Validation of statistical shape modelling to predict hip osteoarthritis in females: data from two prospective cohort studies (Cohort Hip and Cohort Knee and Chingford)

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Abstract

Objectives. To prospectively investigate whether hip shape variants at baseline are associated with the need for future total hip replacement (THR) in women and to validate the resulting associated shape variants of the Cohort Hip and Cohort Knee (CHECK) cohort and the Chingford cohort.

Methods. Female participants from the CHECK cohort without radiographic OA (Kellgren–Lawrence score <2) at baseline were included (1100 hips); 22 hips had a THR within 5 years of follow-up. For the Chingford cohort, with only female participants, hips without radiographic OA at baseline were selected and a nested case–control design was used, with 19 THR cases within 19 years of follow-up and 95 controls matched 5 to 1 for age and BMI. Hip shape on baseline anteroposterior pelvic radiographs was assessed by statistical shape modelling (SSM) using the same model for both cohorts.

Results. In the CHECK and Chingford cohorts, the respective mean age was 55.8 (S.D. 5.1) and 53.6 (S.D. 5.4) and the BMI was 26.14 (S.D. 4.3) and 25.7 (S.D. 3.3), respectively. Multiple shape variants of the hip were significantly (P < 0.05) associated with future THR in both the CHECK (modes 4, 11, 15, 17 and 22) and Chingford (modes 2 and 17) cohorts. Mode 17 [odds ratio (OR) 0.51 (95% CI 0.33, 0.80) in the CHECK cohort], representing a flattened head–neck junction and flat greater trochanter, could be confirmed in the Chingford cohort [OR 0.41 (95% CI 0.23, 0.82)]. Modes 4 and 15 of the CHECK cohort also showed non-significant trends in the Chingford cohort.

Conclusion. Several baseline shape variants are associated with the future need for THR within a cohort. Despite differences in participant characteristics, radiographic protocol and follow-up time, we could validate at least one shape variant, suggesting that SSM is reasonably transferable between cohorts.

Key words: hip shape, morphology, osteoarthritis, total hip replacement, validation, radiography, epidemiology, statistical shape modelling, active shape modelling.

Rheumatology key messages

- Hip shape can predict the future need for total hip replacement in females without definite radiographic OA.
- Some shape variants are consistent in the prediction of OA in two different cohorts.
- Statistical shape modelling can be used as a predictive radiographic biomarker for OA.

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Submitted 3 July 2014; revised version accepted 20 May 2015

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**Introduction**

OA is a common disease that accounts for a detrimental impact on quality of life and a considerable economic burden [1, 2]. Due to the ageing population, the need for total hip replacement (THR) is expected to grow 174%, to more than half a million primary THRs per year by 2030 in the USA alone [3].

Increasing evidence suggests that the shape of the hip plays a causative role in the development of hip OA and the subsequent need for THR [4–8]. A cam deformity, characterized by extra bone formation at the anterolateral head–neck junction, and acetabular dysplasia are consistently found to be associated with hip OA in prospective cohort studies [4, 5, 8–10]. Interestingly, because these shape abnormalities are present before the actual onset of OA, relatively simple measurements (alpha angle [11, 12], centre-edge angle [13]) can strongly predict the future risk of THR [4, 5, 14, 15].

Many other non-optimal shape variants might predict the development of hip OA as well, but these are difficult to capture with linear measurements (i.e. lengths and angles) because of the complex overall hip shape. Statistical shape modelling (SSM) is a technique that recognizes all independent shape variants in a given population and describes them quantitatively. Using this technique, it is possible to identify shape variants at risk of developing OA without any predefined hypothesis. SSM has therefore considerably increased in popularity as a tool to study the association between hip shape and the risk of OA. As a result, multiple subtle shape variants of the proximal femur and/or pelvis have been reported to be associated with OA [6, 7, 16–22]. SSM might therefore be a potential radiographic biomarker that can be used in research and clinical practice. However, all published studies on SSM and OA used different shape models (point sets of the femoral head neck junction or entire proximal femur with or without acetabulum), which makes the results difficult to compare and interpret. Certain shape variants have been associated with hip OA within a single cohort, but their generalizability remains unknown. To this end we have used one identical shape model for anteroposterior (AP) pelvis radiographs in two cohorts.

