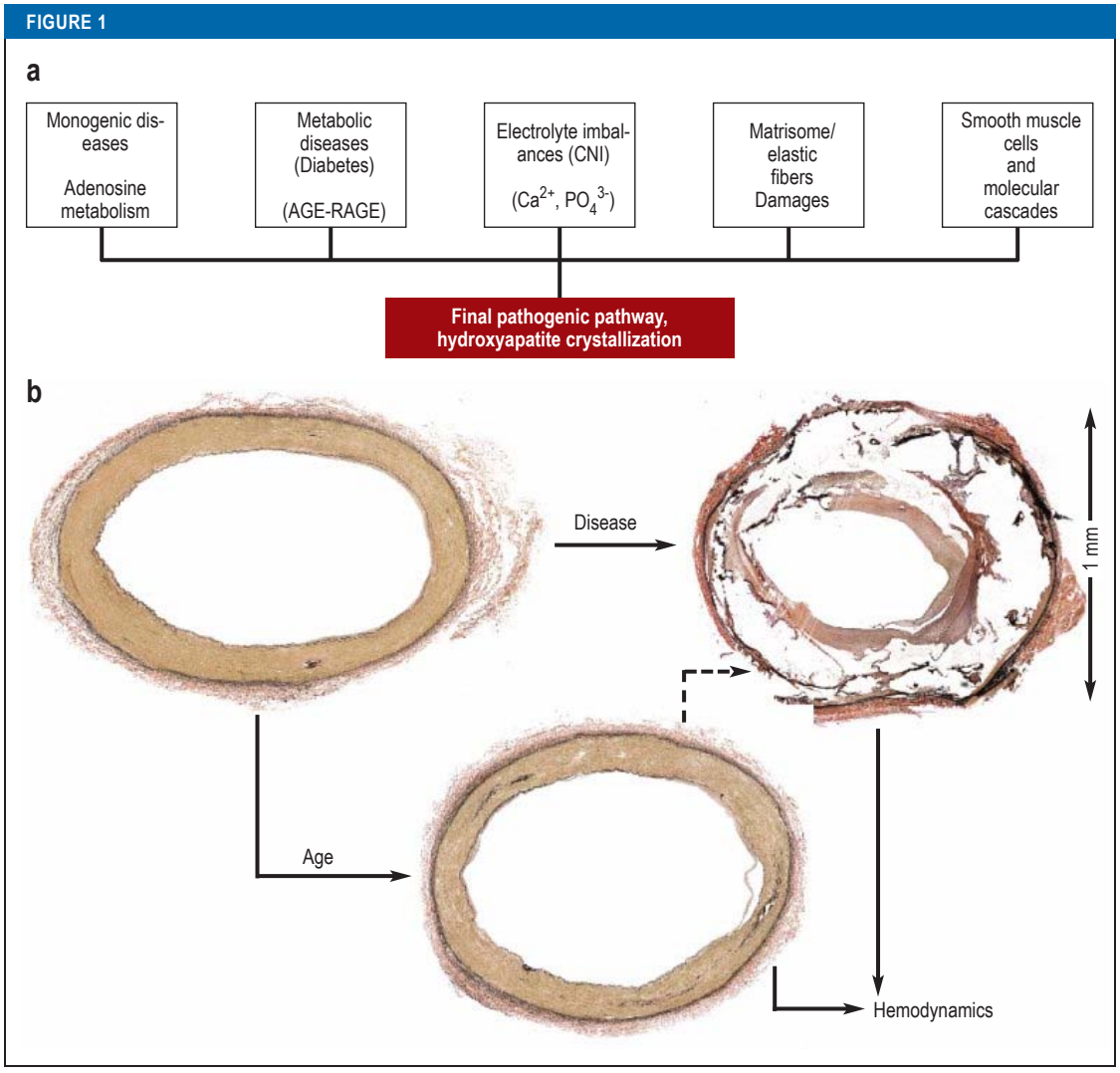
Methods

This review is based on pertinent publications retrieved by a selective search in the PubMed database and with the Google Scholar search engine, using the search terms “Mediasklerose“ (German) and “medial arterial calcification“ (English).

Epidemiology

The prevalence of MeS can be estimated based on ankle-brachial index (ABI) screening data. A prevalence rate of 2.5% (range 1.6% to 10.0%) was determined for the general population; MeS is more

FIGURE 1



Histology images by courtesy of Dr. Alexey Kamenskiy, University Nebraska, Omaha, U.S.A.

Hypothesis of the pathogenesis of medial sclerosis, greatly simplified diagram

a) Medial sclerosis is the final common pathway of diverse conditions with distinct pathogenesis. As a consequence of mechanisms not yet fully understood, a pathogenetic cascade of medial calcification is triggered. In monogenic diseases, there is a defect in the metabolism of adenosine. Especially in diabetes mellitus, advanced glycation end products (AGEs) are thought to play a key role. In patients with chronic kidney disease, disturbances of electrolyte metabolism and electrolyte homeostasis in the medial layer of the arterial wall are of special importance. Damage to elastic fibers and biochemical changes in the extracellular matrix may occur, especially with advanced age. Activations of a number of molecular mechanisms, including transdifferentiation of vascular smooth muscle cells from a contractile to a secretory phenotype and disturbances in the balance between promoters and inhibitors, are thought to be involved in the calcification processes seen in all types of the disease. Common to all processes is the crystallization of hydroxyapatite.

b) Onset of medial calcification already occurs in younger individuals and the process of calcification increases with age. In some cases, severe, abnormal medial calcifications may develop even in otherwise healthy individuals. Non-age-related medial sclerosis is characterized by progressive destruction of the media. The effects of medial sclerosis on hemodynamics are an area of ongoing research.

