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Bone shape and alignment analysed using statistical shape modelling is associated with severity of first metatarsophalangeal joint osteoarthritis

Short title: Bone shape and alignment in first MTP joint OA

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Abstract

Objective

To explore the relationship between bone shape and radiographic severity in individuals with first metatarsophalangeal joint osteoarthritis (first MTP joint OA).

Methods

Weightbearing lateral and dorso-plantar radiographs were obtained for the symptomatic foot of 185 participants (105 females, aged 22 to 85 years) with clinically diagnosed first MTP joint OA. Participants were classified into either none/mild, moderate, or severe categories using a standardised atlas. An 80-point model for lateral radiographs and 77-point model for dorso-plantar radiographs was used to define independent modes of variation using statistical shape modelling software. Odds ratios adjusted for confounders were calculated using ordinal regression to determine the association between radiographic severity and mode scores.

Results

After assessment and grading of radiographs, 35 (18.9%) participants were included in the none/mild first MTP joint OA severity category, 69 (37.2%) in the moderate severity, and 81 (43.7%) in the severe category. For lateral view radiographs, 16 modes of variation were included, which collectively represented 83.2% of total shape variance. Of these, four modes were associated with radiographic severity. For dorso-plantar view radiographs, 15 modes of variation were included, representing 82.6% of total shape variance. Of these, six modes were associated with radiographic severity.

Conclusions

Variations in the shape and alignment of the medial cuneiform, first metatarsal, proximal and distal phalanx of the hallux are significantly associated with radiographic severity of first MTP joint OA. Prospective studies are required to determine whether bone shape characteristics are associated with the development and/or progression of this condition.

Significance and Innovation

- This is the first study to use statistical shape modelling to create a profile of bone shape linked to radiographic severity of first MTP joint OA
- Variations in the shape and alignment of the medial cuneiform, first metatarsal, proximal and distal phalanx of the hallux are significantly associated with radiographic severity of first MTP joint OA.

Osteoarthritis (OA) of the first metatarsophalangeal (MTP) joint is a common condition affecting 7.8% of people aged over 50 years [1, 2]. Characteristics of first MTP joint OA include localised pain and stiffness in the affected joint [3]. Individuals with first MTP joint OA also report lower health-related quality of life, have greater difficulty performing weightbearing tasks, and perceive their feet to be in poorer condition compared to people without the condition [4].

Greater radiographic severity of first MTP joint OA is associated with increased prevalence of pain and reduced range of motion available in the joint, suggesting that it may be a progressive condition [3]. A recent population-based longitudinal cohort study demonstrated the progressive course of first MTP joint OA, with 28% of women recruited with radiographic first MTP joint OA at baseline displaying an increase in radiographic severity over a 19 year period [5]. This study also indicated a discordance in the symmetry of first MTP joint OA progression between left and right feet. For example, the characteristics of first MTP joint OA in left feet were more likely to include joint space narrowing, while the characteristics of first MTP joint OA in right feet displayed greater osteophyte formation. In hand, hip and knee OA, it has also been suggested that discordance in progression, and in particular osteophyte formation, may be due to functional variability as opposed to constitutional or genetic factors [6].

Variations from normal function including parameters such as range of motion and biomechanics are recognised as being a feature of first MTP joint OA. Indeed, range of motion testing (less than 64° dorsiflexion) forms part of the clinical definition of the condition [7], and differences in gait-related biomechanical parameters, primarily pressure distribution, have been observed between individuals with and without first MTP joint OA [8, 9]. Variations from normal function that are associated with first MTP joint OA may be influenced by characteristic changes in skeletal structure. Studies that have investigated skeletal foot structure have primarily focused on bone dimensions and joint angles, finding that individuals with greater severity of radiographic first MTP joint OA exhibit greater width of the first metatarsal and proximal hallux, and increased hallux interphalangeal angle, hallux interphalangeal hyperextension and hallux valgus angle [3, 10]. However, the usefulness of these findings are limited, as measures may be highly correlated with each other, or with other factors such as body size and sex [11].

Statistical shape modelling (SSM) is a statistical technique that can describe the shape and alignment of multiple bones beyond what can be provided by single geometric measurements [12]. Importantly, in joints where statistical shape modelling has been utilised, such as the hip, the analysis of bone shape has been shown to be a biomarker of OA progression [13-16]. The characteristic bone shape profile associated with hip OA can be used to identify and monitor early OA, and can assist in the prediction of total hip replacement [17]. To date, there is only one study relating to foot OA to use statistical shape modelling that explored differences between participants with hallux valgus, first MTPJ OA and controls without first MTP joint pathology [18].

