KNEE

International consensus on the definition and classification of fibrosis of the knee joint

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Aims
The aim of this consensus was to develop a definition of post-operative fibrosis of the knee.

Patients and Methods
An international panel of experts took part in a formal consensus process composed of a discussion phase and three Delphi rounds.

Results
Post-operative fibrosis of the knee was defined as a limited range of movement (ROM) in flexion and/or extension, that is not attributable to an osseous or prosthetic block to movement from malaligned, malpositioned or incorrectly sized components, metal hardware, ligament reconstruction, infection (septic arthritis), pain, chronic regional pain syndrome (CRPS) or other specific causes, but due to soft-tissue fibrosis that was not present pre-operatively. Limitation of movement was graded as mild, moderate or severe according to the range of flexion (90° to 100°, 70° to 89°, < 70°) or extension deficit (5° to 10°, 11° to 20°, > 20°). Recommended investigations to support the diagnosis and a strategy for its management were also agreed.

Conclusion
The development of standardised, accepted criteria for the diagnosis, classification and grading of the severity of post-operative fibrosis of the knee will facilitate the identification of patients for inclusion in clinical trials, the development of clinical guidelines, and eventually help to inform the management of this difficult condition.

Cite this article: Bone Joint J 2016;98-B:1479–88.

Fibrosis affecting joints is a well-recognised pathological process that involves diffuse scarring within a joint and the surrounding soft tissues, leading to limitation of movement and pain. It may be a devastating complication of surgery involving the knee that might require further surgery with debridement, with associated morbidity, risk of adverse effects and a significant risk of recurrence.

Tissue from fibrotic knee joints is composed of a dense, disorganised extracellular matrix of collagen fibrils interspersed with \( \alpha \)-smooth muscle actin containing myofibroblast cells. Well defined intra-articular fibrous bands may be seen at arthroscopy.

Various clinical criteria have been used to diagnose post-traumatic fibrosis, including specific limitations of movement and the presence of fibrotic tissue seen at operation. The lack of a consistent, widely accepted definition of the condition is reflected in the wide range of the incidence reported in the literature for fibrosis after total knee arthroplasty (TKA), which varies between 1% and 15%.

There are also no standardised accepted clinical guidelines for the investigation and management of fibrosis of the knee. Consequently, recommendations on the use of CT scans, MRI and ultrasound imaging and the role of aspiration in making the diagnosis are inconsistent. The role and timing of treatment, such as manipulation under anaesthetic (MUA), is also debated and different guidelines to management have been proposed.

The lack of a precise definition of fibrosis of the knee after surgery presents a challenge for research in this area. Whilst our understanding of the cellular pathology is progressing, our ability to identify affected patients consistently is hindered by a lack of agreement about the diagnostic criteria, grading, role of imaging techniques and forms of treatment. The aim of this study was to develop a definition of post-operative fibrosis of the knee.
THE Delphi Consensus Process followed in the formation of consensus statements on post-operative knee fibrosis.

Patients and Methods

A Delphi process (brainstorming, narrowing down, quantification)\textsuperscript{15} was applied based on previously published consensus statements\textsuperscript{16} and followed guidelines set out by the NHS Research and Development Health Technology Assessment programme\textsuperscript{17} and the British Medical Journal.\textsuperscript{18} The process which was applied is outlined in Figure 1.

An expert panel that included knee surgeons, rheumatologists, basic scientists working on fibrosis, pathologists and musculoskeletal physiologists was selected based on publication record in these areas. Key individuals involved in the diagnosis of arthrofibrosis,\textsuperscript{19,20} the analysis, management and revision of TKA,\textsuperscript{21} the investigation and treatment of post-surgical fibrosis\textsuperscript{1,5,13,14,22-33} and basic research on fibrosis\textsuperscript{34-36} formed the Joint Fibrosis Consensus Working Group. Founding members (SH) and Presidents and Past-Presidents of the European Knee Society (JB, JA), the Past-President of the International Society of Arthroplasty Registries (OF), members of the Knee Society (MM, JN, JB, FH), the Head of the Norwegian Knee Arthroplasty Register (OF), the Past-President of the Arthroplasty Society of Australia (PL), the Deputy Director of the Australian Orthopaedic Association National Joint Replacement Registry (PL), and a member of the British Association for Knee Surgery Research Board (AT) were part of the group. Previous participants in an international consensus group on prosthetic joint infection (MM, FH, RMJ) were also included. Several members have also chaired instructional courses for stiffness of the knee and the management of contracture (MM, AB, PL).