The aim of this study was to investigate which shape variants at baseline in OA-free female hips are associated with the need for THR at follow-up in two prospective cohorts [Cohort Hip and Cohort Knee (CHECK) and Chingford]. Since both cohorts now have an identical model in our study, a comparison can be made between the findings of the shape variants in the two cohorts that are associated with THR at a later time point. Thereby we can test how consistent the associated shape variants are for development of OA in various populations.

**Methods**

**Study population**

Subjects were selected from two prospective cohorts, the Dutch CHECK cohort and the UK Chingford cohort. CHECK is a nationwide multicentre prospective cohort study of 1002 individuals aged 45–65 years (mean 55.9) at baseline with early symptoms of OA (pain) of the hip and/or knee. They had not yet consulted their general practitioner for these symptoms or the first consultation was within 6 months before entry. The CHECK study was approved by the medical ethics committees of all participating centres and written informed consent according to the Declaration of Helsinki was obtained from all participants. An extensive description of the CHECK cohort can be found elsewhere [23]. For the current study, only females in the CHECK cohort were included, to allow comparison with the Chingford cohort. Of the 1002 individuals of the CHECK cohort, 791 (79%) were women; of these, 682 had radiographs available at both baseline and the 5-year follow-up. Of these 682 women, the first 93 women that entered the cohort had AP hip radiographs instead of AP pelvis radiographs obtained and were therefore excluded, as a different radiographic view might influence the morphological appearance of the hip joint on the radiographs. Of the remaining 589 individuals who had AP pelvis radiographs at both time points, 39 women had radiographs of insufficient quality to apply the shape model, most often because the edge of the greater trochanter was missing on the radiographs. Ultimately 550 women (1100 hips) were included. The 241 excluded women did not differ in baseline age ($P = 0.75$) or BMI ($P = 0.69$) from the 550 included individuals.

The Chingford cohort is a population-based cohort of 1003 women aged 44–67 years (mean 54.2) at baseline. These women were registered at a single general practice in London and were invited to participate in a study assessing musculoskeletal disease in the population. The local ethics committee (Outer North East London Research Ethics Committee) approved the Chingford cohort and written consent was obtained from each woman. Yearly clinic visits included morphometric, clinical, biological and radiographic measurements. Subjects who had radiographs obtained both at baseline and at the 19-year follow-up were included using a nested case–control design. To allow comparison with the CHECK cohort, only women without definite signs of radiographic OA [Kellgren-Lawrence (KL) score $<2$] at baseline were included [24]. This selection resulted in 19 cases who received THR within the 19 years of follow-up. For each case, 5 control hips were matched based on age and BMI, resulting in a total of 95 controls. Only one hip per person was included. When a woman received bilateral THR, the left side was selected.

**Radiographs**

In the CHECK study, weight-bearing AP pelvis radiographs were obtained from the 11 participating research centres according to a standardized protocol, taken at baseline and at the 2- and 5-year follow-ups. The feet were positioned such that the medial side of the distal part of the first phalanx touched and a wedge was used to assure $15^\circ$ internal rotation. In the Chingford cohort, each woman had a standardized supine AP pelvis radiograph, taken at years 2, 8 and 20. A small sandbag under...
the knees was used to minimize hip rotation so that the hips were in neutral position. In both the CHECK and Chingford cohorts, baseline AP pelvis radiographs were graded using an atlas-based scoring method (KL), with investigators blinded to all clinical and demographic information [24, 25]. The KL scores were independent of the positioning of the SSM point set.

SSM

From the baseline radiographs of the CHECK and Chingford cohorts, the shape of the proximal femur and pelvis was outlined using SSM software (ASM tool kit, Manchester University, Manchester, UK) [26]. The shape model was created by a set of 75 landmark points that were manually positioned along the surface of the bone in the image (Fig. 1). This was done by three investigators in the CHECK cohort, one of whom also did the point set in the Chingford cohort. The placement of the points has previously shown good reproducibility [6]. Each of the 75 points is positioned on the same anatomical landmark using a standardized manual, allowing for comparison between shapes. CHECK and Chingford data were combined and principal component analysis was used to transform the point sets into an SSM. The SSM consists of a number of modes that together describe the total variation in shape in the study population. Shape aspects that are correlated are captured in one mode such that each single mode represents an independent shape variant. The mean shape of each mode is quantitatively described as zero and the positive or negative deviation from the mean is expressed as the s.d. The modes of variation are ordered in descending order of the percentage of shape variation explained by that mode of variation, so that the resulting first few modes contribute most to the total variation in shape [22]. We retained enough modes to explain 90% of the total variation in hip morphology of the included females.

