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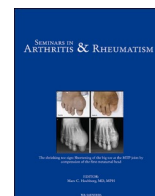
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[¹⁸F]Sodium Fluoride PET has the potential to identify active formation of calcinosis cutis in limited cutaneous systemic sclerosis

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ABSTRACT

Objectives: Calcinosis cutis affects 20-40% of patients with systemic sclerosis (SSc). When calcinosis cutis becomes clinically apparent, it is irreversible in most cases. Detection of active calcification formation might allow early disease-modifying interventions. We assessed the feasibility of visualizing active calcifications using [¹⁸F]Sodium Fluoride ([¹⁸F]NaF) PET/low-dose CT (LDCT) in SSc patients with calcinosis cutis.

Methods: In this cross-sectional, observational pilot study patients underwent a whole body [¹⁸F]NaF PET/LDCT. All patients met the 2013 ACR/EULAR SSc criteria and had clinically detectable calcinosis cutis. (Sub)cutaneous calcifications were described by three investigators.

Results: Nine female patients were included (median age 59.0 years [IQR 51.5-70.5]). [¹⁸F]NaF uptake was mostly visible in the fingers (n=7) and knees (n=5). [¹⁸F]NaF PET showed calcifications in the fingers of 3 patients where calcifications were undetected on LDCT and in the clinic. Ninety-seven percent of [¹⁸F]NaF positive lesions was visible on LDCT. Of all lesions visible on LDCT, 70% was also visible on [¹⁸F]NaF PET.

Conclusion: Imaging of active calcifications in SSc is feasible using [¹⁸F]NaF PET/LDCT. Seventy percent of calcifications on LDCT were [¹⁸F]NaF PET positive. Although these findings require replication, [¹⁸F]NaF PET/LDCT may detect active calcification formation, being potentially suitable for early disease-modifying interventions.

Key messages

- [¹⁸F]Sodium Fluoride PET/low-dose CT has the potential to identify active formation of calcinosis cutis in limited cutaneous systemic sclerosis.
- This pilot underlines the importance of better characterization of calcinosis cutis to select lesions most prone to treatment response.

Introduction

Calcinosis cutis, characterized by subcutaneous or intracutaneous calcium salt depositions, is a difficult to treat complication of systemic sclerosis (SSc). It arises without an apparent disorder in systemic calcium-phosphate metabolism. These patients are prone to severe vasculopathy indicated by more telangiectasia, giant capillaries, and reduced capillary density compared to those without calcinosis cutis [1, 2].

The exact pathogenesis of the calcification process remains elusive, although it has been suggested that ischemia and microtrauma may play

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a role [2,3]. However, this calcification process occurs not only at sites clinically recognized as calcinosis cutis, but can also be detected in skin biopsies taken at sites without overt calcinosis cutis [4]. This suggests a ubiquitous calcification process in SSc.

Macrocalcifications ($\geq 50\mu\text{m}$) in vascular disease are generally regarded as irreversible end-stage of the calcification process, which can be clearly visualized on X-rays or CT scans [5]. On the contrary, microcalcifications ($< 50\mu\text{m}$) which indicate the active formation of calcification are not detected by conventional methods such as X-rays or CT scans, but can be detected using a PET scan with the sodium fluoride tracer (^{18}F]NaF) which mainly binds to microcalcifications [5–9]. ^{18}F]NaF has been routinely used to detect bone disease and metastases, but has also been shown to be a reliable tracer for visualizing skin calcifications in patients with pseudoxanthoma elasticum [10].

Currently, when calcinosis becomes clinically apparent, it is irreversible in most cases [11]. Thus, methods measuring calcinosis activity at which early interventions might be targeted are urgently needed. Detection of active calcinosis cutis formation might potentially facilitate more effective treatments with, for example, bisphosphonates or intralesional sodium thiosulfate [12]. Therefore, we assessed the feasibility of visualizing active calcification formation with ^{18}F]NaF PET/low-dose CT (LDCT) in SSc patients with calcinosis cutis. Moreover, we compared the clinical detection of (sub)cutaneous calcifications with those detected on hybrid ^{18}F]NaF PET/LDCT.