The aim of this cross-sectional study was to use statistical shape modelling to model morphological differences in individuals with differing severities of first MTP joint OA, and explore the relationship between bone shape, alignment and radiographic severity.

Methods

Participants

We recruited individuals from two clinical trials that evaluated non-surgical interventions for first MTP joint OA [19, 20]. Ethical approval was granted by the La Trobe University Human

Ethics Committee (HEC15-128 and HEC18-375). All participants had a clinically-defined diagnosis of first MTP joint OA, which included the following: (i) aged at least 18 years, (ii) reported pain at the first MTP joint on most days for at least 12 weeks, (iii) reported pain rated at least 30 mm on a 100 mm visual analogue scale in the previous week, (iv) described pain on palpation of the dorsal aspect of the first MTP joint and (v) exhibited restricted dorsiflexion of the first MTP joint (<64° of dorsiflexion range of motion). Participants were excluded based on the following: (i) previous first MTP joint surgery, (ii) currently pregnant, (iii) significant first MTP joint deformity such as hallux valgus (defined as a score of 2 or 3 using the Manchester scale [21]), (iv) presence of any condition within the foot or ankle that confound pain and functional assessments of the first MTP joint, such as clinically important pain in a part of the musculoskeletal system other than the first MTPJ and (v) the presence of systemic inflammatory conditions such as gout or rheumatoid arthritis.

Imaging

All radiographic procedures were performed according to the National Health and Medical Research Council of Australia National Statement on Ethical Conduct in Human Research [22]. Weightbearing lateral and dorso-plantar radiographs of the foot were taken for all participants while standing in a relaxed weightbearing position. All radiographs were taken by the same medical imaging equipment. Each foot was radiographed separately. For lateral view radiographs, the x-ray tube was positioned at an angle of 90° and centred at the base of the third metatarsal. For dorso-plantar view radiographs, the x-ray tube was positioned at an angle of 15° cephalad and centred at the base of the third metatarsal. The film focus distance was 100 cm for both projections. If the participant had bilateral first MTP joint OA, radiographs were taken of the most symptomatic foot.

Radiographic grading

The La Trobe University radiographic atlas for foot OA was used to determine the severity of OA at the first MTP joint [23]. The atlas assesses osteophytes and joint space narrowing at the first MTP joint from lateral and dorso-plantar views. The atlas has been shown to have excellent reliability [23]. The presence of osteophytes was graded as absent (score = 0), small (score = 1), moderate (score = 2) or severe (score = 3). The presence of joint space narrowing was graded as absent (score = 0), definite (score = 1), moderate (score = 2) or joint fusion (score = 3). Following grading of osteophytes and joint space narrowing, participants were assigned one of three radiographic severity categories: (i) no or mild OA (defined as one score of 1 or less and no score of 2 or greater for either osteophytes or joint space narrowing from either the dorso-plantar or lateral radiographs), (ii) moderate OA (defined as one score of at least 2 and no scores of 3) or (iii) severe OA (defined as one score of at least 3). Assessments were carried out by two raters who were involved in the development of the atlas (HBM and SEM).

Statistical shape modelling

Statistical shape modelling is a statistical technique used to identify and quantify variations in the shape of bones [24, 25]. Custom made statistical shape modelling software (Shape, Aberdeen University, UK) was used to create a template of easily identifiable landmark points to define the entire shape of the medial cuneiform, first metatarsal, proximal phalanx and distal phalanx. Separate templates were created for lateral view radiographs, comprising 80 points, and dorso-plantar view radiographs, comprising 77 points. Templates were created to include features that were consistently visible in all images, including osteophytes associated with the first MTP joint. Point locations for dorso-plantar and lateral radiographs are shown in Figure 1.

As standard for this technique, the location of points was orientated to define the bone shape for all radiograph images by the same investigator (AKB). To remove the influence of size, point coordinates underwent Procrustes transformation to scale, rotate and translate points to lie on the same scale and as closely aligned as possible. Variations in bone shape were then described with a series of independent orthogonal modes that were derived using principal components analysis. Mode scores for each image were expressed in units of standard deviation to describe how each participant varied from the mean shape for the entire sample.

Reproducibility

Thirty lateral and 30 dorso-plantar images were randomly selected to assess intra-rater reproducibility. Points were placed by the same investigator who analysed the radiographs on two occasions at least 2 weeks apart. Mean point-to-point difference was measured in pixels (1 pixel = 0.8 mm). For lateral radiographs, mean point-to-point difference was 2.6 pixels. For dorso-plantar radiographs, mean point-to-point difference was 2.1 pixels. In statistical shape modelling analysis, a mean point-to-point difference of 3 pixels or less is considered to represent acceptable reproducibility [26].

