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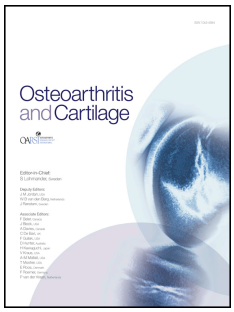

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Title page

‘ACUTE FLARE-UPS’ IN PATIENTS WITH, OR AT HIGH RISK OF, KNEE OSTEOARTHRITIS: A DAILY DIARY STUDY WITH CASE-CROSSOVER ANALYSIS

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ABSTRACT

Objective: To determine the natural history of flare-ups in knee osteoarthritis and their relation to physical exposures.

Design: Adults aged ≥45 years with a recent primary care consultation for knee OA/arthralgia completed a daily pen-and-paper diary for up to 3 months, including questions on average knee pain intensity, pain descriptors, other symptoms, activity interference, and selected physical exposures (prolonged kneeling, squatting, climbing stairs, ladders, and moving/lifting heavy objects). Informed by a systematic review, flare-ups were defined a priori. We calculated the rate of flare-ups in the sample, described their nature and duration, and estimated their association with physical exposures in the prior 48 hours.

Results: 67 participants completed at least one month of diaries,37 (55%) were female, mean age 62 years (SD 10.6) with a mean body mass index of 24.6 kg/m^2 (SD 5.1). 30 participants experienced a total of 54 flare-ups (incidence density 1.09 flare-ups/person-days). The median duration of flare-ups was 8 days (range: 2-30). During a flare-up participants were more likely to report sharp, throbbing, stabbing, burning pain, swelling, limping, stiffness, being woken by pain, taking more analgesia, and stopping usual activities. Exposure to one or more physical exposure increased the risk of a flare-up in the subsequent 48 hours (odds ratio 2.19 (95%CI: 1.22, 4.05)).

Conclusions: Our study with intensive longitudinal data collection suggests acute flare-ups may be experienced by a substantial number of patients. These episodes often last a week

43 or longer, are disruptive, prompt changes in self-management, and may be triggered by
44 high-loading physical activities.

45

46 **Keywords:** Knee, osteoarthritis, flare-up

47

48 **Running headline:** Natural history of flare-ups in knee OA

49

INTRODUCTION

Longitudinal studies following patients with symptomatic knee osteoarthritis over several years suggest that non-progressive symptom trajectories are relatively common[1]. However, within these average long-term trajectories, it is well-recognised that patients can experience substantial variability in the presence, nature, and severity of symptoms over time, including episodes of increased pain that may be experienced as acute events[2, 3]. These events, particularly when they have an unpredictable, sudden onset, can be distressing for patients and can impact on quality of life, normal activities (including productivity losses[4]) and health service use. Yet unlike other long-term conditions, there is still considerable uncertainty around the nature, definitions, and terminology of these phenomena in osteoarthritis. Classification criteria for flare-ups in knee OA have been proposed but have not been widely adopted[5]. Achieving greater clarity and agreement on these matters is an important goal for research and clinical communities[6], toward which observational research can contribute by gaining insight into the natural history of these phenomena, possible triggers[7], and other proximal and more distal determinants.

We sought to describe the natural history of 'flare-ups' in knee OA in a sample of community-dwelling symptomatic adults, using an observational daily diary study. We chose the term 'flare-up' over terms such as 'exacerbation' following workshops with patients and members of the public on their preferred terminology and from more frequently used terminology in the medical literature as found in a recent systematic review[6]

METHOD

Study design and sample

Adults aged 45 years and over registered at one of two General Practices in the West Midlands, England and with a recorded consultation for knee osteoarthritis or knee pain/arthralgia in the previous 2 years were mailed a short questionnaire containing items used to describe the sample, judge eligibility for the daily diary study, and provide baseline values of 'what is normal for me' with respect to knee symptoms, activity, and analgesia (adapted from Trappenburg et al[8]). A standard three-stage mailing procedure was used with non-respondents sent a reminder postcard at two weeks and repeat questionnaire at four weeks. Respondents were eligible for inclusion in the daily diary study if they reported knee symptoms on at least one day in the previous 12 months, provided written informed consent to further contact and indicated their willingness to complete daily diaries for up to three months. Respondents were excluded if they self-reported a diagnosis of inflammatory disease, previous bilateral total knee replacement (TKR) or TKR in the index knee (the worst affected knee) or did not complete baseline knee symptom questions.

