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Author/s:

Fu, K;Makovey, J;Metcalf, B;Bennell, K;Zhang, Y;Asher, R;Robbins, S;Deveza, L;Hunter, DJ

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Role of Hip Injury and Giving Way in Pain Exacerbation in Hip Osteoarthritis: An Internet-Based Case–Crossover Study

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1

2 DR. KAI FU (Orcid ID : 0000-0002-8721-0734)

3 PROF. DAVID J HUNTER (Orcid ID : 0000-0003-3197-752X)

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9 **The Role of Hip Injury and “Giving Way” in Pain Exacerbation in Hip Osteoarthritis: An Internet-**
10 **Based Case-Crossover Study**11 Kai Fu^{1,2} MBBS, MS, Joanna Makovey^{1,2} PhD, Ben Metcalf³ PhD, Kim Bennell³ PhD, Yuqing Zhang⁴
12 DSc, Rebecca Asher⁵ MS, Sarah Robbins^{1,2} PhD, Leticia Deveza^{1,2} MBBS, David J. Hunter^{1,2} MBBS,
13 PhD14 1. *Institute of Bone and Joint Research, Kolling Institute, University of Sydney, Sydney, NSW, Australia*15 2. *Rheumatology Department, Royal North Shore Hospital, Sydney NSW Australia.*16 3. *Centre for Health, Exercise and Sports Medicine, Department of Physiotherapy, University of Melbourne,*
17 *VIC, Australia*18 4. *Division of Rheumatology, Allergy, and Immunology, Massachusetts General Hospital, Harvard School*
19 *of Medicine, Boston, MA, United States*20 5. *NHMRC Clinical Trials Centre, University of Sydney, Sydney, NSW, Australia*

21

22 **Corresponding Author:**

23 Kai Fu, PhD Candidate

24 Institute of Bone and Joint Research, Kolling Institute, University of Sydney, Sydney, NSW, Australia

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1 Level 10, Kolling Building
2 Royal North Shore Hospital
3 St Leonards, 2065
4 Australia
5 Phone: 61 468476117
6 Fax: 61 2 9463 1077
7 Email: kafu7690@uni.sydney.edu.au

8
9

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21 **ABSTRACT**

22

23 **Objective:** To evaluate the association between hip injury/“giving way” and hip pain
24 exacerbations in persons with symptomatic hip OA.

25 **Methods:** We conducted an internet-based case-crossover study to assess hip injury and “giving
26 way” for hip pain exacerbation. Eligible participants with symptomatic hip OA were followed
27 for 90 days and asked to complete online questionnaires at baseline and 10-day intervals (control

1 periods). They also logged on to the study website to complete questionnaires for an episode of a
2 hip pain exacerbation (case periods) defined as an increase of two points in pain intensity
3 compared with baseline on a numeric rating scale (NRS: 0-10). The relationship of hip injury and
4 “giving way” to the risk of pain exacerbation was examined using conditional logistic regression.

5 **Results:** Of 252 patients recruited into the study, we included 133 (53%) subjects who provided
6 data from both case and control periods. Hip injury during the last seven days increased the risk
7 of hip pain exacerbation (odds ratio [OR] 2.74, 95% CI 1.62, 4.62). Hip “giving way” during the
8 last two days was associated with an increased risk of hip pain exacerbation (OR 2.10, 95% CI
9 1.30, 3.39), and showed a significant relationship between the number of hip “giving way”
10 events and risk of hip pain exacerbations ($p < 0.001$).

11 **Conclusion:** Hip injury and episodes of hip “giving way” were significantly related to pain
12 exacerbation in persons with symptomatic hip OA. Methods to prevent exposure to injury may
13 help to reduce the burden of pain in persons with hip OA.

1 **Significance and Innovations**

- 2 • Our findings are novel and extend from the use of novel internet-based methods, and we
3 used each case as his/her own control which is highly applicable to assess the effects of
4 transient exposures (hip injury or “giving way”) on pain exacerbations.
- 5 • This study used data provided by 133 hip OA patients showed a significant association
6 between hip injury/“giving way” and pain exacerbation in persons with symptomatic hip
7 OA.
- 8 • We found that hip injury and episodes of hip “giving way” were risk factors for pain
9 exacerbation in persons with symptomatic hip OA, which could provide some insight into
10 potential mechanisms of pain exacerbation.