Statistical analysis

All analyses were performed using IBM SPSS Statistics Release 24 for Windows (IBM Corp, Armonk, NY, USA). Modes of variation were included for both lateral and dorso-plantar radiographs. Modes were required to represented at least 1% of the total variation of the sample to be included. Associations between mode score and first MTP joint OA severity were represented as odds ratios (ORs) with 95% confidence intervals (CIs), calculated via ordinal regression. Covariates were included in ordinal regression for variables considered to be confounders. Confounders were identified using one-way ANOVA. Any significant differences (p-values < 0.05) between severity categories indicated that the covariate was a confounder. In addition, Bonferroni adjustment for multiple comparison was applied to significant mode association findings ($p<0.05$).

Results

Participant characteristics

A total of 185 participants were included in the study, their characteristics are shown in Table 1. After grading the severity of first MTP joint OA, 35 (18.9%) participants were classified as none/mild severity, 69 (37.2%) as moderate severity, and 81 (43.8%) as severe. Participants in the severe category were significantly older than the none/mild (mean difference = 4.9 years, 95% CI = 0.7 to 9.1) and moderate (mean difference = -3.8 years, 95% CI = 0.5 to 7.2) categories. The severe category also exhibited significantly greater body mass index (BMI) compared with the none/mild category (mean difference = 2.5 kg/m^2, 95% CI = 0.7 to 4.3) and significantly greater weight compared with both the none/mild (mean difference = 9.1 kg, 95% CI = 4.1 to 14.2) and moderate (mean difference = 7.0 kg, 95% CI = 2.9 to 11.1) categories. Participants in the severe category also exhibited significantly greater self-reported duration of symptoms compared with the none/mild (mean difference = 51.9 months, 95% CI = 21.5 to 82.3) and moderate (mean difference = 33.2 months, 95% CI = 8.7 to 57.8) categories. No significant differences were seen for sex and height between the severity of first MTP joint OA categories. Accordingly, age, BMI and duration of symptoms were entered as covariates in the ordinal regression models. Although weight was significantly different between severity categories, it is strongly correlated with BMI and so, was not entered as a covariate to avoid over-correction.

Lateral view radiographs

A total of 16 modes of variation were included as each represented at least 1% of the total variation of the sample. These modes collectively represented 83.2% of total shape variance (Table 2). Significant associations were identified between radiographic severity and 6 modes (modes 1, 2, 5, 6, 8, 9). Following adjustment for confounders, the number of significant associations with the application of Bonferroni adjustment reduced to 4 modes (modes 1, 2, 5, 10). The strongest associations were for mode 1 (OR = 2.77, 95% CI = 1.91, 4.02), and mode 5 (OR = 0.44, 95% CI = 0.32, 0.61).

A representation of the four significant associations (after adjustment) between radiographic severity and mode scores is shown in Figure 2. For lateral mode 1, radiographic severity was positively associated with greater mode scores (+2 standard deviations from the mean represented by solid red line in Figure 1). Greater scores for lateral mode 1 were characterised by a more dorsiflexed first metatarsal, a larger first metatarsal head, a prominent dorsal osteophyte with a posteriorly orientated protuberance, narrower dorsal joint space, a more plantar orientation of the proximal phalanx, and a dorsal osteophyte at the base of the proximal phalanx. For lateral mode 5, radiographic severity was negatively associated with larger mode scores. Smaller lateral mode 5 scores were characterised by a longer first metatarsal, presence of a sharp posteriorly orientated protuberance originating from the dorsal exostosis on the first metatarsal head, and a flatter base of the proximal phalanx of the hallux.

Dorso-plantar view radiographs

There were 15 modes of variation selected as each represented at least 1% of the total variation of the sample, representing 82.6% of total shape variance (Table 3). Significant associations were identified between radiographic severity and 7 modes (modes 2, 3, 8, 9, 11, 14, 15). Following adjustment for confounders, the number of significant associations with the application of Bonferroni adjustment reduced to 6 modes (modes 2, 3, 8, 9, 11, 14). The strongest associations were for dorso-plantar mode 11 (OR = 1.77 95% CI = 0.77, 2.42), dorso-plantar mode 2 (OR = 1.58, 95% CI = 1.17, 2.14) and dorso-plantar mode 3 (OR = 0.66, 95% CI = 0.49, 0.88).

A representation of the six significant associations (after adjustment) between radiographic severity and mode scores is shown in Figure 3. For dorso-plantar modes 11 and 2, radiographic severity was positively associated with greater mode scores. For dorso-plantar mode 11, increased mode scores were characterised by a narrower joint space and wider lateral margin at the base of the proximal phalanx. For dorso-plantar mode 2, increased mode scores were characterised by narrower joint space, wider medial cuneiform, wider base, shaft, and head of the first metatarsal, wider proximal phalanx, and wider and longer distal phalanx. For dorso-plantar mode 3, radiographic severity was negatively associated with greater mode scores. Smaller mode scores were characterised by an overall wider first metatarsal and proximal phalanx, and a wider joint surface of the first MTP joint.