Data collection

All eligible, consenting questionnaire respondents were invited to complete three consecutive one-month pen-and-paper diaries. The diaries contained nine items for each day (see Supplementary Data 1) which participants were asked to fill out at the end of the day. Average pain intensity in the previous 24 hours was assessed using a 0-10 numerical rating scale (NRS)[9]. We included four single items on other symptoms shown by Marty et al[5] to be associated with OA flare-ups: stiffness lasting >20 minutes, swelling, night pain and

limping. Participants were also asked about pain quality using a short list of descriptors which included continuous pain descriptors (dull, aching, throbbing), intermittent pain descriptors (sharp, stabbing), and neuropathic-type pain descriptors (burning, numbness, pins and needles)[3, 10]. Participants were asked if they had undertaken any of a selected list of physical activities which have previously been linked to onset of knee OA[11]. Participants were also asked about any changes in usual medication (more than normal, less than normal, the same) and whether symptoms had stopped them taking part in usual activities.

The study was approved by the North of Scotland Research Ethics Committee (Reference: 13/NS/0049).

Statistical analysis

Scatterplots were used to visually inspect daily pain intensity scores for each participant. To estimate within-person variability we calculated a Variability Index[12] for each participant based on the average standard deviation of their daily pain intensity scores within half-monthly periods. The periods ranged from 14-16 days due to the varying length of the month over the three month study period. The standard deviation was chosen as it is the most common measure of variability which averages the absolute deviation of each day's pain intensity from the mean pain over the 14-16 days period thus capturing any pain fluctuations. This method has also been used in a previous study investigating pain variability of patients with fibromyalgia[12]. The 14-16 day period was chosen based on the number of available data points and to allow for reliable estimation of SD due to the distribution assumptions. The possible values were positive, with zero indicating no

variability and a higher number indicating greater variability. Informed by a systematic review of flare-up definitions in the medical literature[6], and considering flare-up definitions used in other conditions[13] we defined a flare-up a priori as: an increase of at least two points from baseline ('normal for me') in average pain intensity in the past 24 hours (0-10 NRS) which was sustained for at least two consecutive days. A flare-up was judged to be resolved when pain intensity returned to baseline level for five consecutive days.

We then estimated the proportion of respondents experiencing at least one flare-up during the period of observation, the incidence density with 95%CI of flare-ups for the sample as a whole (expressed as the number of flare-ups per 100 person-days at risk, i.e. denominator excluded days in flare-up and the five days needed for it to be judged 'resolved') using Poisson regression taking into account recurrent events, and the duration of flare-ups (median, interquartile range (IQR)).

The time course of an 'average' flare-up was illustrated by plotting combined group-mean daily pain intensity NRS scores across all first flare-ups, anchored to a common timescale with zero representing the first day of flare-up and extending to 7 days prior and 30 days after the flare-up. To describe the nature of flare-ups and their impact on individuals, descriptive statistics (means, SD or proportions) were used to summarise symptoms, change in medication and whether pain had stopped usual activities across all flare-up days and all non-flare-up days, among participants experiencing at least one flare-up. We then used mixed-effect models to estimate the relative frequency (expressed as odds ratios) and severity (expressed as regression coefficients) of symptoms on flare-up versus non-flare-up days accounting for the clustered nature of the observations.

To determine whether exposure to selected physical activities was associated with flare-up onset, we conducted a case-crossover analysis with each individual acting as their own control[14]. Case windows for exposures were defined as the 48 hours prior to the first day of a flare-up. For each case we selected up to four matched ambidirectional control windows which were 48-hour periods on at-risk days which corresponded with the same days of the week as the case window to remove confounding by variation in physical exposures across days of the week (e.g. weekdays versus weekends). We calculated unadjusted exposure odds ratios (OR) based on the conditional maximum likelihood estimate with 95% mid-P exact confidence intervals using OpenEpi (www.OpenEpi.com).

Analyses were performed using Stata, Version 13 (StataCorp 2013).

RESULTS

Of the 220 out of 330 responders to the baseline questionnaire, 106 (48%) were eligible and were invited to take part in the diary study, consented to further contact, and were mailed the first diary. Reasons for non-eligibility included; inflammatory disease (41), TKR (27), missing/blank Q (22), no recent knee pain (14), withdrew/died/moved (10). Of the 67 (63%) participants who completed at least one monthly diary, 37 (55%) were female, mean age 62 years (SD 10.6) with a mean body mass index of 24.6 kg/m^2 (SD 5.1). Of a possible 5491 diary days, 4328 (79%) were fully completed, 1163 (21%) were partially completed, and 111 (2%) were missed completely. Comparing responders to non-responders ages were similar

(mean age 62.2 (SD 10.6) and 61.7 (SD 11.0) respectively) and there were slightly more females amongst the non-responders (25 (64.1%) non-responders versus 37 (55.2%)).