Outcome measure

THR due to OA at follow-up (5 years of follow-up in the CHECK cohort and 19 years of follow-up in the Chingford cohort) was used as an outcome measure. THR was confirmed for all cases on the follow-up radiographs.

Statistical analysis

Differences between baseline characteristics within a cohort and between the cohorts were calculated by independent samples t-test for normally distributed continuous variables, by chi-squared test for sex and KL score in the Chingford cohort and by the generalized estimating equation (GEE) model for KL score in the CHECK cohort to account for the correlation between the left and right hips within an individual. To analyse whether a mode of shape variation was associated with THR in the CHECK cohort, logistic regression with the GEE was used. The model was adjusted for age, BMI and baseline KL score. In the Chingford cohort, these associations were calculated by conditional logistic regression due to the
matched nature of the data. From these models, odds ratios (ORs), 95% CIs and P-values were calculated to describe the strength of the association for each independent mode within each cohort. To analyse the validity of the modes of shape variation for THR as an outcome, a comparison was made between the findings of the shape variants in the two cohorts that are associated with THR. An effect was considered significant at \( P < 0.05 \). All statistical analyses were performed in SPSS version 20.0 (IBM, Armonk, NY, USA).

### Results

**Participants**

The baseline characteristics of the CHECK and Chingford cohorts are presented in Table 1. At baseline, the 550 females (1100 hips) of the CHECK cohort had a mean age of 55.8 years (range 44–66) and a mean BMI of 26.1 (range 17.5–48.9). Of the 1100 hips, 80% had a KL score of 0 and 20% had a KL score of 1. Of these hips, 22 had received THR within the 5-year follow-up period. In the Chingford cohort, the included 114 females (114 hips) had a mean age of 53.6 years (range 46–64) and a mean BMI of 25.7 (range 20.0–37.8) at baseline. The KL score was 0 in 95% of the hips and 1 in 5% of the hips. Between the two cohorts there were significant differences in baseline age (55.8 years in CHECK vs 53.6 in Chingford, \( P < 0.001 \)) and baseline KL (1 score (20% in CHECK vs 5% in Chingford, \( P < 0.001 \)), but no difference in mean BMI was found (26.1 in CHECK vs 25.7 in Chingford, \( P = 0.26 \)).

**Baseline modes associated with THR at follow-up**

A total of 24 modes were extracted from the SSM, which together explained 90% of the total variation in shape that exists in the CHECK and Chingford cohorts together. The association between all baseline modes and THR at follow-up is presented in Table 2, including the ORs, 95% CIs and corresponding P-values. Five modes of shape variation had a significant positive (+) or negative (−) association with THR at follow-up in the CHECK cohort [mode 4 (−), 11 (+), 15 (+), 17 (−) and 22 (+)] and two in the Chingford cohort [mode 2 (+) and 17 (−)] (Fig. 2).

**Discussion**

Multiple shape aspects of the hip as quantified by SSM have previously been shown to be associated with or even predictive of radiographic OA [7, 17–19], clinical criteria of OA [6, 19] and THR [6, 7, 16]. However, because of the application of different shape models (different point sets), it is difficult to compare results between studies. Consequently the generalizability of the resulting modes of shape variation is limited to the characteristics of each specific cohort and therefore the validity in the prediction of OA is unknown. In this study we showed in two prospective cohorts that several shape aspects in female hips without definite features of radiographic OA at baseline were significantly associated with the need for THR at follow-up within each cohort. One shape aspect was associated with THR in both the CHECK and Chingford cohorts. This specific shape variant—describing a flattened head–neck junction together with a flat major trochanter and a prominent acetabular posterior wall—was associated with future THR in both the CHECK and Chingford cohorts (Fig. 2). Moreover, negative values of mode 4 and positive values of mode 15, which were significantly associated with future THR in the CHECK cohort, had the same effect in the prediction of THR in the Chingford cohort, although not statistically significant (\( P = 0.27 \) and \( P = 0.16 \), respectively). For examples of radiographs with the highest positive and negative values of modes 4, 15 and 17, see supplementary Fig. S1, available at *Rheumatology* Online.
Validation statistical shape modelling for hip OA

Table 2 The strength of association between all modes at baseline and THR at follow-up