Discussion

This is the first study to use statistical shape modelling to create a profile of bone shape linked to radiographic severity of first MTP joint OA. We utilised both lateral and dorso-plantar view radiographs to identify modes of variation for the bony anatomy of the medial cuneiform, first metatarsal, and proximal and distal phalanx that were associated with severity determined using the La Trobe University radiographic foot atlas. As there is no standardised reference for bone shape of the first MTP joint or adjacent bones using statistical shape modelling, modes that were associated with radiographic severity can only be differentiated through qualitative assessment of variation. Most of the variation in significant modes can be summarised by the shape of the first MTP joint, and the size and alignment of the first metatarsal and proximal phalanx. The only similar study by Milliken and colleagues investigated the association between bone shape and foot pathology [18]. Although there were similarities in the model design, there were differences in study design as Milliken and colleagues included the whole foot, not just the first MTP joint. Furthermore, their study included participants with hallux valgus, which dominated the earlier modes of the resulting shape model, precluding direct comparisons to our findings.

Analysis of lateral view radiographs identified four modes of variation that were significantly associated with radiographic severity of first MTP joint OA after adjustment for confounders. The variation identified in lateral modes 1 and 2 was contrasting and may suggest differing courses of progression of first MTP joint OA. Lateral mode 1 explained the greatest amount of total shape variance (22.7%) and had the strongest association with radiographic severity. The most distinctive and unique features of mode 1 were the shape of the first MTP joint and sagittal plane alignment of the first metatarsal. Higher mode scores for lateral mode 1 were reflected by focal joint space narrowing in the dorsal aspect of the first MTP joint and relative dorsiflexion of the first metatarsal. In contrast to lateral mode 1, lower scores for lateral mode 2 were associated with radiographic severity. Lateral mode 2 explained the second most amount of total shape variance (12.2%), and greater radiographic severity of first MTP joint OA was characterised by relative dorsiflexion of the first metatarsal, and uniformly distributed joint space narrowing.

There are two mechanical considerations that stem from the variations identified in lateral modes 1 and 2. Firstly, lateral mode 1 aligns with previous studies that have reported a significantly greater dorsiflexion of the first metatarsal in individuals with first MTP joint OA compared to individuals without [27, 28]. Secondly, in regard to the distribution of joint space narrowing across the first MTP joint, the reduced joint space in the dorsal aspect of the joint associated with higher scores for lateral mode 1 suggests that, as is the case in the knee [29], osteoarthritic change can occur unevenly across the joint surface, and may be influenced by mechanical loading. This is also consistent with the surgical literature that has described the distribution of joint degeneration concentrated in the dorsal margins of the joint [30]. The variation identified by lateral modes 1 and 2 suggests a link between sagittal plane alignment of the first metatarsal and distribution of joint space narrowing in individuals with first MTP joint OA. As the cross-sectional nature of this study does not allow temporal relationships to be examined, the interplay between first metatarsal sagittal plane alignment and progression of first MTP joint OA should be a focus of future prospective studies using statistical shape modelling.

The four modes from lateral radiographs that were significantly associated with radiographic severity after adjustment (lateral modes 1, 2, 5 and 10) collectively explained 42% of total shape variance. While there were differences in the features of variation identified, in all modes, greater radiographic severity of first MTP joint OA was associated with an overall larger osteophyte and the presence of a characteristic posteriorly-orientated 'spike' of bone emanating from the main body of the osteophyte. This is an expected finding as the atlas used to classify severity in this study incorporates the assessment of osteophytes.

The functional and clinical importance of osteophytes associated with OA is unique to the joint in which they are located [31]. Osteophytes located at the dorsal margin of the first metatarsal are considered a defining clinical characteristic of first MTP joint OA [32]. Osteophytes associated with first MTP joint OA are unique in that they elicit pain on direct palpation [7]. Although all participants in this study exhibited an osteophyte, statistical shape modelling analysis has provided an in-depth analysis of the characteristic size and shape of the osteophyte across a range of different severities [23]. Future statistical shape modelling research should address the role of osteophyte formation in the development of first MTP joint OA and its association with symptoms.

