

The symptomatic course of foot osteoarthritis phenotypes: an 18-month prospective analysis of community-dwelling older adults.

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Objective: Osteoarthritis (OA) is a heterogeneous disease with symptom progression at the foot unclear. This study investigated the symptomatic course of three pre-defined foot OA phenotypes over an 18-month period.

Methods: The Clinical Assessment Study of the Foot (CASF) is a community-based cohort of adults aged ≥ 50 years in North Staffordshire, UK. Participants who reported foot pain in a postal health survey and underwent radiographic assessment were mailed an 18-month follow-up survey. Changes in descriptive and symptomatic outcomes over 18 months were compared across the three phenotypes to determine within-phenotype changes and between-phenotype differences.

Results: Of 533 participants at baseline, 478 (89.7%) responded at 18 months. All three phenotypes showed small within-phenotype improvements in mean foot pain severity (scale from 0=no pain to 10=worst pain): no or minimal foot OA (18-month

4.0; mean change -1.15 [95% CI -1.46,-0.83]), isolated first metatarsophalangeal joint (MTPJ) OA (18-month 4.1; mean change -0.60 [95% CI -1.11,-0.10]) and polyarticular foot OA (18-month 5.1; mean change -0.77 [95% CI -1.42,-0.12]). The isolated first MTPJ OA phenotype had an increased likelihood of hallux valgus in the left foot (adjusted odds ratio 2.96 [95% CI 1.23,7.12]) compared to the no or minimal foot OA phenotype.

Conclusion: Three foot OA phenotypes showed few descriptive or symptomatic changes over 18 months. Future clinical trials should consider that people recruited with mild-to-moderate symptomatic foot OA appear likely to remain relatively stable with usual care. Longer-term follow-up using additional time-points is required to describe further the natural history of foot OA.

Significance and Innovations

- This is the first investigation of symptomatic change over time in patients with radiographically defined foot OA.
- Despite varying degrees of radiographic severity across phenotypes, few symptomatic changes over 18 months were observed within or between phenotypes.
- Future clinical trials should consider that people recruited with mild-to-moderate symptomatic foot OA appear likely to remain relatively stable with usual care over 18 months.

Introduction

Osteoarthritis (OA) is a multifactorial synovial joint disease, characterised by emerging clinical and structural sub-phenotypes, that once fully explained may facilitate more targeted treatment approaches [1]. Most recently, epidemiological observations of OA have extended to the foot, with symptomatic radiographic foot OA estimated to affect one in six adults aged 50 years and over [2]. Despite recent evidence supporting the contribution of OA to foot pain, distinct progressive and non-progressive symptomatic courses observed at the knee [3], hip [4] and hand [5] have yet to be investigated at the foot. Although only one prospective study has examined the progression of radiographic foot OA [6], the progression of symptoms among individuals with symptomatic radiographic foot OA remains unclear.

Using latent class analysis, we have recently identified three distinct foot OA phenotypes based on the radiographic scoring of five foot joints (first metatarsophalangeal joint (MTPJ), first and second cuneometatarsal joint, navicular first cuneiform joint and talonavicular joint) [7]. These include an isolated first MTPJ OA phenotype and a polyarticular foot OA phenotype; both found to be distinct from a phenotype with no or minimal foot OA [7]. Cross-sectionally, the polyarticular foot OA phenotype demonstrated more pain and functional limitation than the other two phenotypes, as well as stronger associations with female gender, higher body mass index (BMI) and nodal hand OA [7]. The present analyses extend our investigations of these distinctive foot OA phenotypes to describe their natural history over time.

Specifically, the aim of this study was to investigate the symptomatic course of these pre-defined foot OA phenotypes over an 18-month period. Eighteen months is sufficient to detect a clinically meaningful change in OA if present [1]. We hypothesised that symptoms would be relatively stable over 18 months, but that the

polyarticular foot OA phenotype would demonstrate a trend for worsening of symptoms.

Methods

Design and study population

Data were used from the Clinical Assessment Study of the Foot (CASF), which is a community-based cohort of adults aged 50 years and older, registered with one of four general practices in North Staffordshire, UK. A full protocol has been reported previously [8]. Briefly, participants who reported foot pain in the previous 12 months in a baseline postal health survey were invited to attend a research clinic where they underwent weight-bearing anterior-posterior and lateral radiographs of both feet.

