Developing a preliminary definition and domains of flare in knee and hip osteoarthritis. Consensus building of the Flare-in-OA OMERACT group.

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Short running head: Domains in osteoarthritis flare

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Flare in knee and hip osteoarthritis (OA) is more than just an exacerbation of pain.
Unstructured, semi-structured and focus group interviews followed by Delphi surveys with patients and health professionals (HP) generated candidate domains of an OA flare.
Content analysis of interviews with 29 patients and 16 HP extracted 180 statements which were grouped into 9 clusters. Delphi consensus with 50 patients (Australia, Canada and France) and 116 HP (17 countries on 4 continents), identified five flare domains: Pain, Swelling, Stiffness, Psychological aspects, and Impact of symptoms. Elements for a preliminary definition of an OA flare are proposed.

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Introduction

Knee and hip osteoarthritis (KHOA) ranked as the 12th highest contributor to global disability in 2016 (1), with an age-standardized prevalence of 3.8% and 0.85% for knee and hip respectively (2). The most common symptoms associated with OA are pain, stiffness and fatigue, which can flare during the evolution of this chronic condition.

Recent literature has shown that flare in KHOA is more than just an exacerbation of pain. Murphy et al. (3) identified it by quality, timing of symptoms, antecedents and consequences. Our literature review highlighted the wide variation in the definitions of OA flare and the lack of a valid measurement instrument integrating the patient perspective (4,5). Parry et al. (6), recently extending the review, also identified several flare characteristics beyond pain exacerbation.

The concept of flare was defined in previous work on rheumatoid arthritis by an Outcome Measures in Rheumatology (OMERACT) group as "a cluster of symptoms of sufficient duration and intensity to require initiation, change or increase in therapy" (7). It served as a guide for developing measurement instruments (8–10)
. Although sharing some characteristics such as temporary exacerbation of pain as one of its major components, whether this definition can also serve for defining flare in KHOA has to be examined. The lack of a clear and agreed upon definition of a flare in OA underlines the need for a conceptual definition before developing a measurement instrument of flare as a patient-reported outcome (PRO) for clinical trials or longitudinal observational studies. Further, to meet the requirement for a valid measure, OMERACT filter 2.0 mandates the need to first define core outcome domains (COD) before developing or choosing an instrument (11). The Flare-in-OA Working Group (WG) initiative was endorsed by OMERACT and Osteoarthritis Research Society International (OARSI). Currently, flare is on the research agenda for core domain set of KHOA (12).

This paper reports on the generation and selection of relevant domains and components for flare in KHOA and a proposal for preliminary elements for a definition.

Methods

An inductive approach was used simultaneously in two languages, i.e. French and English, with the goal of generating candidate domains labelled with multiple language understanding. Then, consensus building on the selection of the most relevant domains involved participants in 3 continents.

Generation of domains. Unstructured interviews with 10 patients were conducted initially to capture the whole experience of a flare and further generate a semi-structured interview guide developed under the guidance of two senior health psychologists, and cross-validated across languages. This guide was used by health psychologists and health professionals (HP) fully trained in conducting such interviews in France and Australia to elicit the perception of flare characteristics from HP and patients separately.

People recruited for this exploratory step were participants with OA ("patients") at the Royal North Shore Hospital, Sydney, Australia, from the KHOALA cohort study in France, and HP (nurses, physiotherapists, rheumatologists, general practitioners, orthopedic surgeons) from OARSI members, OMERACT Working group members, from the same setting in Australia, and from 5 centers in France. The interviews were recorded, transcribed and prepared for analysis with NVivo in parallel in each country. The content analysis allowed identification of statements obtained verbatim (expressions

extracted from interviews) that were meaningful for HP and patients. The French statements were translated into English. Similar statements were grouped in clusters exploring the same topics. Labelling of each cluster were proposed as domain names.

The WG steering group (see appendix), comprised of clinicians, methodologists and health psychologists, critically analyzed the clustering of statements and the proposed labelling of clusters, based on secondary content examination of the transcripts, taking care to ensure cross-language equivalence.

Selection of domains. Delphi surveys were conducted in two rounds among patients from national settings from the SPARK study and Arthritis Alliance, Australia, from STPR group centers, France and from HP as well as scientists, as per OARSI membership. OMERACT rules for Delphi consensus building were applied at each round, i.e. a threshold of 70% agreement should be reached to make a decision (13).

Final results of the two rounds in each group were presented at the OMERACT 2018 meeting to the WG via a virtual link for finalizing selection of core domains. Elements for a preliminary definition of a flare were identified according to the conceptual framework underlying these choices.