For dorso-plantar view radiographs, there were six modes of variation that were significantly associated with radiographic severity, collectively explaining 32.1% of total shape variance. A common feature of significant modes was the association between greater radiographic severity and an increased overall width of the first metatarsal and proximal phalanx. This observation is consistent with previous studies using the same dataset of radiographs that that used simple geometric measures [10]. Overall, the features of the six significant modes confirms that there is a wider base, shaft and head of the first metatarsal, and overall wider proximal phalanx. However, each mode characterised a different and unique variation of bone width.

A previous study examining bone dimensions on radiographs, not using statistical shape modelling, found that comparatively greater width of the first metatarsal, but without excessive length, results in a comparatively squarer first MTP joint surface that will be predisposed to the development of first MTP joint OA [33]. While features of dorso-plantar modes 2, 3, 9 and 14 indicate that the width of the bone and first MTP joint surface may be related to the severity of first MTP joint OA, dorso-plantar modes 8 and 11 indicate that greater joint width can occur independent of bone width. While our study provides some evidence for the association between greater first metatarsal width and the development of first MTPJ OA, further studies are required to determine the link between the overall morphology of the first metatarsal shaft and head, and the development of the condition.

Four limitations must be considered with our study. First, the study was cross-sectional, so it is not known if the variations in bone shape are a causative factor for the development of first

MTP joint OA, or if variations are a consequence of first MTP joint OA progression. Second, the study used 2-dimensional radiographs to analyse bone shape and did not capture the 3-dimensional form of relevant bones and the first MTP joint. Third, there are likely to be factors other than bone shape and alignment that may contribute to the development and progression of first MTP joint OA such as previous trauma, work/occupation, footwear, and genetics [34]. Last, as this study excluded participants with hallux valgus, inferences cannot be made for individuals with hallux valgus or similar studies that included individuals with both first MTP joint OA and hallux valgus.

Conclusion

Variations in shape and alignment of the medial cuneiform, first metatarsal, proximal and distal phalanx of the hallux are associated with radiographic severity of first MTP joint OA. The outcomes of this study provide insights into the potential influence of mechanical factors in the development of first MTP joint OA. However, it is possible that other factors, such as genetic or lifestyle factors may also contribute to the development of the condition. Prospective studies are required to determine whether these bone shape characteristics are associated with the development and progression of first MTP joint OA.

Author contributions

Conception and design: AKB, JSG, SEM, MM, HBM

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Provision of study materials or patients: AKB, SEM, JJA, JMY, MA, HBM

Statistical expertise: JSG, MM

Administrative, technical, or logistic support: JSG, MA, HBM

Collection and assembly of data: AKB, JSG, SEM, JJA, JMT, MA, KBL, MM, HBM

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Competing interests

There are no conflicts of interest.