Participants with no foot x-rays or an inflammatory arthropathy (non-specific inflammatory arthritis, rheumatoid arthritis or psoriatic arthritis), as identified from medical records or clinical radiology reports, were excluded from the analyses. A follow-up survey was mailed to participants 18 months after clinic attendance.

Participants who did not respond to the 18-month follow-up survey after two weeks were sent a reminder postcard. Participants who did not respond after four weeks from initial mailing were sent a repeat survey. Non-responders to the repeat survey were further invited to complete a shortened minimal data collection (MDC) questionnaire designed to capture key outcome data. MDC was completed by telephone, or if unavailable, by mail [8]. Ethical approval was obtained from Coventry Research Ethics Committee (REC reference number: 10/H1210/5) and all participants provided written informed consent. For this analysis, we retained participants in their previously assigned baseline foot OA phenotypes based on their

radiographic characteristics: no or minimal foot OA, isolated first MTPJ OA and polyarticular foot OA [7].

Descriptive and symptomatic outcomes

Data collected from baseline only included age, gender and BMI (calculated from height and weight measured at the baseline research clinic) [8]. Data collected from both the baseline health survey and 18-month follow-up survey included: foot pain severity in the previous month using a 0-10 Numerical Rating Scale (NRS), anchored at 0= no pain and 10= pain as bad as could be; Rasch-transformed Manchester Foot Pain and Disability Index (MFPDI), which derived an interval-level scale from the original three-part ordinal MFPDI responses [9, 10]; Short Form-12 (SF-12) physical and mental component summary scores (PCS and MCS, respectively) [11]; Hospital Anxiety and Depression Scale (HADS) [12]; frequent foot pain in the previous month; dissatisfaction with foot symptoms persisting; presence of hip and/ or knee pain in the previous year; and hallux valgus. Frequent foot pain was categorised as participants reporting pain or aching or stiffness in their feet on “most days” or “all days” in the previous month. Dissatisfaction with foot symptoms persisting was categorised as participants being “very dissatisfied” or “somewhat dissatisfied” with spending the rest of their lives with their current foot symptoms. Hallux valgus was categorised as unilateral or bilateral using a validated self-report line-drawing instrument [13]. Participants chose one of five line-drawings which best depicted the appearance of each foot. Each line-drawing sequentially increased the hallux valgus angle by 15° ; with the three more severe illustrations categorised as hallux valgus [13].

Additional data collected at 18-month follow-up only included: perceived global change in foot pain over 18 months since baseline clinic attendance, which was categorised as “improved”, “unchanged”, and “deteriorated”; foot injury and foot operation in the previous 18 months; and use of services or treatments because of foot pain in the previous 18 months. Services or treatments included at least one of the following: physiotherapy, hospital specialist, podiatrist, chiropodist, acupuncture, osteopath or chiropractor, drugs on prescription, foot operation, foot injection, or general practitioner (family doctor).

Symptomatic outcomes contained in both the full survey and MDC included: perceived global change in foot pain, MFPDI pain and function scores, and frequent foot pain in the previous month.

Statistical analysis

Descriptive and symptomatic outcomes were analysed with baseline and 18-month data to investigate within-phenotype changes and between-phenotype differences.

Statistical significance was determined as $p < 0.05$. Changes over time within-phenotypes were examined using McNemar’s test for dichotomous variables and paired t-test for continuous variables. Between-phenotypes differences were examined using binary logistic regression for dichotomous outcomes and linear regression for continuous outcomes. The no or minimal foot OA phenotype was used as the reference category for the regression analyses. Estimates were adjusted for baseline scores and the following potential confounders due to observed between-phenotype differences seen at baseline: age, gender and BMI [7]. Using data at 18 months only, differences between the three phenotypes at 18 months were

examined using a Chi-squared test. All analyses were conducted using SPSS Version 21 (IBM Corporation, Armonk, NY, USA).