Members of the working group initially identified specific topics that required the formation of a consensus (brainstorming). A literature review was undertaken (NK) focusing on key areas requiring consensus and this was circulated to the panel for comments. A search was done of Medline (via PubMed), Embase and Cochrane databases for papers on fibrosis of the knee which were published in English between 1950 and June 2015. These formed the start of the Delphi process. The following search terms were used: ‘arthrofibrosis’, ‘fibrosis’, ‘knee’, ‘arthroplasty’, ‘knee replacement’, ‘ligament reconstruction’. Overall, 320 papers were reviewed and information on key topics (definition, classification, diagnosis, investigation,
management) from 47 reports was circulated to the group. The rejected 273 papers were not relevant to post-surgical knee joint fibrosis (e.g. different anatomical site, post-traumatic or spontaneous fibrosis etc.). Feedback was used to define key areas for consensus and to draft initial statements (NK, DJD).

Draft consensus statements were circulated for rating with a scale of 1 (disagree) to 10 (agree), and comments. An online survey tool\(^37\) was used throughout this process. These inputs were integrated, and the amended consensus statements were prepared with a detailed explanation for each revision. Anonymised results from the first round were recirculated for scoring, comments, and proposed revisions for statements that scored 7 or less in the first round. Three rounds were required before final revisions were derived. A predetermined mean score of 7 or more (with three or fewer outliers: defined as scores less than 4) was used to define consensus.

Results

Consensus findings. Consensus was reached on 24 statements that fulfilled the criteria for acceptance. They were grouped into eight key categories (Definition and Classification, Investigations, Diagnosis, Range of Movement, Patho-anatomy, Histology, Prevention and Management and Joint Registries).

Definition and classification. Post-surgical fibrosis of the knee was defined as limited range of movement (ROM) of the knee, in flexion and/or extension, that is not attributable to a bony or prosthetic block to movement from mal-aligned or malpositioned components, hardware, ligament reconstruction, infection (septic arthritis), pain, complex regional pain or other specific causes, and is due to soft-tissue fibrosis that was not present pre-operatively. Joint fibrosis may be spontaneous (primary) or following an insult such as surgery or trauma (secondary).

Spontaneous knee joint fibrosis, in the absence of trauma or surgery, is extremely rare. Post-trauma or post-surgery knee fibrosis is much more clinically important. This classification can be further sub-categorised into post-arthroplasty knee fibrosis, post-ligament reconstruction fibrosis etc., according to the algorithm in Figure 2.

Consensus statements

Post-surgical knee joint fibrosis is defined as restricted ROM, in flexion or extension, that is not attributable to osseous or prosthetic block to movement from malpositioned or incorrectly sized components, metal hardware, ligament reconstruction, infection (septic arthritis), pain, CRPS or other specific causes, and is due to soft-tissue fibrosis that was not present pre-operatively.

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ROM, range of movement; CRPS, chronic regional pain syndrome

At present, fibrosis cannot be diagnosed confidently by, MR imaging, however, it may be useful in the future as metal artifact reducing sequences are being developed for this purpose. In the future, the basis of objective measure-
ments of fibrosis on MRI scans may allow the measurement of perisynovial thickness or the quantification of fibrotic tissue in the parapatellar gutters.

**Diagnosis.** Post-surgical fibrosis of the knee is a clinical diagnosis that can only be made when investigations have been performed to exclude other causes (Table III). The clinical diagnosis may be supported by direct visualisation of fibrosis at surgery, either arthroscopically or by open techniques. Laboratory evaluations and aspiration for microbiological culture should be performed to rule out infection according to the MSIS criteria. A bone scan alone is not recommended to rule out infection. Histological criteria have been proposed, but biopsy is not required to make a diagnosis. Tissue taken at the time of débridement may be sent for histopathological evidence of fibrosis to support the diagnosis.