The median Variability Index across the sample was 0.68 (IQR 0.41, 1.05), and this was higher during non-flare-up days in participants classed as having experienced a flare-up than in those participants who did not experience a flare-up ((median (IQR)): 0.83 (0.51, 1.13) vs 0.52 (0.27, 0.97).

Over the period of observation 30 participants (45%) were classed as having experienced a total of 54 flare-ups (one flare-up (n=16), two flare-ups (n=6), three flare-ups (n=6), four flare-ups (n=2)) giving an estimated incidence density of 1.12 (95%CI 0.80, 1.57) flare-ups per 100 person-days. Illustrative examples of participants with contrasting variability in daily pain scores are provided in Supplementary Data 2.

Those experiencing a flare-up were slightly more likely to be male (50% vs 40%; proportion difference (95% CI): 10% (-14%, 33%)), have a higher BMI (mean (SD) 25.5 (5) vs 23.9 (6) kg/m^2; mean difference (95% CI): 1.6(-0.9, 4.1)), and report previous injury (50% vs 42%; proportion difference (95% CI): 8% (-15%, 33%)), although none of these differences were statistically significant given the relatively small numbers of participants in each group.

The median duration for a flare-up was 8 days (IQR 3, 23; range 2-30). The 'average' time course shows the sudden onset and relatively quick reduction in pain intensity within 48 hours followed by a longish plateau (Figure 1). Flare-up days compared to non-flare-up days were accompanied by a higher occurrence of knee stiffness (OR 10.9; 95% CI: 7.0,

144 17.1), limping (12.4; 7.4, 20.8), swelling (14.5; 8.3, 25.4), being woken by pain (7.0; 4.3,
145 11.2), use of most pain descriptors (but particularly 'throbbing', 'sharp', 'stabbing' pain, and
146 'numbness'), interference with usual activities (26.5; 3.7, 51.5) and taking more medication
147 than normal (23.9; 13.8, 41.4) (Table 1). The above features tended to be at their highest
148 levels during the first two days of a flare-up (data not shown).
149
150 For the case-crossover analysis using physical exposures there were 88 cases periods
151 in total and 328 control periods. The number of control periods per case ranged from 1-4
152 (median:2, mean: 2.43 (SD1.12)). Exposure to one or more of the selected physical
153 exposures (prolonged kneeling, lifting/moving heavy objects, climbing several flights of
154 stairs, prolonged squatting, climbing ladders) was associated with increased risk of acute
155 flare-up in the subsequent 48 hours (odds ratio 2.19; 95%CI: 1.22, 4.05) (Supplementary
156 Data 3). Exposure to each individual physical activity was positively associated with flare-up
157 onset but estimates lacked precision due to small numbers of discordant pairs.
158
159 **DISCUSSION**
160 Our study supports the notion that knee OA, for some people, is characterised by
161 intermittent acute or sudden increases in pain with an associated change in pain quality and
162 knee symptoms.
163
164 Pain intensity in our study was highly variable for some and stable for others.
165 Although not explored in this study, Schneider et al found a link between pain variability in
166 OA and depression[15]. Qualitative studies have highlighted the highly variable nature of pain
167 in OA[2] and when unpredictable can be associated with considerable distress[3].

Predictability of pain is important for episode management and patient understanding. Prior to flare-up onset we saw a marked step up in symptoms rather than a gradual onset. This may be partly due to once daily measurement, however, we found that certain activities reported in the 48-hour period prior to a flare-up were associated with flare-up onset. Zobel et al identified that knee buckling and knee injury were triggers for acute events[7]. Physical activity exposures have previously been associated with long term incidence of osteoarthritis[11]. The link we have found may give an insight into short term events and their intrinsic part in how OA develops and progresses. It is possible that these acute events lead to a cumulative insult on the knee joint that eventually leads to disability.

Identifying potential triggers are important in the management of flare-ups in terms of activity avoidance and for earlier and preventative management strategies. Other management strategies that may lead to early termination of a flare-up include recognising the early changes in symptoms, for example knee stiffness, swelling, limping and night pain which have previously been used as part of the criteria for flare-up identification[5].
In response to flare-ups a third increased usual medication and a small number reported stopping usual activities. Our study did not capture lesser but still problematic interference with activities which may affect quality of life if sustained. We recognise that there may be potential time-varying confounders that could not be controlled in the study, for example, those causing psychosocial stress or a perceived improvement in symptoms, leading to a reduction in medication and increase in activity.