Results

Study population

Of the 533 participants at baseline, after exclusions for no foot x-rays (n=3) and inflammatory arthritis (n=24), 478 returned the 18-month follow-up survey (89.7% response), of which 307 (64.2%) had no or minimal foot OA, 101 (21.1%) isolated first MTPJ OA and 70 (14.6%) polyarticular foot OA. Participants who returned the follow-up survey were generally similar to those lost to follow-up. However, those lost to follow-up were more likely to have dissatisfaction with foot symptoms persisting, hip pain and knee pain (Supplementary Table 1). Reasons for loss to follow-up are outlined in Supplementary Figure 1.

Within-phenotype changes

Overall, all three phenotypes showed small mean and percentage changes between baseline and 18 months (Table 1). Small but statistically significant improvements were observed for mean foot pain severity within all three phenotypes: no or minimal foot OA (18-month 4.0; mean change -1.15 [95% confidence interval (CI) -1.46, -0.83]), isolated first MTPJ OA (18-month 4.1; mean change -0.60 [95% CI -1.11, -0.10]) and polyarticular foot OA (18-month 5.1; mean change -0.77 [95% CI -1.42, -0.12]). Additionally, individuals with no or minimal foot OA showed a statistically significant improvement in mean Rasch-transformed MFPDI pain score (18-month -

0.6; mean change -0.29 [95% CI -0.46, -0.12]), mean SF-12 PCS score (18-month 40.9; mean change +1.71 [95% CI 0.66, 2.75]), mean HADS anxiety score (18-month 6.5; mean change -0.58 [95% CI -0.96, -0.20]) and the proportion of participants reporting frequent foot pain in the previous month (18-month 39.1%; change -10.7%). However, a greater proportion of participants in the no or minimal foot OA phenotype reported hip pain at 18 months than at baseline (18-month 58.8%; change +5.9%). Individuals in the isolated first MTPJ OA phenotype reported dissatisfaction with foot symptoms persisting less frequently (18-month 30.5%; change -12.7%). The polyarticular foot OA phenotype showed statistically significant improvement in the mean HADS anxiety scores (18-month 6.5; mean change -0.72 [95% CI -1.37, -0.08]).

Between-phenotype differences

Following adjustment for baseline scores, age, gender and BMI, generally small between-phenotype differences were seen over 18 months between the isolated first MTPJ OA and polyarticular foot OA phenotypes in relation to the reference category of the no or minimal foot OA phenotype (Table 2). The isolated first MTPJ OA phenotype was significantly more likely than the no or minimal foot OA phenotype to report unilateral hallux valgus in the left foot at 18 months (adjusted odds ratio 2.96; 95% CI 1.23, 7.12).

There were no statistically significant differences in perceived global change in foot pain or foot injuries incurred over 18 months between the foot OA phenotypes (Table 3). However, a higher proportion (40.6%) of individuals in the polyarticular foot OA phenotype perceived that their foot pain had deteriorated compared to the first MTPJ

OA (27.0%) and no or minimal foot OA (27.9%) phenotypes. Approximately half the participants in each phenotype reported using a service or treatment for foot pain in the preceding 18 months. The proportion of participants reporting a foot operation during this period was very low ($\leq 4.0\%$) for each phenotype.

Discussion

This study investigated the symptomatic course of three foot OA phenotypes over an 18-month period. The main finding from this study was a general trend for slight improvements of health outcomes across all three foot OA phenotypes; with small but statistically significant reductions in foot pain severity in particular. Few between-phenotype differences occurred over the 18-month period.

In absolute terms, the reduction in pain severity across the three phenotypes was small (range 0.60– 1.15 NRS points), with all observed values under the accepted two-point reduction threshold applied to denote a clinically important difference in musculoskeletal pain [14]. Therefore, whilst observed changes in pain severity were statistically significant, they are unlikely to represent a clinically meaningful change for the participants. Furthermore, it is impossible to know with certainty whether and how improvements in foot pain severity correspond to sites of radiographic OA.

Potential explanations for the observed reduction in pain may include increased awareness and prioritisation of foot pain after enrolment into the CASF study and regression to the mean. However, those with polyarticular foot OA had a higher proportion of participants that indicated deterioration in their global foot pain over 18 months compared to the other phenotypes, albeit not significantly.

A trend of pain improvement at the first follow-up measurement is consistent with improvements in knee pain trajectories observed in adults with knee OA [3].