<table>
<thead>
<tr>
<th>Mode</th>
<th>aOR (95% CI)</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>M0</td>
<td>0.799 (0.519, 1.232)</td>
<td>0.310</td>
</tr>
<tr>
<td>M1</td>
<td>1.181 (0.671, 2.077)</td>
<td>0.564</td>
</tr>
<tr>
<td>M2</td>
<td>0.823 (0.530, 1.379)</td>
<td>0.388</td>
</tr>
<tr>
<td>M3</td>
<td>1.029 (0.732, 1.445)</td>
<td>0.871</td>
</tr>
<tr>
<td>M4</td>
<td>0.375 (0.204, 0.690)</td>
<td>0.002</td>
</tr>
<tr>
<td>M5</td>
<td>0.893 (0.567, 1.406)</td>
<td>0.624</td>
</tr>
<tr>
<td>M6</td>
<td>1.311 (0.888, 1.935)</td>
<td>0.174</td>
</tr>
<tr>
<td>M7</td>
<td>0.937 (0.578, 1.520)</td>
<td>0.793</td>
</tr>
<tr>
<td>M8</td>
<td>1.441 (0.935, 2.220)</td>
<td>0.098</td>
</tr>
<tr>
<td>M9</td>
<td>1.139 (0.724, 1.793)</td>
<td>0.573</td>
</tr>
<tr>
<td>M10</td>
<td>1.280 (0.899, 1.822)</td>
<td>0.170</td>
</tr>
<tr>
<td>M11</td>
<td>2.179 (1.229, 3.863)</td>
<td>0.008</td>
</tr>
<tr>
<td>M12</td>
<td>0.769 (0.484, 1.222)</td>
<td>0.266</td>
</tr>
<tr>
<td>M13</td>
<td>1.439 (0.874, 2.371)</td>
<td>0.153</td>
</tr>
<tr>
<td>M14</td>
<td>0.783 (0.534, 1.148)</td>
<td>0.211</td>
</tr>
<tr>
<td>M15</td>
<td>1.657 (1.024, 2.681)</td>
<td>0.040</td>
</tr>
<tr>
<td>M16</td>
<td>0.808 (0.500, 1.307)</td>
<td>0.386</td>
</tr>
<tr>
<td>M17</td>
<td>0.513 (0.330, 0.797)</td>
<td>0.003</td>
</tr>
<tr>
<td>M18</td>
<td>1.153 (0.705, 1.885)</td>
<td>0.571</td>
</tr>
<tr>
<td>M19</td>
<td>1.095 (0.662, 1.810)</td>
<td>0.723</td>
</tr>
<tr>
<td>M20</td>
<td>1.275 (0.823, 1.976)</td>
<td>0.277</td>
</tr>
<tr>
<td>M21</td>
<td>1.172 (0.805, 1.707)</td>
<td>0.408</td>
</tr>
<tr>
<td>M22</td>
<td>1.897 (1.194, 2.783)</td>
<td>0.001</td>
</tr>
<tr>
<td>M23</td>
<td>0.928 (0.557, 1.546)</td>
<td>0.775</td>
</tr>
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</table>

The finding that hip shape was associated with the future risk of THR was further supported by other studies. Previous research in the CHECK cohort for both men and women showed five modes predictive of future THR in baseline radiographic-free hips (KL score <2) [6]. The predictive modes primarily described a broad and short femoral neck and a retroverted acetabulum together with a non-spherical femoral head. In the Rotterdam study, especially shape variants related to the superior head–neck junction and the shape of the acetabular socket were significantly associated with the development of OA [27]. Waarsing et al. [19] also found various shape aspects associated with OA that were in line with our findings of mode 17, such as a smaller greater trochanter and a cam-shaped femoral head. It is difficult to speculate on the mechanism by which these shape aspects lead to OA. A small greater trochanter clearly does not have a direct intra-articular effect. A cam-shaped femoral head can cause OA by the mechanism of cam impingement, although the non-spherical femoral head of mode 17 is rather subtle, in contrast to the more pronounced non-spherical femoral head of mode 4. In a retrospective study of patients who presented with hip pain, Barr et al. [16] found one mode of shape variation was significantly associated with THR 5 years later when adjusted for baseline KL score. Subtle shape variations as quantified by SSM have therefore been suggested as a potential radiographic biomarker to predict the future risk of OA. But again, all studies on SSM and OA have used different shape models, so the resulting predictive modes of shape variation cannot be directly compared.