Materials and methods

We performed a cross-sectional, observational pilot study in 9 patients with limited cutaneous SSc (lcSSc) and calcinosis cutis, who underwent a ^{18}F]NaF PET/LDCT. The presence of calcinosis cutis was assessed by routine clinical examination and photo documentation. Inflamed calcinosis cutis was defined as being red, warm, or swollen. Patients were recruited from the University Medical Center Groningen or after reference by collaborating hospitals in the region. All patients met the 2013 ACR/EULAR criteria for SSc with a score ≥ 9 [13].

Exclusion criteria were: currently pregnant or breastfeeding women, women with child bearing potential not using appropriate contraceptive measures, vascular event or chemotherapy in the preceding 3 months [14], inflammation of unknown origin, sepsis, or vasculitis [15], current active bone malignancy or in the previous 6 months [16], disorders affecting bone metabolism, e.g. hyperparathyroidism, Paget's disease [14], and patients who had claustrophobia. Clinical and demographical data were obtained by the researcher's assessment and patient records. The study was approved by the local Medical Ethics Committee of the University Medical Center Groningen, complied with the Declaration of Helsinki, and all participants gave written informed consent.

^{18}F]NaF PET/LDCT imaging technique

Patients underwent a ^{18}F]NaF PET/LDCT on a Siemens Biograph scanner (Siemens Healthineers, Erlangen, Germany). Ninety minutes before imaging, an intravenous injection of 2.0 MBq/kg ^{18}F]NaF was administered. Patients were instructed to consume 1l water 1-3 hours before and 0.5l water after injection. A continuous breathing LDCT (80-120 kV, 20-35 mAs, and 5 mm slice thickness) was performed for visualization of anatomical structures. PET acquisitions were obtained with 2–3 min per bed position in 3D setting. Images were reconstructed according to the European Association of Nuclear Medicine guidelines [17].

Image analysis

Images were reformatted into axial, coronal, and sagittal views, and reviewed by the software provided by the manufacturer (Syngo. Via 30, Siemens Healthineers). The scans were analyzed blinded to patient characteristics and clinical information. The number and location of (sub)cutaneous calcifications were described and assessed independently on ^{18}F]NaF PET/LDCT by three researchers, reaching a

consensus. Calcifications not located in the (sub)cutaneous tissue such as joints, tendons, bursae, muscles, and internal organs were excluded.

Statistical analysis

Data are presented as median with interquartile range (IQR) or number (%). The Spearman's rank correlation and Mann-Whitney test were used as appropriate for associations between relative ^{18}F]NaF activity and calcium phosphate metabolism, renal function, inflammation, vasculopathy, internal organ complications, and duration of SSc and calcinosis. Relative ^{18}F]NaF activity is the percentage of ^{18}F]NaF activity. P-values < 0.05 were considered significant.

Results

Patient characteristics are summarized in Table 1. A total of 9 lcSSc patients were included. All patients were female. The median duration of calcinosis cutis since first presentation was 14.1 years (12.0-19.4). Calcinosis cutis was detected in all patients with ^{18}F]NaF PET/LDCT (Fig. 1 shows a representative image; Table 2). Twenty-two percent had inflamed calcinosis cutis by clinical examination. Clinically, calcinosis cutis was most often detected in the fingers (n=5), elbows (n=2), and knees (n=2). Most common sites of (sub)cutaneous calcifications on ^{18}F]NaF PET were the fingers (n=7) and knees (n=5). In total, 97% of NaF positive lesions were also visible on LDCT, whereas 70% of all detected lesions on CT were also positive on ^{18}F]NaF PET.