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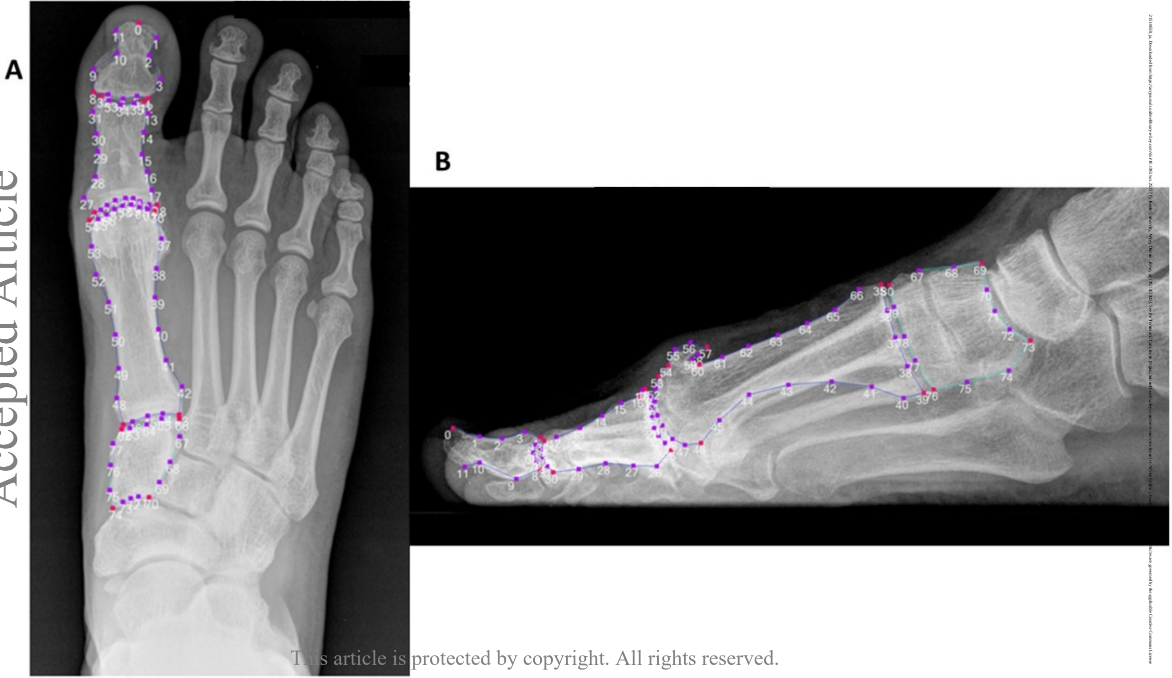
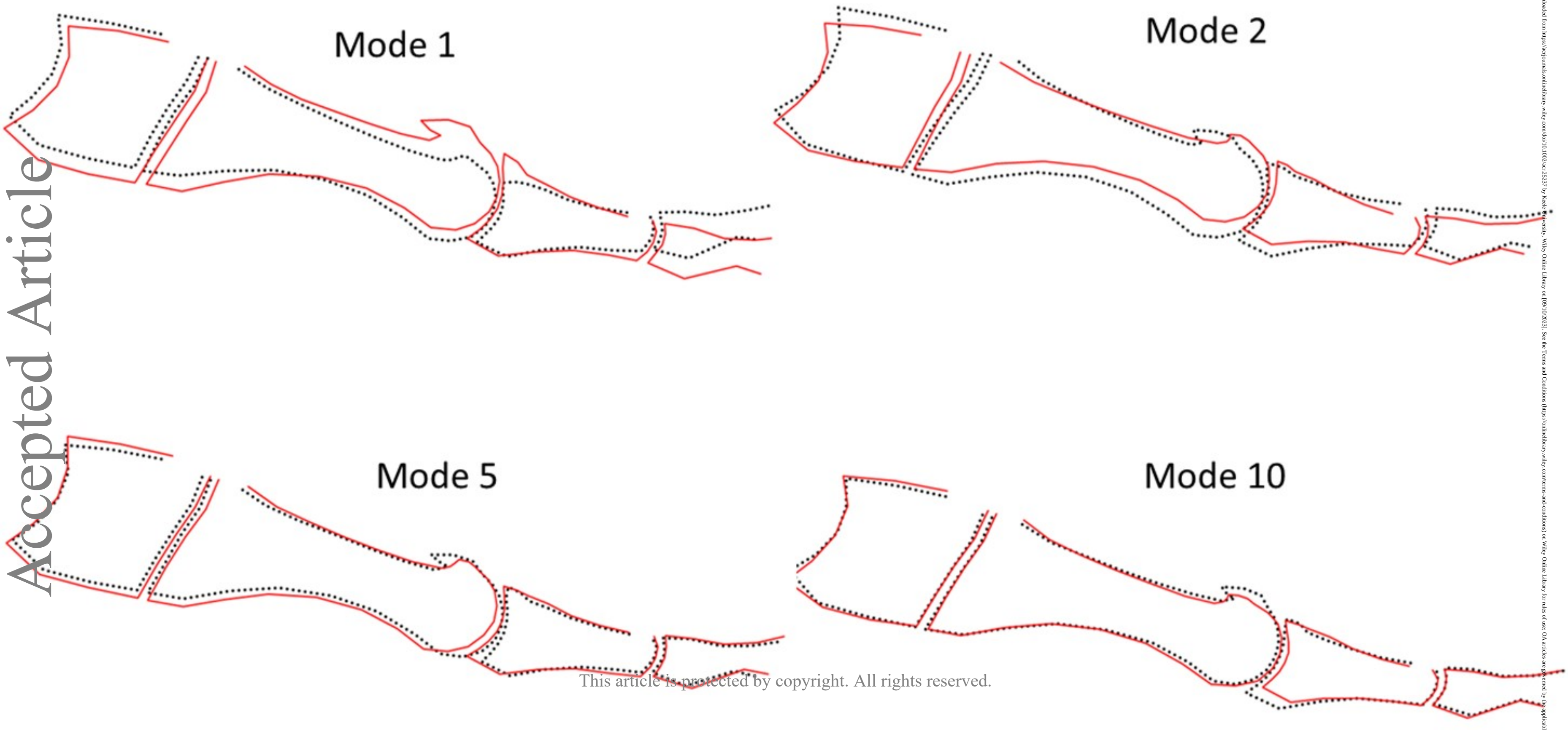
Figure 1. Point placement for statistical shape modelling templates for dorso-lantar view radiographs (A) and lateral radiographs (B).

Figure 2. Modes from lateral view radiographs with significant associations with radiographic severity (+2 standard deviations = red solid line, -2 standard deviations = black broken line).

Figure 3. Modes from dorso-plantar view radiographs with significant associations with radiographic severity (+2 standard deviations = red solid line, -2 standard deviations = black broken line).


