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Mönckeberg's medial calcific sclerosis in diabetic and non-diabetic foot infections

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Abstract

The aim of this study was to evaluate the prevalence and extent of lower extremity Mönckeberg's Medial Calcific Sclerosis (MMCS) in patients with and without diabetes in patients admitted to the hospital for foot infections. This study retrospectively reviewed 446 patients admitted to the hospital with a moderate or severe foot infection. We defined diabetes based on ADA criteria and reviewed electronic medical records for demographics, medical history and physical examination data. Anterior–posterior and lateral foot radiographs were examined to identify the presence and extent of vascular calcification. We categorised MMCS based on anatomical location: ankle joint to the navicular-cuneiform joint, Lis Franc joint to metatarsophalangeal joints and distal to the metatarsophalangeal joints. The prevalence of MMCS was 40.6%. The anatomic extent of MMCS was 19.3% in the toes, 34.3% in the metatarsals and 40.6% in the hindfoot/ankle. Calcification was not common solely in the dorsalis pedis artery (DP) (3.8%) or solely in the posterior tibial artery (PT) (7.0%). Usually, both DP and PT arteries were affected by MMCS (29.8%). The prevalence of MMCS was higher in people with diabetes (in hindfoot and ankle [50.1% vs. 9.9%, $p \leq 0.01$]; metatarsals [42.6% vs. 5.9%, $p \leq 0.01$]; and toes [23.8% vs. 4.0%, $p \leq 0.01$]). People with diabetes were 8.9 (CI: 4.5–17.8) times more likely to have MMCS than those without diabetes. This is a group that often has poor perfusion and needs vascular assessment. The high prevalence of MMCS raises questions about the reliability of the conventional segmental arterial Doppler studies to diagnose PAD.

KEYWORDS
arterial calcification, diabetic foot, infection, lower extremity, Mönckeberg's sclerosis

1 | INTRODUCTION

People with diabetes are at increased risk of developing peripheral arterial disease (PAD).[1] PAD is one of the most important risk factors for people with diabetes to develop foot ulcers, infections and lower

Abbreviations: CKD, chronic kidney disease; DPN, diabetic peripheral neuropathy; ESRD, end-stage renal disease; HSI, hyperspectral imaging; MMCS, Mönckeberg's Medial Calcific Sclerosis; PAD, peripheral arterial disease; SPP, skin perfusion pressure measurements; TCOM, transcutaneous oxygen.

extremity amputations. Mönckeberg's medial calcific sclerosis (MMCS) is defined as calcification of the tunica media of small and medium-sized arteries, first described by Johann Georg Mönckeberg in 1903.[2,3] MMCS is characterised by the degeneration of elastic fibres and hydroxyapatite crystal deposition within the tunica media, with or without calcium pyrophosphate dehydrate.[4] MMCS is an incidental finding on plain radiographs and patients are often asymptomatic.[5] Studies showed that MMCS is often present with PAD and is associated with increased risk of future cardiovascular events and lower extremity amputation in patients with diabetes.[6–9]

Arterial Doppler studies are the most common non-invasive vascular testing approach used to evaluate the presence and severity of PAD. MMCS often makes peripheral arteries stiff and less compressible. This causes arterial Doppler studies to be falsely elevated, if the vessel can be compressed at all.[10] Unfortunately, MMCS often makes the evaluation of PAD by arterial Doppler test and waveforms unreliable. One of the most important unmet needs for high-risk people with diabetic foot complications is better non-invasive technology to evaluate PAD. We were only able to identify one study that evaluated MMCS in patients with and without diabetes.[11] The purpose of this paper was to evaluate the prevalence and extent of lower extremity MMCS in high-risk people admitted to the hospital for foot infection with and without diabetes.

2 | METHODS

These data are part of a retrospective study that included 446 patients with and without diabetes who were admitted to the hospital for moderate and severe infections. This study was approved by the Institutional Review Board at the University of Texas Southwestern Medical Center and Parkland Hospital (Dallas, TX). Patient demographic information, past medical history, medications, clinical examination and admission laboratory testing were included in our assessment. Diabetes was defined by the American Diabetes Association criteria.[12] The severity of infection was based on the criteria established by the International Working Group on the Diabetic Foot.[13]

Anterior–posterior (AP) and lateral foot radiographs were reviewed for each patient. If calcification was noted on plain radiographs, the level of calcification was noted. The level of calcification was placed into three categories based on anatomic location: ankle/hindfoot, metatarsals and toes. The ankle/hindfoot was defined as calcification from the ankle joint to the navicular-cuneiform joint. Metatarsals was defined as calcification from the Lis Franc joint to metatarsophalangeal joints, and digital was defined as calcification distal to the metatarsophalangeal joints. Calcification at the level of the ankle was identified as being in the dorsalis pedis artery, posterior tibial artery or both.