Following initial improvement from baseline, Collins et al. found that all knee pain trajectories remained relatively stable over the remaining five-year follow-up [3]. With only one follow-up time point in this study, it is uncertain whether the small changes in foot pain observed over 18 months are representative of the long-term clinical course of foot OA. Furthermore, pain trajectories are not always stable and may fluctuate over time, as previously observed for hip OA [4]. Our findings suggest mild-to-moderate symptomatic foot OA progression is unlikely to be rapid over 18 months and management can be monitored in primary care without the need for routine referral to secondary care. Future research directed at identifying individuals most likely to have unfavourable prognosis, who would benefit from timely onward referral, would appear important.

Between-phenotype comparisons identified little difference between the foot OA phenotypes in relation to their descriptive and symptomatic characteristics. Following adjustment for potential confounders, there was only one statistically significant between-phenotype difference: an increased likelihood of unilateral hallux valgus in the left foot for the isolated first MTPJ OA phenotype compared to the no or minimal foot OA phenotype. Comparison of actual numbers revealed that overall there were six new cases of unilateral hallux valgus in the left foot for the isolated first MTPJ OA phenotype, and seven fewer cases for the no or minimal foot OA phenotype. Whilst the identification of new cases over an 18-month period is a possibility, the progressive nature of hallux valgus makes an observed reduction in severity appear implausible. The number of reported foot operations and new bilateral hallux valgus cases, suggesting progression from unilateral to bilateral hallux valgus, at 18 months

were insufficient to account for this observation. Misclassification of self-reported hallux valgus may therefore account for some of the reported changes over 18 months, particularly when participants reported borderline hallux valgus. Despite the hallux valgus line drawing instrument previously demonstrating good reliability over a 6-month period, [13] we did not assess reliability again at 18 months and it is plausible that this was lower than that previously reported. Indeed, the wide 95% CI for the odds ratio of the unilateral hallux valgus in the left foot reflects an imprecise estimate. Therefore, although these findings may indicate that the first MTPJ OA phenotype is a risk factor for development of unilateral hallux valgus in the left foot, the finding is possibly spurious and should be interpreted with caution.

The data from this study were derived from CASF, which has a source population broadly representative of the British population, despite having a lower proportion of ethnic minorities [8]. By identifying participants from CASF with foot pain over the previous year, this study provides a sample broadly representative of the British population with foot pain. Additionally, there was a high retention of participants at 18 months (89.7%). However, some limitations need to be considered. Firstly, participants were likely to have foot pain across multiple foot areas. Foot pain can lead to compensatory changes in gait and foot function, thus increasing the risk of pain at other foot areas [15]. Therefore, whether changes in reported foot pain severity related to the same pain sites from baseline to follow-up is uncertain. Secondly, participants lost to follow-up had a trend for being more dissatisfied with foot symptoms persisting, whilst also having more hip and knee pain (Supplementary Table 1). This suggests that participants lost to follow-up had more widespread joint pain. Although this is unlikely to have influenced the relative differences between the phenotypes, it may have resulted in an underestimation of absolute symptom

severity. Thirdly, participants were allocated to foot OA phenotypes at baseline; therefore, whether participants transitioned between phenotypes over time is uncertain.

In conclusion, this is the first study to investigate symptomatic changes in patients with radiographic foot OA over time. Although findings suggest a general statistical trend for slight symptomatic improvement, this is unlikely to be clinically meaningful. Few between-phenotype differences were observed and a statistically significant finding of more prevalent unilateral hallux valgus in the isolated first MTPJ OA phenotype may be an artefact of misclassification. Future clinical trials should consider that people recruited with mild-to-moderate symptomatic foot OA appear likely to remain relatively stable with usual care. Additional follow-up over a longer time period is needed to understand further the natural history of foot OA and whether the course of foot symptoms differs between different phenotypes.

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List of Tables

Table 1 Changes in selected outcomes from baseline to 18 months for the three foot osteoarthritis phenotypes.