Interestingly, ^{18}F]NaF PET not only showed clinically apparent calcinosis cutis, but also (sub)cutaneous calcifications in the fingers of 3 out of 9 patients where calcinosis cutis was clinically undetected. On the contrary, clinically diagnosed calcinosis cutis in the fingers of 2 patients could not be detected on ^{18}F]NaF PET/LDCT. However, it should be mentioned that moving artifacts were present on ^{18}F]NaF PET/LDCT in these 2 patients, and, thereby, could not be assessed properly.

No associations were found between the relative ^{18}F]NaF activity on PET/LDCT and SSc duration, calcinosis duration, a history of digital ulcers, nailfold capillary pattern, internal organ complications, estimated glomerular filtration rate, serum phosphate, erythrocyte sedimentation rate, and C-reactive protein. The relation between relative ^{18}F]NaF activity and a history of pitting scars (p=0.08), gastrointestinal involvement (p=0.07), and calcium levels (r=0.61; p=0.08) showed positive trends.

Discussion

This proof of concept study is the first to demonstrate the feasibility of using ^{18}F]NaF PET/LDCT in patients with SSc and clinically apparent calcinosis cutis. Almost all clinically detected calcinosis lesions were visible on LDCT, of which 70% were considered active since ^{18}F]NaF uptake was present. This suggests that in this long-standing calcinosis cutis population, most lesions are still active and potential targets for therapies aiming to reduce calcifications.

On the contrary, a very limited number of calcinosis lesions were detected with NaF uptake only, not being visible on LDCT. Therefore, ^{18}F]NaF PET seemed rarely to be a suitable imaging modality to detect lesions that cannot be detected by LDCT scanning, but it could be used to detect subclinical lesions as it showed (sub)cutaneous calcinosis in fingers where clinically calcinosis was undetected. This is in line with a study by Davies et al. [4] showing the calcification process not only at sites recognized as calcinosis cutis, but also at sites without overt calcinosis cutis. At these sites, overexpression of calcification related matrix proteins such as osteonectin and matrix gammacarboxyglutamic acid protein have been observed. Both proteins play an important role in the metabolism of calcification. While these observations were more prominent in SSc patients with overt calcinosis cutis, the fact that similar mechanisms seem to play a role subclinically, suggests that calcification may be a ubiquitous process in SSc. As a result, identification of

Table 1
Patient characteristics.

	Total (N=9)
Sex, n(%)	
Female	9 (100.0%)
Age in years, median(IQR)	59.0 (51.5-70.5)
Race, n(%)	
Caucasian	8 (88.9%)
Mixed	1 (11.1%)
Current smoker, n(%)	0 (0.0%)
Previous smoker, n(%)	6 (66.7%)
RP duration in years, median(IQR)	34.6 (19.7-43.8)
SSc duration in years, median(IQR)	20.0 (17.5-30.5)
Calcinosis in the past, n(%)	9 (100.0%)
Duration of calcinosis in years, median(IQR)	14.1 (12.0-19.4)
ACR/EULAR score, median(IQR)	17.0 (13.0-19.0)
Skin thickening of the fingers of both hands extending proximal of the MCP joints, n(%)	1 (11.1%)
Sclerodactyly, n(%)	9 (100.0%)
Digital tip ulcers, n(%)	3 (33.3%)
Pitting scars, n(%)	5 (55.6%)
Telangiectasia, n(%)	9 (100.0%)
Raynaud's phenomenon, n(%)	9 (100.0%)
Nailfold capillary microscopy, n(%)	
Normal	1 (11.1%)
Nonspecific	0 (0.0%)
Early	1 (11.1%)
Late	7 (77.8%)
Serology, n(%)	
ANA-positive	8 (88.9%)
Anti-centromere	7 (77.8%)
Anti-RNA polymerase III	0 (0.0%)
Anti-topoisomerase I	0 (0.0%)
mRSS score, n(%)	
Score ≤ 3	4 (44.4%)
Score 4-7	4 (44.4%)
Score 8-10	1 (11.1%)
Clinically diagnosed lung abnormalities, n(%)	
ILD	2 (22.2%)
PAH	2 (22.2%)
No lung abnormality	6 (66.7%)
Clinically diagnosed gastro-intestinal abnormalities, n(%)	6 (66.7%)
Clinically diagnosed kidney abnormalities, n(%)	2 (22.2%)
Hypertension	2 (22.2%)
eGFR in ml/min/1.73m ² , median (IQR)	83.0 (76.5-99.0)
Inflammation blood parameters, median(IQR)	
ESR in mm/hour	7.0 (5.5-24.0)
CRP in mg/L hour	2.0 (0.9-3.7)
Ca in mmol/L	2.4 (2.3-2.5)
P in mmol/L	1.1 (1.0-1.2)
Medication, n(%)	
Immunosuppression (cellcept, methotrexate, hydroxychloroquine)	5 (55.6%)
Colchicine	1 (11.1%)
Calcium channel blockers (nifedipine, diltiazem)	5 (55.6%)
Alfa1 blockers (ketensin)	1 (11.1%)
Antiplatelet (acetylsalicylic acid, direct oral anticoagulant, ascal)	4 (44.4%)
Statin	0 (0.0%)