A
B



Mode 1
Mode 2
Mode 5
Mode 10

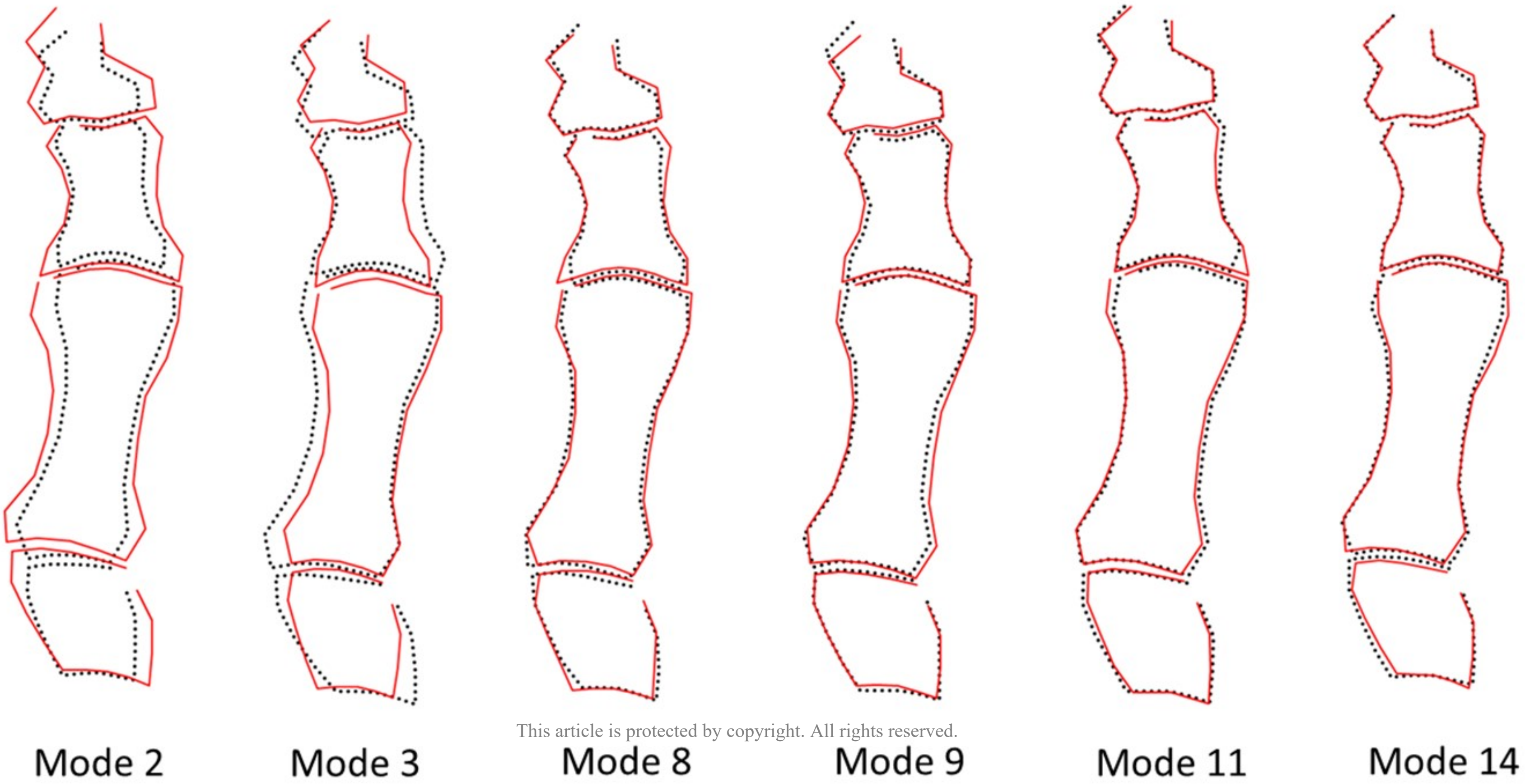

Mode 2
Mode 3
Mode 8
Mode 9
Mode 11
Mode 14

Table 1. Participant characteristics according to radiographic severity of first MTP joint OA.*

	None/mild (n=35)	**Moderate (n=69)**	**Severe (n=81)**	***p*-value**
Age (years)	55.0 (13.4)	56.1 (10.8)	59.9 (8.9)	0.026†#
Female, n (%)	22 (62.9)	44 (63.7)	39 (48.1)	0.101
Height (cm)	166.7 (8.5)	165.2 (8.7)	168.4 (8.3)	0.574
Weight (kg)	74.2 (13.2)	76.3 (11.3)	83.4 (13.7)	<0.001†#
BMI (kg/m^2)	26.8 (4.5)	28.0 (4.6)	29.3 (4.6)	0.017†
Duration of symptoms (months)	35.8 (42.3)	56.6 (66.6)	86.5 (93.8)	<0.001†#

* Values shown represent mean (SD) unless otherwise stated

† Significant difference between none/mild and severe

Significant difference between moderate and severe

Table 2. Associations between radiographic severity and modes of variation from lateral view radiographs.