common in men than in women. The prevalence ranged from 9% to 34% in individuals at high cardiovascular risk, from 9% to 41% in patients with diabetes mellitus and was 25% in patients with severe chronic kidney disease, and up to 93% in patients with chronic critical leg ischemia (*eTable 1*). In the scientific literature, however, a number of different threshold values have been used, including ABI>1.3, >1.4, >1.5, non-compressible, >260 mm Hg, as well as specific differences in blood pressure measurements. Furthermore, the accuracy of prevalence data is somewhat limited as a result of the limited sensitivity and specificity of blood pressure measurements in early stages of the disease and due to extravascular indurations. The occurrence of MeS lesions in general specimens varies with age; in patients aged ≤ 20, 21–30, 31–40, 41–50, 51–60, 61–70, and > 71 years, a histology-based prevalence rate of 7%, 17%, 16%, 48%, 46%, 64%, and 61%,

respectively, was found (4). Given the high prevalence of MeS lesions in the general population, their clinical significance must be put into perspective and, for the time being, probably limited to patients with documented impaired perfusion. Yet, considering the present inconsistency in screening, a high number of unreported cases of MeS with potential clinical significance may be assumed as well. Typically, MeS affects the arteries of the lower limbs, but it may occur in other vascular regions as well (*eTabelle 2*). MeS is most commonly found in patients with diabetes mellitus or with chronic kidney disease; however, MeS is also part of the phenotype of other diseases (*eTable 3*). Moreover, severe MeS can occur in patients with no known disease (5). In view of the rising incidence of diabetes mellitus and the impact of demographic change, the prevalence of MeS is expected to continue to increase further.

Risk factors

Major risk factors for MeS include diabetes mellitus, chronic kidney disease and age. With the exception of diabetes mellitus, the typical risk factors of atherosclerosis are of no significance.

Pathogenesis

MeS is characterized by increasing calcifications in the middle layer of the arterial wall, the tunica media. The pathogenesis which involves the crystallization and accumulation of hydroxyapatite, a compound that contains phosphate and calcium (6), has not yet been well understood, with the exception of monogenetic disease (7). However, in patients with diabetes or chronic kidney disease, strong evidence for possible involvement of specific molecular cascades has been found. In patients with diabetes, for example, the accumulation of toxic advanced glycation end-products (TAGEs) is thought to be of pathogenic significance (8). TAGEs are thought to contribute to vessel wall injury through both their accumulation and their numerous cell-toxic intracellular effects which are mediated by the receptor for advanced glycation end-products (RAGE) (9). In patients with chronic kidney disease, one of the pathogenic mechanisms is the increased uptake of phosphate in vascular smooth muscle cells by means of inorganic phosphate transporter receptors (PiT-1,2) with subsequent increase in Runt-related transcription factor 2 (RUNX2) which initiates a number of toxic intracellular processes. Among these, osteogenic transdifferentiation of vascular smooth muscle cells is of particular significance. Recently, sirtuins (SIRTs), a group of enzymes with high metabolic activity, have been reported to prevent osteogenic smooth muscle cell transformation in patients with chronic kidney disease (10). The clinical significance of the numerous experimentally identified promoters and inhibitors of calcium phosphate precipitation and hydroxyapatite crystallization (*eTable 4*) remains uncertain. *Figure 1* provides an overview of the different hypotheses of the pathogenesis of MeS.

Histopathology

The histological appearance of MeS is characterized by disseminated, confluent, and, in advanced stages, ring-like calcifications of the media. In the intima, myointimal hyperplasia – hyperplasia without signs of atherosclerosis – is often noted. Additional ectopic bone formation is common. eFigure 1 compares the *histologi*es of MeS and atherosclerosis side by side. eFigure 2 shows the histological *stages of* MeS (11).

Hemodynamics

Progressive stiffening of the affected arteries impairs the buffering (Windkessel) function of the aorta and downstream arteries, increases the afterload of the left ventricle and promotes the development of left heart failure. The increased pulsatility leads to additional damage to parenchymal organs, such as the brain, liver, and kidney (12). The hemodynamic impact of MeS on small artery function and microcirculation is an area of on-going research.

Diagnosis

Clinical picture

MeS is usually clinically silent for a prolonged period of time and may even remain undiagnosed for life. The initial lack of clinical signs and symptoms in patients with overt MeS is explained by the absence of hemodynamically significant stenoses. Moreover, the clinical manifestation of the disease is mitigated by the development of collaterals. We, as the authors, have many years of experience in the management of patients with tissue necrosis as the initial manifestation of MeS. Such late initial manifestations presumably reflect the exhaustion of collateral reserves and the resulting microcirculatory decompensation. Consequently, these patients may not always present with intermittent claudication, a typical symptom of Fontaine stages IIa/IIb peripheral arterial occlusive disease.