SSc: systemic sclerosis; RP: Raynaud's phenomenon; ANA: antinuclear antibodies; mRSS: modified Rodnan skin score; ILD: interstitial lung disease; PAH: pulmonary arterial hypertension; eGFR: estimated glomerular filtration rate; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; Ca: calcium; P: phosphate; RP duration was defined since first Raynaud's symptom, and SSc duration was defined since first non-Raynaud's symptom.

developing calcinosis lesions may lead to early initiation of disease-modifying therapies. Additionally, a recent study showed that calcinosis lesions may resolve spontaneously [11]. Whether these lesions have a specific appearance on [¹⁸F]NaF PET is subject to further study.

It has been suggested that bisphosphonates may be a useful treatment option for calcinosis cutis [18–20]. Bisphosphonates are known to inhibit calcium turnover and reduce bone resorption, underlying their

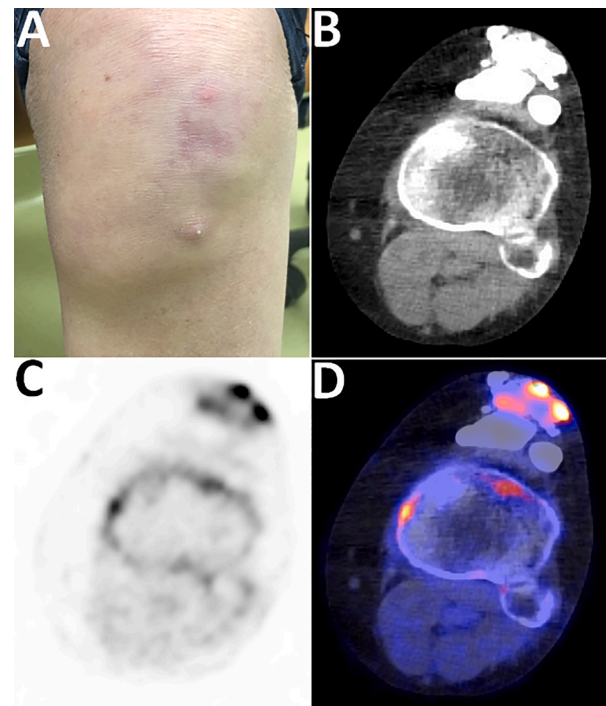


Fig. 1. Representative image of calcinosis cutis of the left knee (A). B: CT scan; C: [¹⁸F]NaF PET scan; D: Fused PET/LDCT scan. The hotspots (yellow/red) show [¹⁸F]NaF uptake.

potential ability to reduce bone turnover in the calcinosis development [21]. Since our findings show active bone turnover in the majority of calcinosis lesions, bisphosphonates may be promising. However, given the paucity of studies on bisphosphonates in SSc, well-designed prospective studies are required to assess treatment responses of calcinosis lesions. Recently, intralesional sodium thiosulfate has gained interest as it may intervene with the active calcification process [22].