TABLE 1 Demographics and prevalence of Mönckeberg's sclerosis in patients with and without diabetes.

	Total ($N = 446$)	Diabetes ($N = 345$)	No diabetes ($N = 101$)	Odds ratio (95% confidence interval)	*p*-Value
Male	332 (74.4)	256 (74.2)	76 (75.2)	0.9 (0.6–1.6)	0.832
Age	52.6 ± 12.1	53.0 ± 10.9	51.0 ± 15.5	(0.6–4.8)	0.128
BMI (kg/m^2)	31.3 ± 9.1	32.3 ± 9.5	27.9 ± 6.7	(2.4–6.4)	<0.001
Neuropathy	367 (82.3)	312 (90.4)	55 (54.5)	9.6 (5.7–16.1)	<0.001
Retinopathy	98 (22.0)	98 (28.4)	0 (0.0)	80.8 (5.0–1313.3)	<0.001
Nephropathy	148 (33.2)	156 (40.3)	9 (8.9)	6.9 (3.4–14.1)	<0.001
CKD stages 1–4	138 (30.9)	120 (34.8)	18 (17.8)	2.5 (1.4–4.3)	0.001
ESRD	39 (8.7)	36 (10.4)	3 (3.0)	3.8 (1.1–12.6)	0.023
PAD	284 (63.7)	244 (70.7)	40 (39.6)	1.9 (1.2–2.9)	<0.001
Previous foot ulcer	261 (58.5)	224 (64.9)	37 (36.6)	3.2 (2.0–5.1)	<0.001
Previous amputation	140 (31.39)	129 (37.4)	11 (10.9)	4.9 (2.5–9.5)	<0.001
Arteries with MMCS					
Dorsalis pedis	17 (3.8)	17 (4.9)	0 (0.0)	10.8 (0.6–181.4)	<0.001
Posterior tibial	31 (7.0)	28 (8.1)	3 (3.0)	2.9 (0.9–9.7)	<0.001
Both	133 (29.8)	126 (36.5)	7 (6.9)	7.7 (3.5–17.2)	<0.001
Mönckeberg's sclerosis	181 (40.6)	171 (49.5)	10 (9.9)	8.9 (4.5–17.8)	<0.001
Toes	86 (19.3)	82 (23.8)	4 (4.0)	7.6 (2.7–21.2)	<0.001
Metatarsals	153 (34.3)	147 (42.6)	6 (5.9)	11.8 (5.0–27.6)	<0.001
Hindfoot/ankle	181 (40.6)	171 (49.5)	10 (9.9)	8.9 (4.5–17.8)	<0.001

Note: Dichotomous variables are presented as number (%) with odds ratios (95% confidence intervals). Continuous variables are presented as mean (standard deviation) with (95% confidence intervals).
Abbreviations: CKD, chronic kidney disease; ESRD, end-stage renal disease; MMCS, Mönckeberg's Medial Calcific Sclerosis; PAD, peripheral arterial disease.

Patient data were summarised using descriptive statistics. Mean and standard deviation were used for continuous variables, while frequency and percentage were used for categorical variables. Dichotomous variables were compared with Chi square or Fisher's exact test. Continuous variables were compared with T-test. Odds ratios with 95% confidence intervals were reported for comparisons of proportions and 95% confidence intervals were reported for continuous variables.

3 | RESULTS

A total of 446 patients were analysed. Overall, the prevalence of MMCS was 40.6%. When comparing patients with and without diabetes, there were many factors that were significant (Table 1). For instance, patients without diabetes had lower BMI (27.9 vs. 32.3, $p \leq 0.01$). Patients with diabetes had significantly greater prevalence of chronic kidney disease (CKD) (34.8% vs. 17.8%, $p \leq 0.01$) and end-stage renal disease (ESRD) (10.4% vs. 3.0% $p = 0.03$), sensory neuropathy (90.4% vs. 54.5%, $p \leq 0.01$) and PAD (70.7% vs. 39.6%, $p \leq 0.01$).

When MMCS was identified, it was seen in the dorsalis pedis alone in 7 people (5.1%), the posterior tibial artery alone in 14 people (10.2%) and in both arteries in 116 people (84.7%). The most distal involvement of subjects with MMCS extended to the toes in 19.3% of patients, to the metatarsals in 34.3% of patients and to the ankle and hindfoot in 40.6% of patients (Figure 1). Calcification was typically not found solely in the dorsalis pedis artery (3.8%) or solely in the posterior tibial artery in (7.0%). When these arteries had MMCS, often both arteries were affected (29.8% of the patients).