Ankle-brachial index

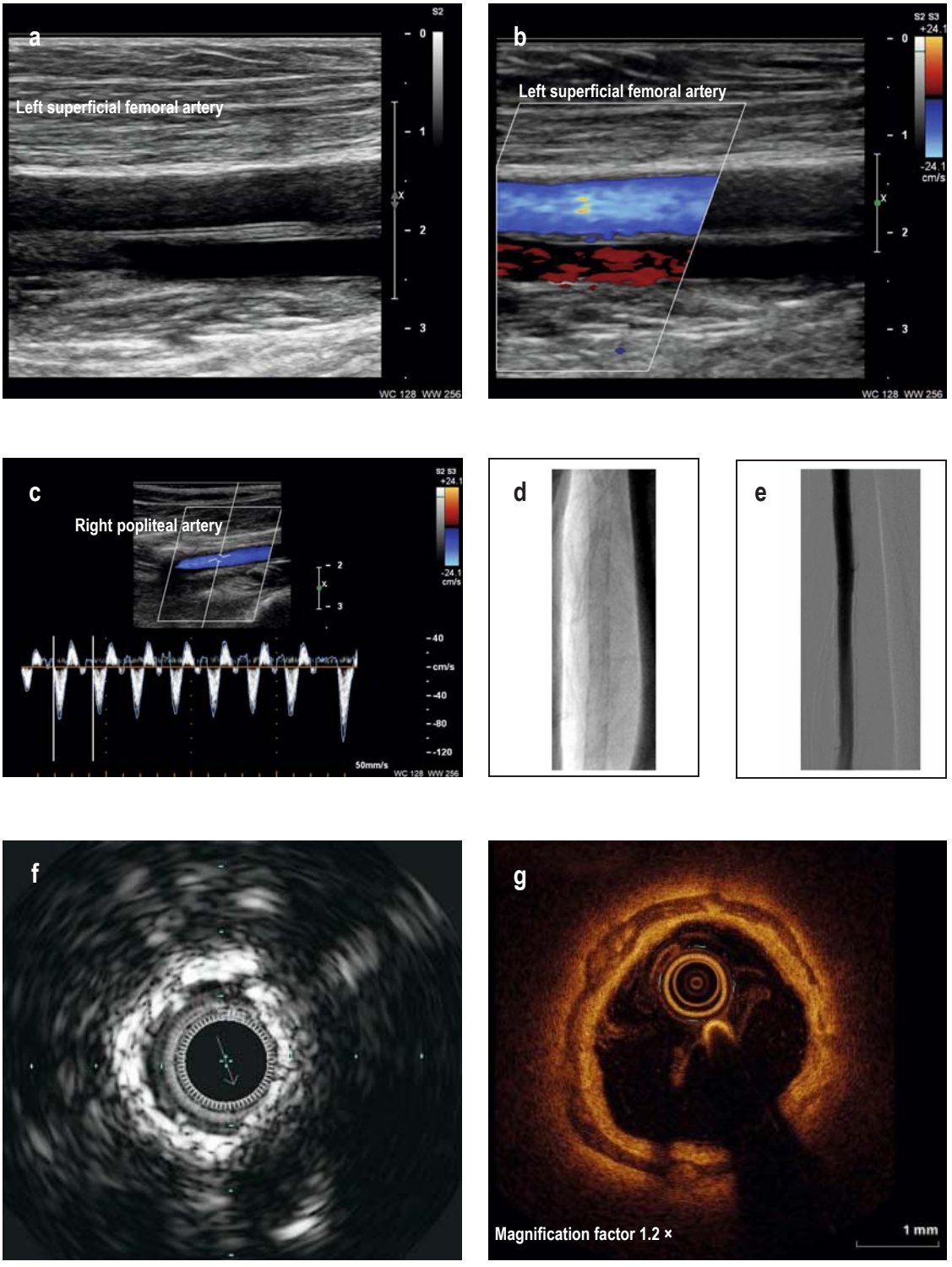
Screening for MeS is performed by determining the ankle-brachial index (ABI). Here, the threshold is an ABI >1.4 (13). In patients with MeS, determining the ABI after a defined stress (for example, rising up on the toes for 20 times) is of no significance. In case of inconclusive findings, the great toe-brachial index can be determined; however, its significance in clinical practice is limited.

Pulse wave velocity

Due to vascular stiffening, pulse wave velocity (PWV) is increased in patients with MeS. According to the standardized and reproducible measurements, a PWV of 10 m/s is considered as the threshold (14).

Conventional radiography

In MeS, plain radiographs show a typical “railroad track” pattern of calcification. In contrast to the coarse granular pattern of calcification in atherosclerosis, MeS calcifications present as uniform and continuous fine granular stripes (15).



a–c) adapted from Lanzer et al. J Am Coll Cardiol 2021; 78:1145–65 (by courtesy of Elsevier).

Figure 2: Imaging diagnosis of medial sclerosis

a)B-scan ultrasound shows medial sclerosis as stripes with increased echogenicity of the arterial wall; the endothelial interfaces are smooth and free of atherosclerosis.

b) Color duplex imaging shows laminar blood flow.

c) Color duplex imaging using pulse wave (PW) technology shows normal triphasic arterial flow.

d) Plain radiograph of the brachial artery shows the railroad track pattern of calcification characteristic of medial sclerosis.

e) Corresponding x-ray angiography reveals smooth endothelial interfaces.

f) In intravascular ultrasound of the superficial femoral artery, the medial calcifications appear as annular, echogenic structures.

g)On optical coherence tomography of the popliteal artery, the calcifications of the media appear as dark stripes or rings.

Vascular ultrasound

On B-scan ultrasound, MeS is diagnosed by homogeneous, hyperechoic streaks within the arterial wall with smooth endothelial interfaces. In routine clinical practice, ultrasound scoring methods are rarely used to determine the severity of MeS (16).

Computed tomography

Computed tomography (CT) shows MeS calcifications as narrow, uniform stripes within the arterial wall which are typically circular in cross-section and almost continuous.

When compared with histological findings, the sensitivity of CT scans for calcifications in MeS and in atherosclerosis was determined to be approximately 70%. This sensitivity equals the sensitivity of conventional radiography (17).

Intravascular ultrasound

Intravascular ultrasound (IVUS), with a spatial resolution of approximately 100 µm, show MeS calcifications as uniform stripes or rings in contrast to the coarse, lump-like pattern of calcification seen in atherosclerosis. Unlike the calcifications in atherosclerosis, acoustic shadowing is rarely observed with MeS calcifications.

Optical coherence tomography

Optical coherence tomography (OCT), with a spatial resolution of approximately 10 µm, shows MeS calcifications as dark, low-intensity signal, often inhomogeneous, but always sharply demarcated arc- to ring-shaped stripes or rings. Typically, these calcifications can be clearly located in the middle layer of the vessel wall. In *Figure 1 a–g*, the imaging findings in MeS are illustrated with typical examples.

Laboratory testing

In MeS, clinical laboratory testing is limited to screening for risk factors (*eTable 5*). Testing for specific biomarkers of vascular calcifications (18) has not yet been adopted for clinical use.

Figure 2 shows the recommended diagnostic algorithm for patients with suspected MeS.

Clinical significance

In patients with chronic critical leg ischemia, MeS is a common finding. It can occur both with and without atherosclerosis. In histological studies of distal artery specimens from amputated limbs, MeS was found significantly more frequently than atherosclerosis (11). Patients with critical leg ischemia and an ABI of > 1.3 are at an increased risk of amputation (19, 20). MeS of below-the-knee arteries is a major risk factor for both chronic critical leg ischemia (odds ratio [OR] 13.25, 95% confidence interval [1.69; 104.16]) (21) and amputation (relative risk [RR] 2.27, [1.89; 2.74]) (22). Patients with peripheral arterial occlusive disease and high-grade compared to low-grade calcifications have significantly increased risks for both amputation (OR 2.88, [1.18; 12.72]) and mortality (OR 5.16, [1.13; 21.61]) (23). In Germany, 63 430 amputations were performed in 2018 (24). Thus, MeS in below-the-knee and foot arteries is a common cause of amputation in Germany according to the literature.