11 **Introduction**

12 Osteoarthritis (OA) is the most common form of arthritis with the hip being the second most
13 affected large joint (1). The lifetime risk of developing hip OA can be up to 25% with the
14 incidence rate being 13 per 1000 person-years (2, 3). Hip OA is a major public health problem,
15 particularly as it often leads to costly total hip replacement surgery (4). With increasing life
16 expectancy and hence an ageing population, the burden of hip OA is expected to worsen (1, 5).

17 Joint pain is the hallmark symptom of OA and is also the major driver of clinical decision-
18 making. Hip pain, together with stiffness and other functional limitations, substantially impairs
19 health and quality of life of patients suffering from hip OA (6). Among patients with hip or knee
20 OA, there are two distinct pain types described: one is a dull, aching pain which becomes
21 constant over time (persistent “background” pain); the other one is an intermittent intense pain
22 which presents with episodes of unpredictable and more severe pain (7). The latter pain has a
23 greater impact on quality of life, but risk factors triggering these exacerbations are largely
24 unknown (8). Previous studies showed that knee injury or buckling, negative affectivity and
25 passive pain coping strategies could trigger pain exacerbations in patients with knee OA, but
26 there are few studies on the risk factors of hip OA pain exacerbations (9, 10).

27 Mechanical insult to the hip from acute injury or previous hip injury is a risk factor for the
28 development of hip OA (11, 12). “Giving way” or buckling of the joint means perception of the
29 sudden loss of postural support across the joint. The joint “giving way” is usually caused by

1 joint pain or joint instability but is rarely described in uninjured (non-orthopaedics related) joints
2 (13). The role of hip injury or “giving way” in pain exacerbations in persons with hip OA
3 remains unclear. This study evaluated data from the Internet-based Hip Osteoarthritis Pain
4 Exacerbation (iHOAP) study to determine whether there was any association between hip injury
5 (within seven days) or hip “giving way” (within two days) and pain exacerbations in persons
6 with symptomatic hip OA.

7

8 **Patients and Methods**

9 *Study design* We conducted an Internet-based case-crossover study to assess a range of potential
10 risk factors, including hip injury and hip “giving way”, for hip pain exacerbation. This method
11 has been previously described in knee OA pain exacerbation studies (9, 10, 14, 15). In brief, the
12 case-crossover design uses each participant as his/her own control to assess the effects of
13 transient exposures (triggers) on episodic events (e.g. pain exacerbation). The study was
14 approved by the ethics committees of the University of Sydney (HREC 2014/801) and
15 University of Melbourne (HREC 1443509), and all participants provided informed consent.

16 *Participants* An online screening survey tool was designed for the recruitment of eligible study
17 participants in Australia from May 2015 to June 2017. This tool identified participants that
18 qualified for the study based on their answers to the eligibility criteria questions and eliminated
19 those that were not. The screening survey website link was provided at the websites and local
20 newspapers chosen for advertising the study. We also emailed the link to individuals from
21 previous hip OA studies who gave their consent to be contacted for future research projects.
22 When a potential study candidate registered his/her interest in participation through the screening
23 survey tool, their contact details were emailed to a study coordinator. The study coordinator then
24 contacted participants for further assessment and enrolment. Prospective participants were also
25 asked to provide their most recent hip x-ray.

26 The inclusion criteria were ≥ 40 years old; hip pain on most days (5 -7 days/week or 20-30
27 days/month) that fluctuates in intensity; at least one hip meeting American College of
28 Rheumatology Criteria for hip OA (clinical (without ESR) plus radiological criteria) (16);
29 Kellgren and Lawrence Classification of hip OA grade ≥ 2 (17); an active e-mail account and

1 access to the internet and computer; and good understanding of spoken and written English. The
2 exclusion criteria were: a history of total hip replacement in the index hip or plan to have a total
3 hip replacement of the symptomatic hip(s) in the next six months; history of inflammatory
4 arthritis, osteonecrosis or Paget's disease affecting the hip.