Overall, people with diabetes were 8.9 times (CI: 4.5–17.8, 49.5% vs. 9.9%, $p \leq 0.01$) more likely to have MMCS. This trend continued for each anatomic level (toes 23.8% vs. 4.0%, $p \leq 0.01$) and metatarsals (42.6% vs. 5.9%, $p \leq 0.01$) and hindfoot/ankle (49.5% vs. 9.9%, $p = 0.01$, Table 2).

4 | DISCUSSION

Our results show that the prevalence of MMCS was significantly higher in people with diabetes, with distal involvement of the toes and metatarsals being more common. A higher prevalence in patients with diabetes was expected as there is a higher prevalence of MMCS associated with diabetes, neuropathy and end-stage kidney disease.[14,15] Our population

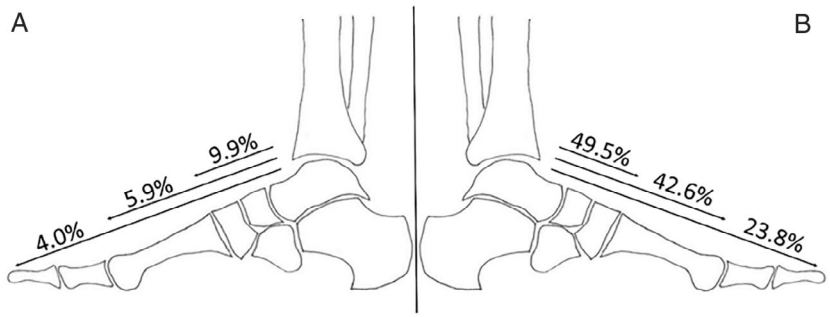

FIGURE 1 Prevalence and Extent of Mönckeberg's sclerosis. (A) Prevalence and extension of Mönckeberg's sclerosis without diabetes. (B) Prevalence and extension of Mönckeberg's sclerosis with diabetes.

TABLE 2 Demographics and history of patients with and without Mönckeberg's sclerosis.

	MMCS ($N = 181$)	No MMCS ($N = 265$)	Odds ratio (95% confidence interval)	*p*-Value
Male	141 (77.9)	191 (72.1)	1.4 (0.9–2.1)	0.166
Age	55.4 ± 11.0	50.6 ± 12.5	(2.6–7.1)	<0.001
BMI (kg/m^2)	30.6 ± 7.4	31.7 ± 10.0	(2.9–0.5)	0.178
Diabetes	171 (94.5)	174 (65.7)	8.9 (4.5–17.8)	<0.001
PAD	149 (82.3)	135 (50.9)	16.5 (8.3–32.6)	<0.001
Neuropathy	163 (90.1)	204 (77.0)	8.7 (5.1–15.0)	<0.001
Retinopathy	60 (33.1)	38 (14.3)	3.0 (1.9–4.7)	<0.001
Nephropathy	93 (51.4)	55 (20.8)	4.0 (2.7–6.1)	<0.001
CKD stages 1–4	64 (35.4)	74 (27.9)	1.4 (0.9–2.1)	0.096
ESRD	37 (20.4)	2 (0.8)	33.8 (8.0–142.2)	<0.001
Previous foot ulcer	122 (67.4)	139 (52.5)	1.9 (1.3–2.8)	0.002
Previous amputation	76 (42.0)	64 (24.2)	2.3 (1.5–3.4)	<0.001

Note: Dichotomous variables are presented as number (%) with odds ratios (95% confidence intervals). Continuous variables are presented as mean (standard deviation) with (95% confidence intervals).

Abbreviations: CKD, chronic kidney disease; ESRD, end-stage renal disease; MMCS, Mönckeberg's Medial Calcific Sclerosis; PAD, peripheral arterial disease.

with diabetes had a very high prevalence of peripheral sensory neuropathy and CKD/ESRD.