Although patients with chronic critical leg ischemia typically present with a slowly progressive course, MeS can also be fulminant in individual cases (25). The causes of a fulminant course are still not known.

In cases with asymptomatic disease, MeS is probably a benign condition secondary to degenerative, age-related changes in the media; however, with increasing age, severely impaired peripheral perfusion may develop in some cases, even in the absence of additional risk factors (4).

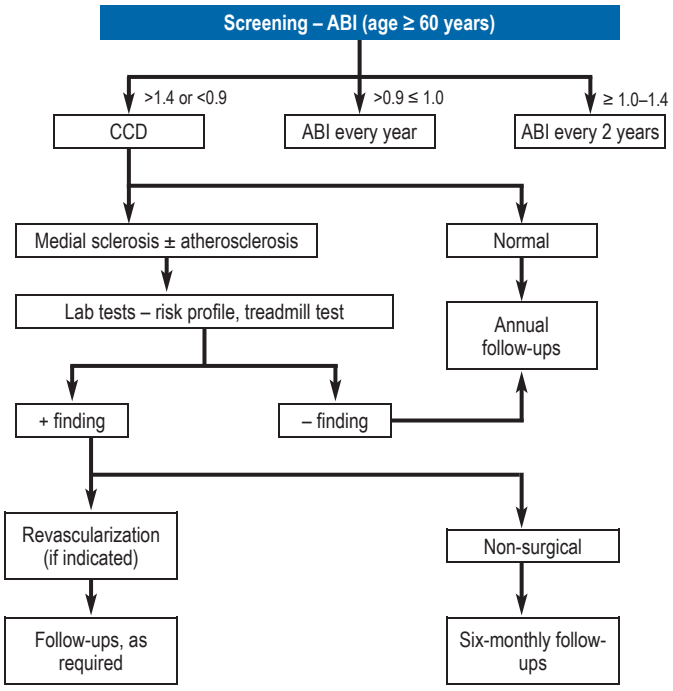
In patients with acute or chronic dissection of the thoracic aorta, MeS was frequently diagnosed based on chest CT findings (26). However, a causal relationship was not concluded from these radiographic findings.

Arterial wall stiffening due to MeS could impair positive remodeling and thereby contribute to the clinical manifestation of atherosclerosis (27).

Management

There is no known causal therapy for MeS. The clinical studies performed so far, evaluating the use of phosphate binders, vitamin K preparations, pyrophosphate,

FIGURE 3



Diagnostic algorithm for medial sclerosis
ABI, ankle-brachial index; CCD, color-coded duplex sonography

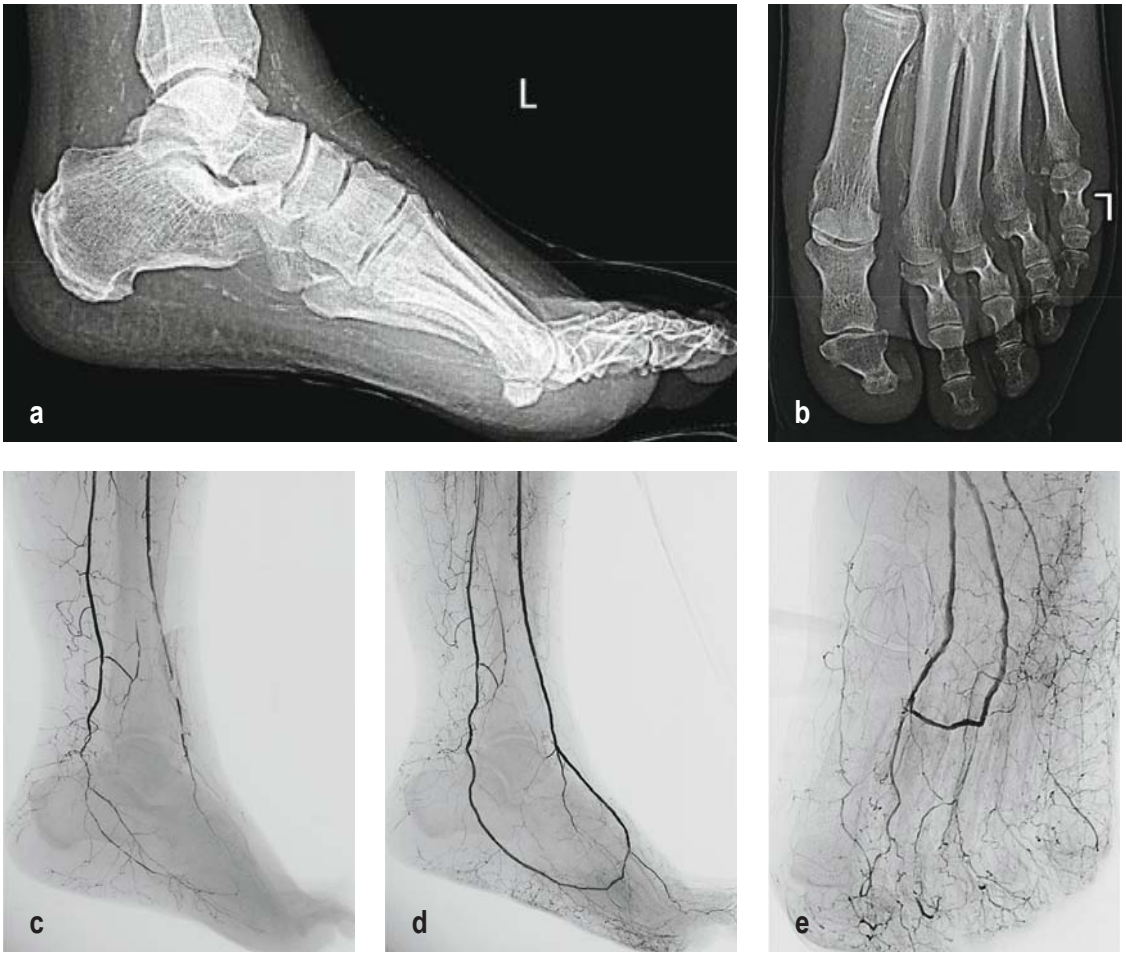


Figure 4: Percutaneous transluminal angioplasty in patients with type 2 diabetes and marked medial sclerosis of the below-the-knee and foot arteries

a) The latero-lateral projection of the foot on plain radiograph shows the typical railroad track pattern of medial calcifications of the dorsalis pedis artery and lateral plantar artery.