Our results are in line with previously published articles showing that certain shape variants of the hip can predict the risk of a THR within a cohort. More importantly, however, we found that one shape variant was predictive for a THR in both the CHECK and Chingford cohorts. There are several explanations for the fact that not all predictive shape variants of the CHECK cohort could be validated in the Chingford cohort, including differences in follow-up time, radiographic protocol and participant characteristics. First, there was a difference in follow-up time between the

5 years in the CHECK cohort and 19 years in the Chingford cohort. The statistically significant modes (P < 0.05) are highlighted in bold. aOR corrected for age, BMI and KL grade at baseline. The presented ORs represent every increase in 1 S.D. of that specific mode. aOR: adjusted odds ratio; CHECK: Cohort Hip and Cohort Knee; KL: Kellgren and Lawrence; OR: odds ratio; THR: total hip replacement.
FIG. 2 Modes significantly predictive of THR are shown

The odds ratios presented in Table 2 represent every increase in s.d., but for clarity the –3 s.d. (left column) and +3 s.d. (right column) from the mean (middle column) are presented. The extremes that are associated with THR are indicated in boxes. THR: total hip replacement.
two cohorts, and the pathophysiology of fast-progressing OA (THR within 5 years in the CHECK cohort) might be different from slow-progressing OA (THR within 19 years in Chingford). This is supported by a study showing that the predictive value of hip shape and other risk factors at baseline decreased when using a longer follow-up time [27]. An example is a cam deformity that results in fast-progressing hip OA [4], which will be detected at 5 years but is less likely to be detected at 19 years of follow-up, as other factors may dilute the predictability of a cam deformity. Lower values of mode 4, representing a non-spherical femoral head (together with a shallow acetabulum), and higher values of mode 15 might be modes that are more strongly associated with fast-progressing OA (Fig. 2). Though not as strong as in the CHECK cohort, the predictive effect of these modes was still present in the Chingford cohort, though not statistically significant ($P = 0.27$ for mode 4 and $P = 0.16$ for mode 15). Second, the radiographic protocol was different between the two cohorts: in the CHECK cohort, AP pelvic weight-bearing radiographic views with 15° internal hip rotation were obtained, while in the Chingford cohort, AP pelvic supine radiographs were obtained in neutral position. The differences between the amount of hip rotation and differences in position (the standing position may influence pelvic inclination) can affect how the outline of the bone, and thus hip shape, appears on the radiograph. Third, although no difference in BMI was found between the cohorts and the significant difference of 2.2 years in baseline mean age is probably negligible, differences in other participant characteristics might play a role. In the CHECK cohort there is a larger proportion of females presenting with hip and/or knee pain (as first onset of knee and/or hip pain was an inclusion criterion), whereas Chingford women were recruited from the general population. This difference might influence the association between hip shape and OA. Furthermore, there might be other (unknown) differences between the two cohorts, for example, genetics, which is known to affect both hip shape and the relationship between hip shape and OA [20, 21].

It is not known whether the shape variants found to be associated with OA are causative factors for OA or whether they represent early changes in bone morphology as a result of OA. As the shape variants of our model describe the overall hip shape, it is unlikely to be a result of the OA process. Furthermore, most modes associated with THR show some variation in the head-neck junction, which might reflect different subtypes of cam deformity, resulting in OA by a motion-dependent process of cam impingement [28]. Interestingly, a cam deformity is known to be highly associated with OA and develops during growth, probably as a bone adaptation to high-impact athletic activities [14, 15, 29]. It is not known whether other predictive shape variants are also present before the onset of OA.

Several potential limitations of this study need to be acknowledged. First, we only included females and thus the results of this study might be different for males, as there might be a gender difference in how much hip shape contributes to the prediction of OA and also the predictive shape variants might be different between males and females [18]. Second, the rotation of bones might influence the projected radiographic shape, which was minimized by the use of a standardized radiographic protocol. Third, THR is a surrogate measure for OA; as it is a surgical endpoint, questions might arise about accessibility to health care and THR. In this study, all THRs were a result of OA, a THR was confirmed on follow-up radiographs and THR is a validated and clinically relevant outcome measure [30]. Further, four of the five modes that associated with THR in the CHECK cohort (modes 4, 11, 15 and 17) were also significantly associated with radiographic OA (KL score $\geq 2$, $n = 41$) at follow-up. Also, both the Netherlands and the UK have a public health system in which all people have equal access to THR. Moreover, the definitions of radiographic OA and clinical OA also have their [6].