5 **Procedures** The Internet was used in this study to collect data. Once qualified, the person was
6 enrolled and provided access to the study website. Eligible participants were followed up for 90
7 days and asked to complete questionnaires (including demographic details, baseline pain level,
8 hip injury and "giving way") at baseline and every succeeding 10-day interval (control periods).
9 The pain level was assessed using the numeric rating scale (NRS; ranged from 0 – "no pain" to
10 10 – "the worst pain possible") for pain (18, 19). We asked participants to indicate how bad their
11 hip pain was at its mildest, usual and worst times at the baseline online visit. Pain exacerbation
12 was then operationally defined as an increase ≥ 2 points in the participant's pain level
13 compared with his/her mildest hip pain level reported at the baseline visit (a disabling increase in
14 the hip symptoms lasting for more than 8 hours without settling), which was also used in
15 previous studies (9, 10, 14, 15, 20, 21). We chose the threshold for pain exacerbation which was
16 also based on the OARSI Clinical Trial Response Criteria definition for a meaningful change in
17 symptoms (15, 22). When a participant considered he/she was experiencing a pain exacerbation
18 and logged onto the study website, the online questionnaire automatically determined whether
19 the participant had a pain exacerbation or not based on the operational definition and guided
20 them to complete the questionnaires (case periods). Participants were not allowed to know what
21 amount constituted a pain exacerbation to avoid subjectivity or bias. Risk factor assessment
22 questionnaires for control periods and case periods were the same for all online visits.

23 Participants were asked whether they had an injury (such as fall, slipped, sports injury, tripped)
24 involving the index hip (most painful/affected hip) that limited usual activities during the last
25 seven days and whether they experienced any episodes of the hip "giving way" (defined as
26 sudden loss of postural support across the hip at a time of weight bearing) in the last two days at
27 control periods. As hip "giving way" was assumed more frequently than hip injury, two days'
28 period prior to pain exacerbations was selected for hip "giving way". They were also asked the
29 same questions about whether any injury had occurred to the index hip that limited usual
30 activities during the seven days before the pain exacerbation and whether there were any

1 episodes of the hip "giving way" during the two days before the pain exacerbation at case periods.
2 All data were collected on a secure password protected study website which was located on a
3 secure server.

4 **Statistical methods** Baseline characteristics were summarised as mean (SD) for continuous
5 variables and frequency (%) for categorical variables. Patients who did not provide data on both
6 case periods and control periods were excluded from the analyses. For hip injury, controls that
7 were within seven days before or after a reported flare were excluded. Flares reported within
8 seven days of a previous flare were also excluded. The same rule was applied to hip "giving way"
9 (within two days). Characteristics were summarised for all patients enrolled into the study and
10 for the subgroup included in the analysis. Case periods that occurred within two days prior to a
11 preceding case period were excluded from the analysis. The association of hip injury or "giving
12 way" to the risk of hip pain exacerbation was assessed by conditional logistic regression analysis.
13 The dose-response relationship between number of "giving away" events and risk of pain
14 exacerbation was assessed by conditional logistic regression analysis choosing zero "giving way"
15 event as reference. Odds ratios (OR) and 95% confidence intervals (CI) for the risk factors (hip
16 injury and "giving way") were reported. All analyses were conducted using STATA version 15.

17

18 **Results**

19 Of the 252 participants recruited, three failed to answer the questionnaires. One hundred and
20 nineteen patients only provided data on control periods only. One hundred and thirty-three (53%)
21 patients provided data from both periods and were subsequently included in the analysis; one
22 further patient was excluded from the hip "giving way" analysis due to missing data. Baseline
23 demographic characteristics of all participants (n=252) and those with risk factor data included in
24 the current analysis are summarised in Table 1. Participants included in the analyses were
25 representative of all participants recruited and were predominantly female (85%), had an average
26 body mass index around 29 kg/m², and an average age of 62.4 years (SD ± 8.2). More than 60%
27 of the participants received a tertiary education (higher than high school education) and more
28 than 70% performed light physical work (sedentary work or standing occupation). On average,
29 the usual hip pain level was around 4.5 (SD ± 2.2; NRS scale) while the mildest pain level was 2
30 to 3 and the worst pain level was 8 (SD ± 1.8).

1 On average (252 participants), patients completed the questionnaire 9.5 times (median: 10; range:
2 0-21). The average number of control periods was 8.1 and the average number of case periods
3 was 1.4.