b) The anteroposterior projection of the foot on plain radiograph shows the medial calcifications of the metatarsal and digital arteries.

c) Lateral imaging of the foot using digital subtraction angiography (DSA) shows marked rarefaction of the entire arterial bed with numerous stenoses and vascular occlusions prior to percutaneous transluminal angioplasty (PTA).

d) The lateral DSA image of the foot after PTA shows improved vascularization of the forefoot.

e) The corresponding antero-posterior image shows the persisting marked rarefaction of the arterial terminal vessels.

tenapanor, acetazolamide, and aldosterone, have not shown convincing results (3). In patients with advanced chronic kidney disease, treatment with myo-inositol hexaphosphate, aimed at stopping the progression of MeS by inhibiting appositional HAP crystal growth, showed benefits in first randomized clinical trials (28). Likewise, the administration of magnesium appears to offer therapeutic advantages in this patient population (29). In view of the potential promotion of the clinical manifestation of atherosclerosis, strict adherence to prevention should be recommended in patients with MeS.

With endovascular treatments, MeS in the foot is a significant risk factor for treatment failure (OR 4.0, [1.1; 16.6] and for the risk of major amputation, with significant increases in risk with increasing severity of calcification (HR 10.6 [1.4; 80.7] to HR 15.5 [2.0; 119]) (30). In patients with vascular calcifications of below-the-knee arteries who underwent open surgical revascularization, lower patency rates and higher treatment failure rates were found during follow-up (31). Considering the distinctive features of MeS compared to atherosclerosis, especially with regard to the massive calcifications, to the marked myointimal hyperplasia, and to the largely exhausted perfusion reserves in these patients, endovascular treatments, in particular, should be performed exclusively by surgeons who are familiar with this condition in order to avoid unnecessary complications. *Figure 4* shows a typical example of endovascular treatment in a patient with peripheral arterial occlusive disease secondary to MeS.

Outlook

Pharmacotherapy of MeS requires a thorough understanding of the pathogenesis of the disease. Despite

advances in basic research over the past 20 years, the pathogenesis of MeS has remained largely hypothetical until today. As an additional drawback, lack of interest, partly due to the frequent confusion with atherosclerosis, has meant that MeS has rarely been the focus of clinical research.

In the future, the new possibilities offered by molecular biological single-cell omics technologies in combination with electronic data processing will provide the opportunity to comprehensively analyze the genome, transcriptome and metabolome of single, topographically well identified cells in a targeted manner and then integrate the results into the network of molecular cascades (33). Such precise and targeted techniques would be particularly beneficial in MeS, given that the media is well demarcated anatomically. Clinical research should provide understanding of conditions exhibiting the MeS phenotype and enable their differentiation from age-related medial calcifications. It would be of particular interest to shed light on the significance of so-called "deep" calcifications in the coronary arteries. Last but not least, broader clinical awareness of this as yet underestimated disease should contribute to improving the management of patients with MeS.

Conclusion

Medial sclerosis has historically been considered a rare nosological entity without major clinical significance (34). Today, it is well established that medial sclerosis is an important risk factor for chronic critical leg ischemia, amputations, and primarily endovascular treatment-related complications. Reorientation of basic research and greater clinical awareness are crucial prerequisites for successfully preventing and treating medial sclerosis in the future..

Conflict of interest statement
The authors declare that no conflict of interest exists.

Manuscript received on 7 February 2022, revised version accepted on 7 March 2023.

Translated from the original German by Ralf Thoene, MD.

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Cite this as:
Lanzer P, Ferraresi R: Medial Sclerosis—epidemiology and clinical significance.
Dtsch Arztebl Int 2023; 120: 365–72. DOI: 10.3238/arztebl.m2023.0066

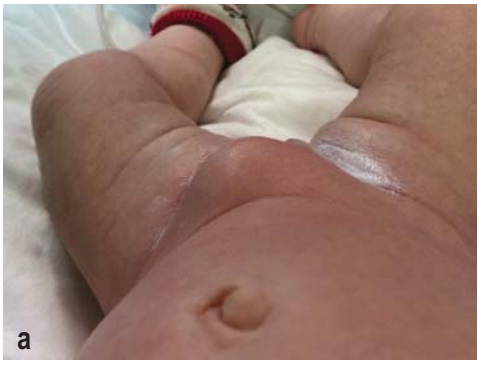
► **Supplementary material**

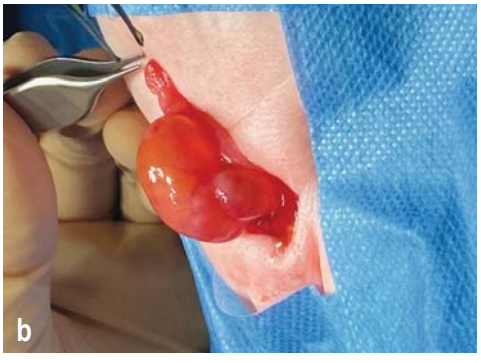
eReferences, eTables, eFigures:
www.aerzteblatt-international.de/m2023.0066

CLINICAL SNAPSHOT

Adnexal Prolapse in Infant Inguinal Hernia

A 3-month-old, prematurely born female infant presented with a several-hour history of swelling in the right groin at the upper aspect of the labia *(Figure a)*. An almond-shaped, coarse, and movable point of resistance could be palpated. Ultrasound showed an oval, hyperechoic structure. We operated on the infant on the day of presentation via a short inguinal incision. Once the inguinal ring and hernia sac had been opened, it was possible to perform manual and atraumatic reduction of the edematous and enlarged ovary withattached uterine tube *(Figure b)*. The hernia sac was closed and the excess portions removed. Following an uncomplicated postoperative course, the infant was discharged on the following day. In all, 20% of pediatric inguinal hernias affect girls, and the adnexal prolapse, with an incidence of 30%, is a typical manifestation of congenital inguinal hernia in the female newborn. From a differential diagnostic perspective, intestinal incarceration is possible. Predilection factors include premature birth, persistent processus vaginalis, infancy, as well as excessive descent of the gonads. The urgency of surgery is recommended due to possible incarceration as well as an increased risk of torsion involving organ loss.