Predictive shape variants might be dependent on many factors, including follow-up time, inclusion criteria of the cohort and radiographic protocol. Despite the differences in these factors between the two cohorts, we could validate one mode (mode 17), while two modes (modes 4 and 15) that were significantly associated with THR in the CHECK cohort showed trends in the same direction in the Chingford cohort, although not statistically significant. Therefore SSM might be a useful tool as a radiographic biomarker. For this purpose the manual positioning of landmark points is labour intensive, but recently developed fully automatic shape modelling software might provide future opportunities [31].

In conclusion, we found several shape variants that were associated with the future need for THR within a cohort and one shape variant in the CHECK cohort that could be validated in the Chingford cohort. Despite differences in participant characteristics, radiographic protocol and follow-up time, SSM as a predictive radiographic biomarker for THR was reasonably transferable between cohorts.

Acknowledgements

The authors thank C. F. Vermeulen and J. van Egmond for their involvement in positioning the landmark points on the radiographs for the statistical shape modelling, as well as all the participants of the CHECK cohort. The CHECK cohort study is initiated by the Dutch Arthritis Association and performed within the Erasmus Medical Centre Rotterdam; Kennemer Gasthuis Haarlem; Leiden University Medical Centre; Maastricht University Medical Centre; Martini Hospital Groningen/Allied Health Care Centre for Rheum and Rehabilitation Groningen; Medical Spectrum Twente Enschede/Ziekenhuisgroep Twente Almelo; Reade, formerly the Jan van Breemen Institute/ VU Medical Centre Amsterdam; St Maartens-kliniek Nijmegen; University Medical Centre Utrecht and Wilhelmina Hospital Assen. The CHECK cohort was funded by the Dutch Arthritis Association. The Chingford cohort is supported by Arthritis Research UK and the Oxford National Institute for Health Research Musculoskeletal Biomedical Research Unit. The sponsors of the study had no role in study design, data collection,
data analysis, data interpretation, writing of the report or the decision to submit the paper for publication. The corresponding author had full access to the study data and had final responsibility for the decision to submit for publication.

Funding: This work was supported by the Arthritis Research UK Centre for Sport, Exercise and Osteoarthritis (grant reference 2019).

Disclosure statement: N.K.A. has received honoraria, held advisory board positions (which involved receipt of fees) and received consortium research grants from Merck, Merck Sharp and Dohme, Roche, Novartis, Smith and Nephew, Q-MED, Nicox, Servier, GlaxoSmithKline, Schering-Plough, Pfizer and Rottapharm. All other authors have declared no conflicts of interest.

Supplementary data

Supplementary data are available at Rheumatology Online.

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27. Castano-Betancourt MC, Van Meurs JB, Bierma-Zeinstra S et al. The contribution of hip geometry to the prediction...
Clinical vignette

Ultrasound is a useful adjunct in diagnosis of eosinophilic fasciitis

This 28-year-old male presented with progressive skin tightening and limited joint mobility for 11 months, involving legs up to mid-shin and forearms up to elbows, preceded by painless swelling involving affected regions, sparing fingers and toes. Systemic features were absent. There was peripheral eosinophilia (leucocytes: 11600/μl, eosinophils 52%, absolute eosinophil count: 6032/μl), raised acute-phase reactants and hypergammaglobulinaemia. Nail-fold capillaroscopy was non-contributory. RP, digital ulcers, dysphagia, reflux and pulmonary arterial hypertension were absent. ANA was positive, and Scl70 and anticentromere antibodies were negative.

High-resolution US of legs (Fig. 1A and C) using an 18-MHz linear array transducer showed thickening and altered echotexture of subcutaneous fat (Fig. 1B) from a healthy person for comparison. MRI of legs (Fig. 1D) showed thickening of fascia, along with increased contrast enhancement of the myofascial plane, corroborating US findings. He was diagnosed as having eosinophilic fasciitis (EF) and put on prednisolone.

Apart from histology, MRI is also useful for the diagnosis of EF [1]. The role of US elastography has been studied in scleroderma, and has demonstrated reduction of strain in the dermis of the forearm due to loss of elasticity [2]. Here we present a case of EF characterized ultrasonographically with MRI corroborations.

Funding: No specific funding was received from any funding bodies in the public, commercial or not-for-profit sectors to carry out the work described in this manuscript.

Disclosure statement: The authors have declared no conflicts of interest.

References