**Range of movement of the knee.** Reduction in flexion and/or extension is required for a diagnosis of fibrosis (Table IV). The severity of loss of movement can be graded. This criterion is active rather than passive ROM, as examiners may apply varying degrees of pressure. For simplicity, an absolute ROM is used for grading of severity. Comparison with pre-operative ROM and with the contralateral knee may be useful clinically, but these comparisons can be affected by pre-operative stiffness and the presence or absence of contralateral disease. The goal of TKA includes the establishment of a good ROM, therefore absolute limitation of movement forms part of the criteria for the diagnosis of fibrosis. Three levels of severity were agreed according to the amount of restriction (mild, moderate and severe). Extreme loss of movement, with global ROM < 30° in total, which may happen in ankylosis following septic arthritis as described by Bae et al., does not form part of the classification of the severity of post-surgical fibrosis of the knee. The severity of fibrosis is not solely due to the degree of limitation of movement; other factors including pain, are important.

**Pathological anatomy.** Information about the pathological anatomical location can be gained from clinical examination and correlation with areas of swelling or a particular deficit in movement (Table V). However, direct visualisation is the benchmark for the determination of the location of fibrosis. MRI may become a useful tool for identifying areas of fibrosis. Focal fibroses such as infra-patella contraction syndrome (IPCS) do not generally cause severe limitation of movement. Thorpe et al. described a syndrome of painful patellofemoral dysfunction, without limitation of movement, following TKA in 11 of 635 patients. Intra-articular lesions were found transversely on the patella, or between the patella and the fat pad or the intercondylar notch. The symptoms resolved following arthroscopic removal of these lesions without a change in active ROM. Without a limitation of ROM...
these lesions do not form part of the definition of post-surgical fibrosis.

**Histopathology.** Criteria for a tissue diagnosis have been proposed. Histopathologically, post-surgical fibrosis of the knee is characterised by a varying degree of cellularity of fibroblasts. In one report, a count of β-catenin positive cells above a threshold level of > 20 per high power field, 0.307 mm² allows, in conjunction with the clinical information, the histopathological diagnosis of fibrosis. Histopathological analysis of tissue taken during surgery performed to débride fibrotic lesions is useful to support the diagnosis, but biopsy is not required for the diagnosis, particularly as it requires an invasive procedure that may cause infection (Table VI).

**Prevention and management.** There is some evidence that aggressive rehabilitation regimes can reduce the incidence of fibrosis, but in some patients this may precipitate or worsen fibrosis. There is evidence that optimised post-operative pain control can reduce the requirement for MUA after TKA. The pharmaceutical modulation of inflammation with steroids and the interleukin-1 receptor antagonist Anakinra has been used to reduce the inflammatory response and decrease the formation of fibrotic tissue and pain post-operatively.
The management of fibrosis depends on its staging. Early fibrosis, which often has a ‘soft endpoint’ to movement of the knee, may be treated successfully with physiotherapy and manipulation. Analgesia and relaxation techniques may be helpful. In addition, mechanical soft-tissue stimulation using instruments such as Astym (Performance Dynamics Inc., Muncie, Indiana) that provides topical administration of pressure and shear force designed to stimulate regeneration of damaged tissues and breakdown of scar tissue, has shown good early results in stiff TKAs.

Established fibrosis, typically present three to six months after surgery, often has a hard endpoint to movement of the knee. There is evidence that MUA performed within three months post-operatively is more effective than that performed after three months. The risk of iatrogenic fracture should be borne in mind when considering MUA, particularly in patients with inflammatory conditions such as rheumatoid arthritis. The timing of MUA was debated within the group; some members felt that MUA is safe and effective up to six months post-operatively. This debate is reflected in the range of time after surgery that MUA is considered an option (three to six months) although it is emphasised that efforts should be made to exclude other causes of stiffness as soon post-operatively as possible to allow MUA to be performed before fibrosis becomes established (Table VII, Fig. 4).

MUA should be performed at a time of maximum muscle relaxation by flexing the hip to 90° and grasping the tibia proximally to avoid leverage on the joint. The knee is flexed slowly and gently until palpable and audible separation of adhesions no longer occurs, as described by Fox and Poss. Consensus was reached that established fibrosis requires arthroscopic or open débridement. Revision of the components may be required to re-establish movement.