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Conflict of interest statement: The authors declare that no conflict of interest exists.

Translated from the original German by Christine Rye.

Cite this as: Baranski T, Tröbs RB, Weber J: Adnexal prolapse in infant inguinal hernia.
Dtsch Arztebl Int 2023; 120: 372. DOI: 10.3238/arztebl.m2023.0032

Supplementary material to:

Medial Sclerosis—Epidemiology and Clinical Significance

by Peter Lanzer and Roberto Ferraresi

Dtsch Arztebl Int 2023; 120: 365–72. DOI: 10.3238/arztebl.m2023.0066

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eTABLE 1

Compilation of available data on the epidemiology of medial sclerosis in different populations (selection)*

Population	Number of subjects	Prevalence of medial sclerosis (%)	Methods	References
Pelvis/legs				
General population	4 735	10 (total) 13.3 (men) 6.9 (women) 0.6 (total) 1.1 (men) 0.5 (women) 0.6 (total)	ABI >1.3 ABI >1.5 >260 mm Hg	(e1)
	48 294	2.5 (total) 2.8 (men) 2.2 (women)	ABI >1.4	(e2)
	6 647	1.6 (total)	ABI ≥ 1.4 or noncompressible	(e3)
Cardiovascular disease or high risk	718	25 (total) 8.7 (total)	CT (extremities) ABI >1.4	(e4)
Diabetes mellitus	623	9 (total)	BP difference >50 mm Hg or non-compressible	(e5)
	662	4.45 (total)	ABI ≥ 1.3	(e6)
	1 059	41.5 (total)	Radiography (plain) Femur	(e7)
	133	17.3 (total) 23 (men) 11 (women)	Radiography (plain) Femur	(e8)
	250	 20.4 (total) vs control 8 23.6 (total) vs control 8.8	Radiography (plain) Knee Feet	(e9)
Cardiovascular disease or high risk and diabetes				
Risk **Diabetes mellitus**	 520 198	 34 23.1 34.2 30.8	CT (dominant medial pattern) Femur Lower leg Femur Lower leg	(e10)
Severe chronic kidney disease	202	26.7 (total)	Radiography (plain) Pelvis and femur	(e11)
Peripheral arterial occlusive disease (PAOD)	204	 75 93.5 80.5 57.9 85 78.6	CT (full body) Foot Lower leg Femur Pelvis Abdominal aorta Thoracic aorta	(e12)
PAOD (critical chronic leg ischemia or amputation)	1 413	24.8	ABI > 1.4	(e13)
Suspected stroke				
Internal carotid artery, intracranial	1 132	46.9	CT (head)	(e14)

* The considerable differences in reported data presumably reflect different testing methods (ABI, radiography, CT), different cut-off values for ABI (1.3; 1.4; 1.5; noncompressible, pressure difference, >260 mm Hg), and different age distributions in the studied populations.
ABI, ankle-brachial index; CT, computed tomography; PAOD, peripheral arterial occlusive disease; vs, versus

eTABLE 2

Occurrence of medial sclerosis by vascular regions

Vascular region	References
Peripheral, visceral and coronary arteries	(e15)
Temporal artery	(e16)
Facial artery	(e17)
Mammary arteries	(e18)
Intracranial arteries	(e19)
Visceral arteries	(e20)
Thoracic aorta	(e21)

eTABLE 3

Occurrence of medial sclerosis in association with various diseases (examples) with references

Disease	Key feature	Additional soft-tissue calcifications	References
Diabetes mellitus	Carbohydrate metabolism disorders	No	(e7)
Chronic kidney disease	Impaired excretory and metabolic renal function	No	(e11)
Aging	Unknown; disorders of the extracellular matrix? Destruction of elastic fibers?	No	(e22)
Primary medial sclerosis	Unknown, hereditary genetic disorder?	No	(e23)
Disorders of Vitamin K metabolism	Inhibition of anti-inflammatory factors, particularly mediated by the NF-kB pathway; inhibition of matrix Gla protein (MGP) carboxylation	No	(e24)
Disorders of Vitamin D metabolism	Stimulation of calcium absorption, synergistic effect with parathyroid hormone on bone resorption?	No	(e25)
Atherosclerosis	Intimal calcification	Yes	(e26)
Pseudoxanthoma elasticum	Defect of the ABCC6 gene ATP Binding Cassette Subfamily C Member 6	Yes	(e27)
Rheumatoid arthritis?	Disorders of human leucocyte antigen (HLA), major histocompatibility complex (MHC), cytokine promotors, T-cell signaling pathway, and others	Yes	(e28)
β-thalassemia	Mutation of the β-globulin gene, resulting in absent or low production of β-globulin	Yes	(e29)
Calciphylaxis	Unknown	Yes	(e30)
Kawasaki disease	Unknown; generalized inflammatory reaction secondary to infection in predisposed children?	Yes	(e31)
Singleton-Merten syndrome and other forms of type I interferonopathies	Genetic mutation associated with activation of type I interferon activity	Yes	(e32)
Parathyroid gland dysfunction	Disorders of parathyroid hormone metabolism	Yes	(e33)
Generalized Arterial Calcification of Infancy (GACI)	Gene mutations affecting *ectonucleotide pyrophosphatase/phosphodiesterase 1* (ENPP1), which cleaves ATP to inorganic pyrophosphate (PPi) and adenosine monophosphate (AMP) (extracellular)	Yes	(e34)
Arterial Calcification due to CD73 Deficiency (ACDC)	*Ecto-5'-nucleotidase* (NT5E) gene mutation which codes CD73—with its mutation, the conversion of adenosine monophosphate (AMP) into adenosine is defective	Yes	(e35)
Idiopathic Basal Ganglia Calcification (IBGC)	Impaired extracellular transport of inorganic phosphate by mutations of the SLC20A2, PDGFRB, PDGFB, XPR1, and MYORG genes.	Yes	(e36)
Scleroderma	Autoimmune disease frequently associated with changes in the human leukocyte antigen (HLA) complex	Yes	(e37)
Hutchinson-Gilford progeria syndrome	Single nucleotide substitution in the *LMNA* gene	Yes	(e38)