Limitations of the study include the potential for inaccurate recall of average pain scores over the 24-hour period and the extent to which participants may have retrospectively filled in diary entries. We also acknowledge the bias that may be introduced by missing data. Our case-crossover analysis was unable to explore individual physical exposures due to small numbers and the use of ambidirectional control windows assumes no strong effect of flare-ups on subsequent exposure levels.

In providing an operational definition of a flare-up we recognise the need for continued empirical work. Sensitivity analyses in larger datasets could usefully explore whether absolute or relative (to baseline) increases in pain are best for defining flare-ups as well as the minimum duration of these.

Conclusion

Our study with intensive longitudinal data collection suggests acute flare-ups may be experienced by a substantial number of patients. These episodes often last a week or longer, are disruptive, prompt changes in self-management, and may be triggered by high-loading physical activities.

Author Contributions

All authors were involved in conception and design of the study, analysis and interpretation of data, drafting the article, critical revision of the article for important intellectual content, final approval of the article. GP takes responsibility for the integrity of the work as a whole from inception to finished article.

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The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Competing interest

GP received consultancy fees from InFirst plc and Good Relations plc.

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279 **FIGURE LEGENDS**

280 **Figure 1.** Time course of an 'average' flare from 7 days prior to 30 days after the onset of a
281 flare (day 0). Points are group-mean pain intensity for all participants' first flares combined
282
283 **Table 1:** Table 1: Severity and occurrence of symptoms and impact experienced during flare
284 days versus at-risk days among participants experiencing one or more flare (n=30).

285
286 **Supplementary data 1:** Example diary page
287
288 **Supplementary data 2:** Illustrative examples of variability in daily knee pain intensity (0-
289 10NRS) and flares for two participants
290
291 **Supplementary data 3:** Crude ORs for physical activity exposures using discordant pairs

292

293 **Table 1: Severity and occurrence of symptoms and impact experienced during flare-up**
294 **days versus at-risk days among participants experiencing one or more flare-ups (n=30).**

	Flare-up days† *(n=299)*	Non-flare-up days‡ *(n=1958)*	Relative frequency/severity on flare-up days vs non-flare-up days*
Average knee pain intensity (0-10NRS): mean (SD)	5.4 (1.9)	3.1 (2.0)	2.5 (2.3, 2.6)
Pain descriptors			
Dull	52 (17)	673(35)	0.4 (0.2, 0.7)
Aching	218 (73)	1122 (59)	6.9 (4.1, 11.6)
Throbbing	95 (32)	301 (16)	18.1 (9.8, 33.3)
Sharp	146 (49)	206 (11)	11.2 (6.8, 18.6)
Stabbing	108 (36)	269 (14)	11.8 (7.2, 19.5)
Burning	73 (24)	171 (9)	6.7 (4.0, 11.1)
Numbness	72 (24)	15 (1)	6.7 (1.9, 23.1)
Pins and needles	1 (<1)	1 (<1)	-
Other	9 (3)	45 (2)	1.3 (0.6, 3.1)
Knee swelling	149 (50)	668 (35)	14.5 (8.3, 25.4)
Limping	191 (64)	804 (42)	12.4 (7.4, 20.8)
Knee stiffness lasting >20 mins	178 (60)	505 (26)	10.9 (7.0, 17.1)
Woken at night by knee pain	103 (35)	189 (10)	7.0 (4.3, 11.2)
Taking more medication than usual	94 (34)	181 (12)	23.9 (13.8, 41.4)
Pain stopped usual activities	44 (15)	76 (4)	26.5 (13.7, 51.5)

Figures are n (%) unless otherwise stated

† Days during a flare-up (i.e. from start of flare-up to first day when pain returned to 'normal' levels for 5 consecutive days; ‡ excludes flare-up days as well as the 5 consecutive days after last flare-up day

NRS Numerical rating scale; SD Standard deviation

*From mixed-effect model (logistic for binary and linear for continuous outcome). Results are expressed as odds ratios (95% CI) except average knee pain intensity which is expressed as a regression coefficient (i.e. mean difference) and 95% CI

295

296

297

Table 1: Severity and occurrence of symptoms and impact experienced during flare-up days versus at-risk days among participants experiencing one or more flare-ups (n=30).

	Flare-up days† *(n=299)*	Non-flare-up days‡ *(n=1958)*	Relative frequency/severity on flare-up days vs non-flare-up days*
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*From mixed-effect model (logistic for binary and linear for continuous outcome). Results are expressed as odds ratios (95% CI) except average knee pain intensity which is expressed as a regression coefficient (i.e. mean difference) and 95% CI

Figure 1: Time course of an 'average' flare-up from 7 days prior to 30 days after the onset of a flare (day 0). Points are group-mean pain intensity for all participants' first flare-ups combined