Ethics and consent. This research was approved by the national institutional review board in France (CNIL DR-2015-134) and by the Human research ethics committee at the University of Sydney, NSW Australia. All patients and health professionals gave informed consent to participate in the research.

Results

Generating domains: individual semi-structured interviews with 29 patients and 16 HP generated 180 statements specific to an OA flare. Content analysis involved grouping the statements into 9 clusters, which were labelled by names reflecting the covered topic (supplementary Table S1 and S2). The WG steering group approved clustering and labelling of these topics.

Selecting domains: participants in the Delphi survey were HP (researchers, rheumatologists, physiotherapists, orthopedic surgeons, nurses) from 17 countries on four continents, and patients from Australia, Canada and France.

During the first Delphi round, 91 patients rejected the domain *Buckling.*

In the second round, 50 patients retained seven domains: *Pain, Swelling, Stiffness, Triggers, Consequences of the symptoms, Psychological aspects, Protective factors* and rejected two domains: *Buckling, Other symptoms* (Table 1).

In the first round, 165 HP participated and rejected two domains, namely: *Buckling, Other symptoms*. In the second round, 116 HP participated and retained seven domains: *Pain, Swelling, Stiffness, Triggers, Consequences of the symptoms, Psychological aspects, Protective factors;* and rejected two domains namely: *Buckling, Other symptoms* (Table 2).

Finally, the consensus reached by the OMERACT 2018 meeting participants was that
- *Pain, Swelling,* and *Stiffness* domains were fully supported by both HP and patients;
- *Buckling* and *Other symptoms* domains were removed by both HP and patients;
- *Psychological aspects* domain showed slightly discrepant results between patients (72%) and HP (67.2%) rating somewhat below the pre-specified threshold. In keeping with new OMERACT guidance for reaching consensus (13) that recommends a 70% threshold in either

Patient or combined 'Other Stakeholder 'groups, this domain was retained. As flare is a patient perception that conditions their health care use, it was considered relevant to weigh patients' opinions higher than that of others and retain this domain.

- *Triggers* domain, endorsed by both HP and patients in the Delphi survey, was finally removed as further discussion determined that this domain reflected possible causes of the flare rather than the flare itself.
- *Consequences of the symptoms* and *Protective factors* were endorsed by both HP and patients, but the meeting participants advised to merge them into one domain, namely *Impact of the symptoms,* as *Protective factors* was considered to be a behavioral protection adopted when the flare occurred as an attempt to limiting its impact (like resting, changing activity).

From the discussion at OMERACT 2018, several elements emerged from this framework for setting a preliminary definition of a flare in KHOA: it is a transient state, different from the usual state of the condition, with a duration of a few days, characterized by onset, worsening of pain, swelling, stiffness, impact on sleep, activity, functioning and psychological aspects, that can resolve spontaneously or lead to a need to adjust therapy.

Discussion

From a large number of statements, five core domains characterizing a flare in KHOA, were selected based on consensus by patients, HP and OA researchers. Their final selection took care to avoid missing important but rare manifestations and accounted for health providers having a comprehensive view of the disease combined with patients statements of their actual experience.

The advantage of conducting domain definition and choice using an inductive approach was that domain labelling was informed by patients' statements extracted verbatim from qualitative research. Such a bottom-up approach gives accuracy and relevance to the domain labelling, which is usually the first way people approach a questionnaire to assess content (face validity). This helped the generation of candidate domains in developing a conceptual framework through an inductive approach.

Our proposed preliminary definition has several points in common with previous attempts to define OA flare in the literature. Several experts in the committee participated to previous qualitative work conducted to understand the pain experience in OA (14).What it adds is a characterization of impact and delineating the construct as a state, different from the patient's usual condition. *Parry et al.* (6) proposed focusing on onset/worsening of symptoms and signs, attainment of a minimum symptom threshold during flare, speed of onset/worsening and duration of elevated symptoms/signs, while *Murphy et al.* (3) reported pain flares were common, fleeting, and often experienced in the context of activity engagement. These definitions and ours are convergent, with some differences, e.g. about onset mode, and require further refinement before a final definition is accepted.

Only two languages were used to generate domains which might leave the meaning of domains labels uncertain for further translation. Such initiative at the very beginning of a data-driven approach is not frequent (15), leading to carefully examine their meaning and its correct

correspondence with statements generated from patients, helpful for translation into other languages. Another limitation was that the Delphi process missed some relevant stakeholders (regulators, industry).

In conclusion, this work provides a framework for defining a flare in KHOA and identified domains that form the basis for developing items for a patient-reported outcome instrument that incorporates components relevant to OA flare.

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