eTABLE 4

Promotors and inhibitors of vascular calcifications

Promotors	Inhibitors	Reference
Collagen I, fibronectin, BMP 2 (bone matrix protein), LDLox (oxidized LDL), leptin, vitamin D3, inorganic phosphate, calcium, osteocalcin, alkaline phosphatase, oncostatin, TNF-α (tumor necrosis factor-α), Wnt signal transduction cascade, parathyroid hormone 7–84, MSX-2 transcription factor, FGF-23 (fibroblast growth factor– 23)-clotho/and RUNX2 (Runt-related transcription factor 2)	Fetuin, collagen IV, osteoprotegerin, parathyroid hormone-related protein, matrix GLA protein, osteopontin, parathyroid hormone 1–34, pyrophosphate, and BMP 7 (bone morphogenetic protein)	(e39, e40)

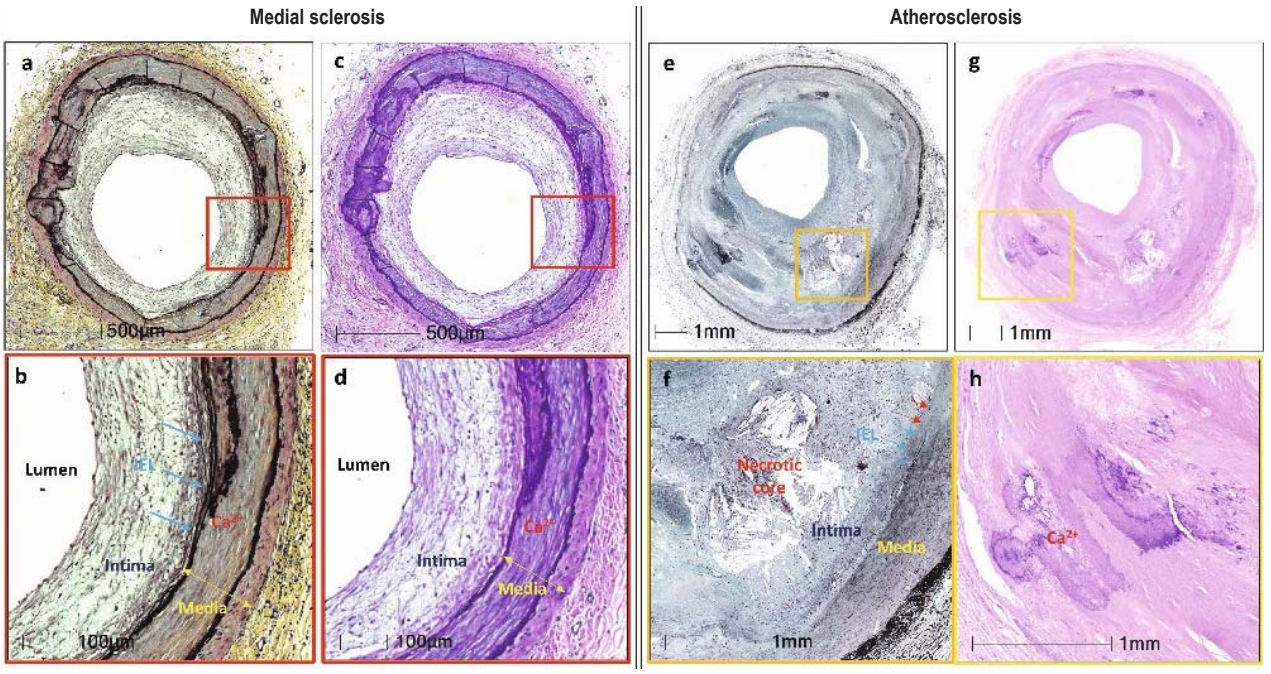
eTABLE 5

Overview of clinically relevant and preclinical laboratory tests

Biomarker		References
Clinical		
Type 2 diabetes mellitus	Glucose (fasting) ≥ 126 mg/dL (2×) or HbA1C ≥ 7% or glucose (postprandial) >198 mg/dL	(e41)
Chronic kidney disease	Glomerular filtration rate ≥ 90 mL/min /1.73 m2; urinary albumin excretion <2 mg/L or <80 mg/24 h	(e41)
Parathyroid diseases	Parathyroid hormone <10–55 pg/mL	(e41)
Vitamin D metabolism	25-hydroxy vitamin D <20 ng/mL (50 nmol/L) and between 21–29 ng/mL (52.5–72.5 nmol/L), respectively; 1,25-dihydroxy vitamin D < 20 or 45 pg/mL; (<48 and >108 pmol/L)	(e41)
Electrolyte imbalances	Calcium (total) [<8.5 or >10.2 mg/dL], phosphate [<2.4 or >4.1 mg/dL], magnesium [<1.8 or >3.6 mg/dL]	(e41)
Experimental		
Vitamin K metabolism	Dp-ucMGP, PIVKA II	(e42)
Bone metabolism	Osteocalcin, osteonectin, osteopontin	(e43, e44)
Inflammation	IL-6, IL-8, TNFα	(e43, e44)
Other	Fibroblast growth factor-23, Klotho, Fetuin-A, bone morphogenetic proteins, pyrophosphate, fibrillin, SMADs, carbonic anhydrase, calcium-sensing receptor, sclerotin	(e43, e44)