	No or minimal foot OA phenotype		Isolated first MTPJ OA phenotype		Polyarticular foot OA phenotype	
	18-month score: mean (SD)	Mean change (95% CI)	18-month score: mean (SD)	Mean change (95% CI)	18-month score: mean (SD)	Mean change (95% CI)
Foot pain severity rating (0-10 Numeric Rating Scale) in the previous month ^a	4.0 (2.8)	-1.15 (-1.46, -0.83)	4.1 (2.8)	-0.60 (-1.11, -0.10)	5.1 (2.5)	-0.77 (-1.42, -0.12)
Rasch-transformed MFPDI pain score	-0.6 (1.7)	-0.29 (-0.46, -0.12)	-0.8 (1.6)	-0.22 (-0.51, 0.07)	0.1 (1.4)	-0.12 (-0.40, 0.16)
Rasch-transformed MFPDI function score	-0.9 (2.1)	-0.03 (-0.20, 0.14)	-1.0 (2.1)	+0.01 (-0.30, 0.31)	0.2 (2.1)	+0.07 (-0.27, 0.41)
SF-12 PCS score	40.9 (12.2)	+1.71 (0.66, 2.75)	40.8 (11.1)	-0.34 (-2.29, 1.61)	37.6 (11.8)	+1.12 (-0.98, 3.22)
SF-12 MCS score	49.5 (10.7)	+0.03 (-1.13, 1.19)	50.2 (10.6)	-1.04 (-2.98, 0.90)	47.9 (11.9)	-0.96 (-3.72, 1.79)
HADS anxiety score	6.5 (4.3)	-0.58 (-0.96, -0.20)	5.9 (4.2)	-0.55 (-1.23, 0.13)	6.5 (3.8)	-0.72 (-1.37, -0.08)
HADS depression score	5.1 (3.8)	-0.26 (-0.55, 0.35)	4.6 (3.6)	-0.13 (-0.67, 0.41)	6.1 (3.8)	-0.15 (-0.72, 0.41)
	18-month score: n (%)	Change: % (P-value)	18-month score: n (%)	Change: % (P-value)	18-month score: n (%)	Change: % (P-value)
Frequent foot pain in the previous month ^b	116 (39.1)	-10.7 (<0.01)	38 (38.0)	-10.0 (0.1)	38 (55.9)	-13.2 (0.12)
Dissatisfaction with foot symptoms persisting ^c	122 (40.9)	-6.1 (0.08)	29 (30.5)	-12.7 (0.04)	32 (48.5)	-13.6 (0.12)
Bilateral hallux valgus ^d	49 (17.0)	+0.7 (0.87)	27 (27.8)	0.0 (1.00)	22 (32.8)	-6.0 (0.45)
Unilateral hallux valgus ^d – left foot	21 (7.3)	-2.4 (0.27)	12 (12.4)	+6.2 (0.07)	8 (11.9)	+1.5 (1.00)
Unilateral hallux valgus ^d – right foot	39 (13.5)	+0.7 (0.87)	9 (9.3)	-1.0 (1.00)	7 (10.4)	+2.9 (0.75)
Hip pain in the previous year	171 (58.8)	+5.9 (0.04)	60 (61.2)	+7.1 (0.19)	45 (68.2)	0.0 (1.00)
Knee pain in the previous year	218 (74.7)	+2.4 (0.38)	77 (78.6)	+5.1 (0.41)	55 (83.3)	-6.1 (0.29)

CI= confidence interval; HADS= Hospital Anxiety and Depression Scale (higher HADS score indicate worse psychiatric ratings); MCS= mental component summary; MFPDI= Manchester Foot Pain and Disability Index (higher MFPDI scores indicate higher pain/ function); MTPJ= metatarsophalangeal joint; OA= osteoarthritis; PCS= physical component summary; SD= standard deviation; SF-12= 12-Item Short-Form Health Survey (higher SF-12 PCS and MCS scores indicated better health); ^a= The numeric rating scale included verbal anchors of “no pain” at 0 and “pain as bad as could be” at 10; ^b= defined as frequent pain, aching or stiffness on all or most days in the previous month; ^c= defined as participants being very or somewhat dissatisfied with the foot symptoms persisting for the rest of their lives; ^d= Hallux valgus was defined according to Roddy et al.’s [13] self-report instrument and dichotomised definition. Results with Bold text indicate that the result is statistically significant (p <0.05).

Table 2 Between-phenotype differences for the isolated first metatarsophalangeal joint osteoarthritis and polyarticular foot osteoarthritis phenotype at 18 months using the no or minimal foot osteoarthritis phenotype as the reference category.