4 During the 90-day follow-up, 133 (53%) participants had 350 hip pain exacerbations (case
5 periods); on average, patients experienced 2.6 exacerbations (median: two; range: 1-11).The
6 others (116 participants) provided only control periods or case periods that were excluded as they
7 are not informative for this particular design and analysis. Fifty-one (39%, 51/132) participants
8 had at least one hip injury. Of these, questionnaires were completed for 304 case periods plus
9 807 control periods were used for the final analysis of the association of hip injury within the last
10 seven days and hip pain exacerbation. Results showed that hip injury increased the odds of pain
11 exacerbations (OR 2.74, 95% CI 1.62, 4.62) compared with no injury to the hip (Table 2).

12 For hip “giving way”, information was completed for 347 case periods and 905 control periods
13 which were used for the final analysis. Among them, 86 (65%, 86/133) participants had at least
14 one hip “giving way”. Four participants (1.3%, 4/319) reported falling due to the hip “giving
15 way”. Hip “giving way” during the last two days was associated with increased odds of hip pain
16 exacerbation (OR 2.10, 95% CI 1.30, 3.39), and showed a significant dose-response relationship
17 between the number of hip “giving way” events and risk of hip pain exacerbations (Table 3).

18

19 **Discussion**

20 This study showed a significant association between hip injury/“giving way” and pain
21 exacerbation in hip OA patients, though hip injury was less frequent than hip “giving way” in
22 this study.

23 Many studies showed that patients with hip or knee OA experience recurrent pain exacerbations,
24 but the underlying mechanisms are still not well-understood (7, 23, 24). Traditionally, pain
25 associated with OA was attributed to inflammation or tissue (joint) injury (referred as
26 “nociceptive pain”), which may cause inflammatory mediators released into the joint and
27 peripheral sensitization (25). Pain fluctuation was shown to be related to changes in bone
28 marrow lesions (BMLs) and synovitis in knee OA patients (23). As a result, injury to the joint
29 was thought to be a potential factor leading to the inflammatory response in the joint and

1 hyperalgesia/allodynia (9, 25, 26). Moreover, many injuries like slipping or falling may also be
2 the trigger of activity-related pain (25).

3 Patients with hip or knee OA often have the sensation of joint instability or “giving
4 way”/buckling which is also a cause of falls and fractures (27, 28). In our study, 65% (86/133) of
5 the hip OA population reported at least one episode of hip “giving way” during the 90-day
6 follow-up. Only four falls occurred due to the hip “giving way” which could be explained by the
7 relatively younger age of our sample compared with those at higher risk of falls (29). Buckling
8 or “giving way” was found to be significantly associated with activity limitation and poor
9 physical function (28). The causes of joint (knee/hip) “giving way” in OA patients are still
10 unknown, though biomechanical impairments such as muscle weakness were hypothesized as
11 important causal factors in self-reported knee or hip “giving way” (30). The sudden “giving way”
12 can also occur because of OA pain (13). Studies of knee OA patients found that joint instability
13 could influence knee pain level and that “giving way” events were significantly associated with
14 pain exacerbations (9, 31). Nevertheless, whether hip “giving way” events could trigger pain
15 exacerbations has been scarcely studied previously in OA patients. The results of this study also
16 demonstrated that those who had more episodes of hip “giving way” during the last two days
17 further increased the strength association with pain exacerbations. Similar results were also
18 found in knee OA patients (9).

19 The aetiology of OA pain is complex and is often considered within the construct of a
20 biopsychosocial model influenced by many factors (32). Mechanical factors, anxiety, depression
21 or the patients’ pain coping strategies can all influence the person’s pain experience (33).
22 Lifestyle behavioural management strategies such as exercise and weight loss combined with
23 proper medical treatment or psychological therapy are recommended for improving OA pain (34-
24 37). There is also evidence showing that greater strength of the major hip and thigh muscles is
25 associated with better self-reported physical function in patients with hip OA (38). Relevant
26 muscle strengthening and balance training are potential ways to improve hip instability. However,
27 avoiding hip joint injuries such as slipping or twisting could effectively reduce the fluctuation of
28 pain in daily life which will also decrease pain-related fear and increase the patients’ adherence
29 to exercise (39).

1 Our study also has some limitations. Most participants were Caucasians and all required access
2 to the internet and a good understanding of English. Thus, the findings may not generalize to all
3 patients with hip OA. The study relied on retrospective self-report of the risk factors and as such,
4 there is potential for recall bias. Participants were required to complete numerous questionnaires
5 at regular intervals over 90 days. This may have caused participant fatigue leading to
6 underreporting of pain exacerbations and incomplete questionnaires. However, such a potential
7 bias, if it exists, is likely to dilute any association. While we have demonstrated an association, it
8 is not known whether hip injury or “giving way” is a causative factor for hip OA pain
9 exacerbations.