Dp-ucMGP, dephosphorylated uncarboxylated matrix Gla-protein; IL, interleukin; TNF-α, tumor necrosis factor alpha; PIVKA II, protein synthesized in vitamin K deficiency; Smads, suppressor of mothers against decapentaplegic

eFIGURE 1



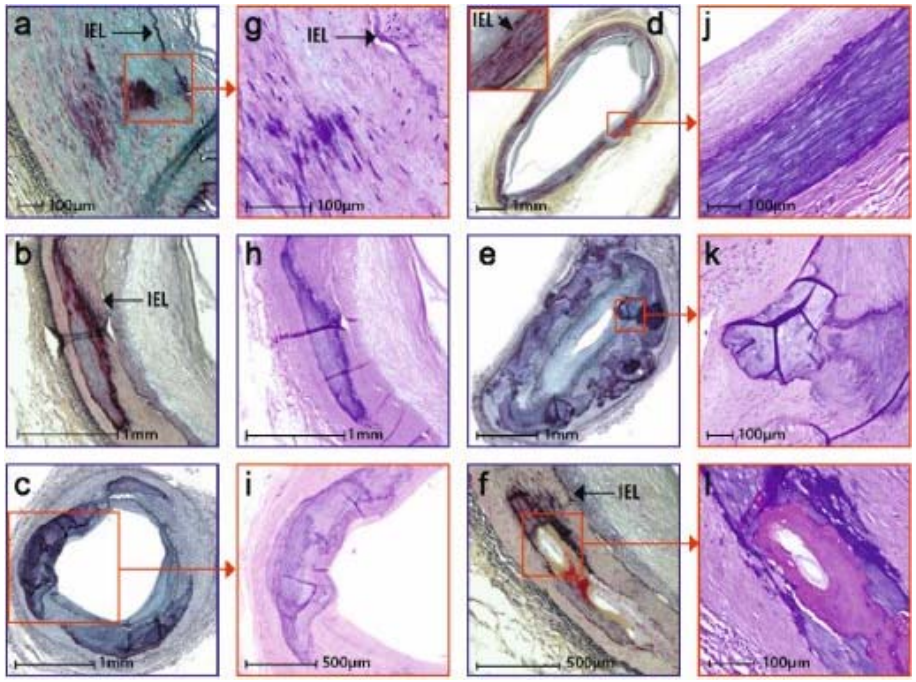
Adopted from Lanzer et al. Eur Heart J 2022; 43: 2824–6.

Comparison of typical histological features of medial sclerosis (a–d) and atherosclerosis (e–h)

Both diseases are shown in lower (a, b and e, f, respectively) and higher (c, d and g, h, respectively) magnification.

The typical histological picture of medial sclerosis of the popliteal artery is depicted. Medial sclerosis is characterized by circular calcification within the media and moderate intimal hyperplasia. The typical histological picture of atherosclerosis of the superficial femoral artery is shown. Intimal lesion with necrotic nucleus, penetration of the internal elastic lamina and calcified focus, clearly assigned to the intima, are shown. Internal elastic lamina (IEL) marked with arrows.

eFIGURE 2



Lanzer et al. J Am Coll Cardiol 2021; 78:1145–65 by courtesy of Elsevier)

Histological stages and histological characteristics of medial sclerosis

Staging is based on the extent of calcifications.

The various stages and morphological characteristics are shown in lower (Figures a, b, c, d, e, f) and higher (Figures g, h, i, j, k, l) magnifications.

Stage I: Calcifications of the elastica interna with or without extension into the media (Figures a, g).

Stage II: Formation of larger calcifications (1 to 3 mm) (Figures b, h)

Stage III: Calcifications >3 mm to >90° of medial circumference (Figures c, i)

Stage IV: Annular calcifications of the entire circumference (Figures d, j)

Nodular calcifications as globular calcification foci with fibrin deposits (Figures e, k)

nd bone formation as proper bone foci, rarely associated with chondroid metaplasia, occur mostly in stages III/IV, rarely in stage II (Figures f, l).

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Questions on the article in issue 21–22/2023:

Medial Sclerosis—Epidemiology and Clinical Significance

cme plus

The submission deadline is 29 May 2024. Only one answer is possible per question.
Please select the answer that is most appropriate.

Question 1

What is the prevalence of medial sclerosis in the general population?

a) 0.8 %
b) 2.5 %
c) 15.1 %
d) 32.5 %
e) 52.1 %

Question 2

In patients with medial sclerosis, what is deposited in the tunica media of the arterial wall?

a) Hydroxyapatite crystals
b) Oxalic acid crystals
c) Uric acid crystals
d) Calcium carbonate crystals
e) Sodium chloride crystals

Question 3

What does the abbreviation ABI stand for in the text?

a) Arm-leg index
b) Ankle-body index
c) Anterior leg index
d) Ankle-brachial index
e) Arm-body index

Question 4

Which of the following factors are listed as major risk factors for medial sclerosis in the text?

a) Pulmonary hypertension, kidney stones, age
b) Emphysema, gout, hypertension
c) Diabetes mellitus, chronic kidney disease, age
d) Monoclonal gammopathy, pulmonary hypertension, gout
e) Kidney stones, age, hypertension

Question 5

Which of the following elements is found in the calcification of the vessel wall in medial sclerosis?

a) Calcium
b) Potassium
c) Magnesium
d) Sodium
e) Iron

Question 6

What term is used to describe the change of the intima frequently observed in medial sclerosis?

a) Macro-intimal hyperplasia
b) Micro-intimal necrosis
c) Myointimal hyperplasia
d) Media-intima hyperplasia
e) Minor intima necrosis

Question 7

According to the text, what are the effects of medial sclerosis-related changes in hemodynamics on cardiac function?

a) Increase in right ventricular afterload
b) Increase in left ventricular preload
c) Increase in right ventricular preload
d) Increase in left ventricular afterload
e) Increase in biatrial preload

Question 8

In screening for medial sclerosis, what is the threshold used?

a) ABI >1.4
b) ABI <0.8
c) ABI >4.3
d) ABI <1.0
e) ABI >0.5

Question 9

With regard to the diagnosis of medial sclerosis, which of the following statements is true?

a) There is usually a lack of collateral vessels.
b) Transient claudication is always the first symptom.
c) Medial sclerosis is usually diagnosed at a young age.
d) At times, tissue necrosis emerges as the first symptom.
e) In medial sclerosis, imaging reveals coarse granular calcifications.

Question 10

Which of the following methods cannot be used to diagnose medial sclerosis?

a) Intravascular ultrasound
b) Optical coherence tomography
c) Computed tomography
d) Radiographic assessment
e) Testing for specific biomarkers