Furthermore, our findings showed several positive trends for the association between relative [¹⁸F]NaF activity and vasculopathy, gastro-intestinal complications, and the calcium metabolism. We could not identify clear determinants of [¹⁸F]NaF activity, although these trends may underline a role for ischemia in the formation of calcinosis.

This study has some limitations. The first limitation is the sample size. Second, since small lesions are generally only visible on CT, due to lower resolution and physical properties of [¹⁸F]NaF PET (max 3-4 mm), calcinosis lesions may be missed by [¹⁸F]NaF PET. This could account for the 30% of all detected lesions, which were visualized by CT, but not by PET. Third, the patients with clinically detected calcinosis which could not be detected on [¹⁸F]NaF PET/LDCT were not well assessable due to finger movements.

In conclusion, this study demonstrated that [¹⁸F]NaF PET/LDCT is feasible in visualizing calcinosis cutis in patients with SSc. Moreover, we showed active uptake of [¹⁸F]NaF in the majority of these calcinosis lesions on LDCT, whereas calcinosis lesions invisible on LDCT were very unusual. However, this may be due to the limitation of the PET system resolution. With the current insights, no curative treatment is available for calcinosis cutis in patients with SSc. Still, it may be of added value to know which calcifications are modifiable, and, potentially, suitable for interventions reducing calcifications. In particular, this study should encourage further studies to encounter the dynamic and interindividual heterogeneity of calcinosis cutis in SSc in order to pave the way for therapeutic solutions.

Table 2

Number of lesions on patient levels and in total.

Patient	1	2	3	4	5	6	7	8	9	Median (IQR)	Total
CT pos, n	4	6	17	74	8	3	7	13	67	8 (6-17)	199
CT pos NaF neg, n	1	3	5	23	0	0	0	4	24	3 (0-5)	60
CT pos NaF pos, n	3	3	12	51	8	3	7	9	43	8 (3-12)	139
CT pos NaF pos, %	75	50	71	69	100	100	100	69	64	NA	70
NaF pos, n	3	3	13	51	8	4	7	11	43	8 (4-13)	143
NaF pos CT neg, n	0	0	1	0	0	1	0	2	0	0 (0-1)	4
NaF pos CT neg, %	0	0	8	0	0	25	0	18	0	NA	3

Pos: positive; neg: negative; IQR: interquartile range; NA: not applicable.

Compliance with ethical standards

Funding statement

The study was supported by a grant from Sanofi, the Netherlands.

Author contributions

Conceptualization and methodology, IM Atzeni and DJ Mulder; Formal Analysis, IM Atzeni, EM Hogervorst, RHJA Slart, and DJ Mulder; Investigation, IM Atzeni and EM Hogervorst; Resources, AJ Stel, K de Leeuw, M Bijl, R Bos, and RHJA Slart; Data Curation, IM Atzeni; Writing – Original Draft Preparation, IM Atzeni; Writing – Review & Editing, EM Hogervorst, AJ Stel, K de Leeuw, M Bijl, R Bos, J Westra, H van Goor, MC Bolling, RHJA Slart, and DJ Mulder; Visualization, IM Atzeni; Supervision, J Westra, RHJA Slart, and DJ Mulder; Project Administration, IM Atzeni.

Data availability

All data relevant to the study are included in the article.

Conflicts of interest

DJM has received a grant from Sanofi, the Netherlands. MB has received lecture fees from Novartis Pharma, not related to this manuscript. RHJAS has received independent research grants from Siemens Healthineers, all not related to this manuscript. Other authors declare no competing interests.

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