Mode	Variance explained (%)	Odds ratio (95% CI)	*p*-value	Adjusted odds ratio (95% CI)†	*p*-value
1	22.7	3.01 (2.11 to 4.31)	<0.001*	2.77 (1.91 to 4.02)	<0.001*
2	12.2	0.65 (0.49 to 0.87)	0.004*	0.69 (0.50 to 0.92)	0.014*
3	10.3	0.81 (0.61 to 1.06)	0.131	1.15 (0.86 to 1.52)	0.344
4	8.3	1.19 (0.91 to 1.57)	0.198	1.18 (0.88 to 1.58)	0.249
5	4.7	0.47 (0.34 to 0.64)	<0.001*	0.44 (0.32 to 0.61)	<0.001*
6	4.2	1.32 (1.00 to 1.72)	0.044*	1.26 (0.94 to 1.68)	0.111
7	3.5	0.83 (0.63 to 1.09)	0.193	0.82 (0.61 to 1.08)	0.173
8	3.2	0.71 (0.54 to 0.93)	0.017*	0.75 (0.56 to 1.00)	0.058
9	2.5	1.09 (0.83 to 1.43)	0.511	1.11 (0.84 to 1.47)	0.441
10	2.4	0.59 (0.44 to 0.80)	<0.001*	0.60 (0.44 to 0.81)	0.001*
11	2.1	0.85 (0.65 to 1.13)	0.281	0.79 (0.59 to 1.05)	0.106
12	1.8	1.21 (0.92 to 1.59)	0.170	1.19 (0.90 to 1.57)	0.216
13	1.5	1.05 (0.80 to 1.35)	0.696	1.00 (0.76 to 1.33)	0.948
14	1.3	1.08 (0.82 to 1.42)	0.566	1.00 (0.75 to 1.33)	0.975
15	1.2	0.88 (0.67 to 1.15)	0.374	0.84 (0.63 to 1.11)	0.232
16	1.1	0.97 (0.74 to 1.27)	0.833	1.03 (0.78 to 1.37)	0.799

* Significant at $p<0.05$

† Adjusted for age, duration of symptoms (months) and BMI

Table 3. Associations between radiographic severity and modes of variation from dorso-plantar view radiographs.

Mode	Variance explained (%)	Odds ratio (95% CI)	*p*-value	Adjusted odds ratio (95% CI)†	*p*-value
1	27.2	0.93 (0.71 to 1.22)	0.628	0.96 (0.72 to 1.27)	0.790
2	13.7	1.71 (1.26 to 2.30)	<0.001*	1.58 (1.17 to 2.14)	0.003*
3	10.7	0.68 (0.51 to 0.90)	0.007*	0.66 (0.49 to 0.88)	0.006*
4	5.7	1.09 (0.83 to 1.44)	0.496	1.08 (0.82 to 1.43)	0.578
5	4.9	1.01 (0.77 to 1.32)	0.951	0.88 (0.66 to 1.17)	0.382
6	3.7	1.24 (0.94 to 1.63)	0.129	1.12 (0.84 to 1.50)	0.413
7	3.0	1.09 (0.83 to 1.43)	0.528	1.01 (0.77 to 1.34)	0.901
8	2.7	1.32 (1.01 to 1.74)	0.045*	1.33 (1.01 to 1.77)	0.043*
9	2.2	1.42 (1.07 to 1.89)	0.014*	1.47 (1.10 to 1.98)	0.009*
10	1.9	1.15 (0.88 to 1.52)	0.297	1.12 (0.84 to 1.49)	0.416
11	1.6	1.75 (1.29 to 2.37)	<0.001*	1.77 (0.77 to 2.42)	<0.001*
12	1.5	0.93 (0.89 to 1.41)	0.610	1.04 (0.78 to 1.37)	0.802
13	1.3	0.91 (0.69 to 1.19)	0.138	0.94 (0.71 to 1.24)	0.451
14	1.2	0.71 (0.54 to 0.95)	0.021*	0.70 (0.52 to 1.06)	0.019*
15	1.1	1.38 (1.04 to 1.82)	0.022*	1.32 (0.99 to 1.76)	0.084

* Significant at $p<0.05$

† Adjusted for age, duration of symptoms (months) and BMI