	Isolated first MTPJ OA		Polyarticular foot OA	
	Adjusted ^e β	(95% CI)	Adjusted ^e β	(95% CI)
Foot pain severity rating (0-10 Numeric rating scale) in the previous month ^a	0.29	(-0.27, 0.85)	0.46	(-0.21, 1.13)
Rasch-transformed MFPDI pain score	0.02	(-0.28, 0.33)	0.37	(<-0.01, 0.74)
Rasch-transformed MFPDI function score	0.00	(-0.31, 0.31)	0.27	(-0.11, 0.65)
SF-12 PCS score	-1.04	(-2.96, 0.88)	0.69	(-3.11, 1.73)
SF-12 MCS score	-0.49	(-2.57, 1.59)	-0.69	(-3.32, 1.94)
HADS anxiety score	-0.08	(-0.76, 0.60)	-0.16	(-0.96, 0.65)
HADS depression score	-0.06	(-0.60, 0.49)	0.20	(-0.46, 0.86)
	Adjusted ^e OR	(95% CI)	Adjusted ^e OR	(95% CI)
Frequent foot pain in the previous month ^b	0.94	(0.57, 1.56)	1.43	(0.79, 2.59)
Dissatisfaction with foot symptoms ^c	0.64	(0.38, 1.09)	1.00	(0.55, 1.82)
Bilateral hallux valgus ^d	1.45	(0.75, 2.81)	1.26	(0.58, 2.72)
Unilateral hallux valgus ^d – left foot	2.96	(1.23, 7.12)	2.18	(0.76, 6.30)
Unilateral hallux valgus ^d – right foot	0.67	(0.30, 1.52)	0.77	(0.31, 1.95)
Hip pain in the previous year	0.84	(0.48, 1.49)	0.94	(0.46, 1.93)
Knee pain in the previous year	0.82	(0.43, 1.60)	1.55	(0.67, 3.59)

β = regression coefficient; CI= confidence interval; HADS= Hospital Anxiety and Depression Scale (higher HADS score indicate worse psychiatric ratings); MCS= mental component summary; MFPDI= Manchester Foot Pain and Disability Index (higher MFPDI scores indicate higher pain/ function); MTPJ= metatarsophalangeal joint; OA= osteoarthritis; OR= odds ratio; PCS= physical component summary; SD= standard deviation; SF-12= 12-Item Short-Form Health Survey (higher SF-12 PCS and MCS scores indicated better health); ^a= The numeric rating scale included verbal anchors of “no pain” at 0 and “pain as bad as could be” at 10; ^b= defined as frequent pain, aching or stiffness on all or most days in the previous month; ^c= defined as participants being very or somewhat dissatisfied with the foot symptoms persisting for the rest of their lives; ^d= Hallux valgus was defined according to Roddy et al.’s [13] self-report instrument and dichotomised definition; ^e= includes adjustment for baseline scores, age, gender, and body mass index. Results with Bold text indicate that the result is statistically significant ($p < 0.05$).

		No or minimal foot OA	Isolated first MTPJ OA	Polyarticular foot OA	P-value
Perceived global change in foot pain in previous 18 months: n (%)	Improved	95 (31.6)	26 (26.0)	13 (18.8)	0.108
	Unchanged	122 (40.5)	47 (47.0)	28 (40.6)	
	Deteriorated	84 (27.9)	27 (27.0)	28 (40.6)	
Foot injury in previous 18 months: n (%)		18 (6.2)	8 (8.1)	7 (10.8)	0.404
Use of services or treatment for foot pain in previous 18 months ^a : n (%)		146 (48.5)	45 (45.5)	37 (54.4)	0.519
Foot operation in previous 18 months: n (%)		1 (0.3)	4 (4.0)	2 (2.9)	^b

Table 3 Descriptive and symptomatic outcomes analysed using only 18-month data.

MTPJ= metatarsophalangeal joint; OA= osteoarthritis; ^a Services or treatment for foot pain included at least one of the following: physiotherapy, hospital specialist, podiatrist, chiropodist, acupuncture, osteopath or chiropractor, drugs on prescription, foot operation, foot injection, or general practitioner (family doctor); ^b Not calculated as expected cell counts below five for all three phenotypes.