The prevalence of MMCS in our study population with diabetes was like other MMCS reports. There are few studies that report the prevalence of MMCS in people with Type 2 diabetes. The range of MMCS is from 17.0% to 41.5%.[6,7] We could only identify one study that evaluated MMCS in people with and without diabetes. Young and colleagues evaluated the prevalence of MMCS in patients with diabetic foot ulcers and neuropathy compared to patients with no diabetes. The prevalence of MMCS was 78.8% ($N = 54$) in people with diabetic foot ulcers with neuropathy compared to 22.5% ($N = 50$) in the control group. This prevalence was higher in people with and without diabetes compared to our results. This may be explained by a few differences between the studies and groups that were evaluated. MMCS has been reported to be more common in people with ESRD, PAD and in advanced age.[16–20] Young et al. did not report the prevalence of PAD, CKD or ESRD. The median age in the subjects with diabetes with neuropathy was 60.5 years compared to 52.6 years in our group. Increased age could be a factor in developing calcifications, as cited in other studies.[17] In addition, their patients may have had more severe diabetic peripheral neuropathy (DPN) because they used VPT of 30 V or higher to define DPN. Our group used 25 V and/or abnormal 10-g monofilament testing as a criterion for DPN with loss of protective sensation. About 10% of our patients with diabetes did not have DPN, while all their subjects had DPN in the group with 78.8% prevalence of MMCS.[11]

The risk factors for MMCS in our study were not surprising. We identified many of the classic disease processes associated with MMCS including aging, CKD, ESRD and PAD. In addition, sensory neuropathy, retinopathy and CAD are likely representative of end-stage disease processes associated with diabetes.[19,21,22] All these factors are also disease processes that are significantly more common in people with diabetes and foot infections as demonstrated in Table 1. The odds ratios may help understand the magnitude of these risk factors.

We also studied the location of the calcification in the foot and ankle in patients with MMCS. Quantifying this is important and can help us better understand, interpret and use ankle and toe pressure measurements. Our results show that calcifications decrease the more distal in the foot the vessels are. In patients with diabetes, this resulted in 49.5% of the calcifications being in the hindfoot and ankle, 42.6% extending to the metatarsals and 23.8% extending to the toes. The same is true in our patient group without diabetes, with 9.9% of the calcifications being in the hindfoot and ankle, 5.9% extending to the metatarsals, and 4.0% extending to the toes. This corresponds to Young et al.'s findings. They reported a gradient in the distribution of MMCS with a greater prevalence at the hindfoot and ankle compared to the toes in all the subject groups.[11]

An important unmet need in treating patients with diabetic foot wounds is assessing perfusion. In the present-day clinic, we rely heavily on arterial Doppler studies and ABIs to diagnose PAD and predict wound healing. However, our results show that almost half of the patients with diabetes had MMCS. These findings imply that conventional studies may not be reliable. Medial arterial calcification (MMCS) is associated with non-compressible ABI's, which is defined as an ABI equal to or greater than 1.4.[23] This can camouflage clinically significant PAD in the patient and could influence the choices made for further treatment.[24,25] This shows the relevance of our study results, as it makes clear that MMCS is very prevalent in patients with diabetic foot infections (49.5%). While this study does not provide evidence that arterial Doppler's are unreliable, the association between arterial calcifications and non-compressible vessels has been reported several times in the literature.[26–28] We have not identified any studies that report that MMCS is a risk factor for poor healing based on either the presence or extent of calcification. MMCS is also not commonly evaluated as a risk factor in wound healing studies in people with diabetes.

There are alternative diagnostic methods that are not influenced by arterial calcification including hyperspectral imaging (HSI), skin perfusion pressure measurements (SPP) and transcutaneous oxygen (TCOM), and pulse volume recordings (PVRs). PVRs have been reported to be better than ABIs to assess wound healing.[29] HSI is a promising tool that can measure tissue oxygenation by using near infrared light, but it is still a relatively new technology and not widely used. TCOM is a good method to evaluate tissue oxygenation, but it is unsuited for measurements on the plantar aspect of the foot due to the thicker skin, the measurements give information on only one point on the surface of the foot or leg, it is not available in many clinical settings and the measurements consume more time than the other options.

There are several limitations to this study. Selection bias is an important factor. We evaluated a large cohort of subjects with moderate and severe foot infections that were admitted to the hospital. Our study population had peripheral sensory neuropathy, PAD and CKD that were significantly more common in the population with diabetes. These factors have been associated with MMCS. Our study population may not be representative of other selected populations. We probably also had detection bias since we used radiographs to define the prevalence and extent of MMCS. Other studies have used a similar approach. However, we may only be able to identify end stage disease with radiographs. A logical conclusion was that MMCS was associated with a high rate of non-compressible arteries in this study population.

We compared the prevalence and anatomic extent of Mönckeberg's sclerosis among high-risk patients with foot infections. This is a group that often has poor perfusion and needs vascular assessment. People with diabetes were 8.9 times more likely to have MMCS. The presence of MMCS should raise the clinicians' index of suspicion that arterial Doppler studies may not be accurate to identify PAD. More research is needed to clarify the association between MMCS, wound healing and perfusion.

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The authors have nothing to report.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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