10 Our findings are novel and extend from the use of novel web-based methods that allow such
11 questions to be asked. In this study, we used each case as his/her own control which is highly
12 applicable to assess the effects of transient exposures (hip injury or “giving way”) on pain
13 exacerbations. To address the limitations of traditional study methods, we used the Internet
14 which can facilitate real-time data capture as a powerful resource for efficient data collection
15 (40).

16 In conclusion, this study found that hip injury and episodes of hip “giving way” were risk factors
17 for pain exacerbation in persons with symptomatic hip OA. The results provide some insight into
18 potential mechanisms of pain exacerbation. Reducing or avoiding activities that lead to hip injury
19 or “giving way” may decrease the risk of hip pain exacerbations in persons with hip OA.

20 **Author contributions**

21 DH, KB, YZ, JM and BM were involved in the conception and design of the study, participants’
22 recruitment and data collection. KF, JM, BM, YZ, RA and DH were involved in data cleaning
23 and data analysis. All authors contributed to drafting the manuscript or revising it. All authors
24 read and approved the manuscript for publication.

25

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20 Tables

21 **Table 1.** Demographic characteristics of participants

Characteristics (Mean ±SD or %)	All participants/n=252*	Participants/n=133**	Participants /n=119***
Age (years)	62.2 ± 8.3	62.5 ± 8.3	62.0 ± 8.3
Female	199 (79%)	113 (85%)	86 (72.3%)
BMI (kg/m ²)	28.69 ± 6.05	29.12 ± 6.33	28.27 ± 5.72
Index hip (right)	143 (56.7%)	72 (54.1%)	72 (60.5%)
Race			
Caucasian	242 (96%)	126 (94.7%)	116 (97.5%)

Others	10 (4%)	7 (5.3%)	3 (2.5%)
Education Level			
Less than high School	37 (14.7%)	22 (16.5%)	15 (12.6%)
Completed high school	58 (23%)	28 (21.1%)	31 (26.1%)
Higher than high school	157 (62.3%)	83 (62.4%)	73 (61.4%)
Past occupational physical workload level			
Sedentary (mostly sitting) work	111 (44%)	56 (42.1%)	55 (46.2%)
Standing occupation, physically light work	90 (35.7%)	49 (36.8%)	41 (34.5%)
Manual work	47 (18.7%)	25 (18.8%)	22 (18.5%)
Heavy manual work	4 (1.6%)	3 (2.3%)	1 (0.8%)
Baseline pain level (0-10)			
Mildest	2.3 ± 1.9	2.5 ± 2.0	2.0 ± 1.7
Usual	4.3 ± 2.1	4.5 ± 2.2	4.1 ± 2.1
Worst	7.6 ± 1.9	8.0 ± 1.8	7.3 ± 2.0

1 * Three patients failed to answer.

2 ** With both case and control periods. One patient was further excluded for the hip injury analysis.

4 *** With only control periods or failed to answer.

1 **Table 2.** Association in last seven days' of hip injury and hip pain exacerbation (132 subjects)

Hip injury	Case periods (n=304)	Control periods (n=807)	OR (95% CI)	P-value
No	253 (83%)	760 (94%)	-	-
Yes	51 (17%)	47 (6%)	2.74 (1.62, 4.62)	<0.001

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1 **Table 3.** Association of hip “giving way” in last two days and hip pain exacerbation (133
 2 subjects)

	Case periods (n=347)	Control periods (n=905)	OR (95% CI)	P-value
Hip “giving way”				
No	215 (62%)	718 (79%)	-	-
Yes	132 (38%)	187(21%)	2.10 (1.30, 3.39)	0.002
Number of hip “giving way” events				
0	215 (62%)	718 (79%)	-	-
1	43 (12%)	87 (10%)	1.86 (1.14, 3.04)	
2-5	64 (18%)	92 (10%)	3.39 (2.00, 5.75)	<0.001*
≥6	25 (7%)	8 (1%)	7.86 (2.74, 22.55)	

3 *Type III P-value.