Joint registries and fibrosis. Joint replacement registries do not currently allow sufficiently granular identification of patients with post-surgical fibrosis of the knee (Table VIII). ‘Arthrofibrosis’ or stiffness is often used as an umbrella term for stiff knees, lack of movement and true fibrosis (intra-articular scarring causing restricted ROM), thus it is difficult to define patients with true fibrosis. Furthermore, procedures for treating stiffness caused by fibrosis, such as MUA and arthroscopic débridement, where open surgery is not performed and components are not changed, are not recorded in most registries.
Discussion

This international consensus provides agreement amongst a multi-disciplinary panel for the definition, classification and diagnostic criteria of post-surgical fibrosis of the knee. This is considered to be a clinical diagnosis characterised by limitation of movement of the knee. The severity of fibrosis may be graded according to the degree of limitation of movement and a scale is proposed from mild, moderate to severe according to the degree of restriction of ROM. The diagnosis may be supported by direct visualisation of fibrosis at surgery and by the histopathological analysis of tissue from the knee, although formal biopsy is not indicated or required.

Post-surgical fibrosis presents both a diagnostic and therapeutic challenge. It is considered a diagnosis of exclusion that requires thorough investigation to establish that the symptoms do not have another cause. The list of possible causes is long, but infection and malalignment of components or surgical error in particular must be excluded. Investigation algorithms have been presented for the analysis of the stiff TKA. A significant proportion of failed TKAs are due to malrotation of components, and this must be ruled out before making a diagnosis of fibrosis. The cornerstones of investigation remain clinical examination, aspiration of the knee and laboratory evaluation to rule out infection, and plain films and CT scan to analyse the

Table VIII. Consensus statements – Joint Registries

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<td>Registries in their current form do not provide a robust resource for identifying patients who have post-surgical joint fibrosis due to several limitations, including lack of a current, accepted disease definition and diagnostic criteria and most national registries do not include re-operations without component removal or change or closed procedures.</td>
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Fig. 4

Management algorithm for post-operative fibrosis of the knee (ROM, range of movement; MUA, manipulation under anaesthesia; TKA, total knee arthroplasty). *Important to investigate patient to exclude causes of stiff TKA whilst non-operative treatments are employed.
alignment of the components. MRI scans with artifact reducing sequences may in the future provide a non-invasive method of describing intra-articular fibrosis.

Fibrosis may co-exist with other conditions such as following trauma or mechanical conflict caused by malalignment of components, and may be triggered by them. Fibrosis in this context was not considered post-operative fibrosis, which currently has an unknown aetiology. Tissue from fibrotic joints is composed of a dense, disorganised extracellular matrix of collagen fibrils interspersed with smooth muscle actin containing myofibroblast cells which form intra-articular fibrous bands. The molecular mechanism underlying the development of post-traumatic fibrosis is not known. It is likely that different triggers converge on a common ‘fibrotic pathway’, involving myofibroblasts and transforming growth factor (TGF)-β signalling. Furthermore, there is some evidence that fibrotic conditions are heritable.

There may be several different locations of the fibrosis, but it must be sufficient to cause limitation of movement. Limited pathology in local fibroses that do not cause limitation of movement, such as IPCS syndrome, is not considered to be fibrosis of the knee.

Alongside imaging, aspiration of the knee is recommended to rule out infection. Provided that this is performed in sterile conditions, the risk of introducing infection is outweighed by the need to establish whether stiffness is due to infection. Histopathology may be used to support the diagnosis of fibrosis, and recent publications have provided diagnostic criteria, such as the number of β-catenin staining cells, but these criteria need validation before biopsy can be recommended to establish a diagnosis.

There was considerable debate about the limitation of movement and whether this should be measured relative to pre-operative values or to those of the contralateral knee. Several grading systems have been proposed. Agreement was reached on the grading of the severity by absolute limitation of movement irrespective of pre-operative stiffness or the ROM of the contralateral knee. The limitation of the grading which was chosen is that knees with reduced ROM pre-operatively often do not regain ROM post-operatively. The important message is that some degree of limitation of movement in either flexion, extension, or both is absolutely required for a diagnosis of post-surgical fibrosis. It is also important to note that to judge success solely on ROM achieved would miss the main reason for TKA, namely reduction in pain.

Rehabilitation protocols aimed at restoring movement have reduced the incidence of stiffness post-operatively, particularly following anterior cruciate ligament reconstruction (ACL), but the optimum regime remains unknown. Similarly, the management of the stiff TKA remains challenging and evidence for particular forms of treatment is not available. There is evidence that optimised pain control can reduce the requirement for MUA in stiff knees following TKA. One critical concept in the approach to fibrosis is of early versus late fibrosis. The fibrotic condition is a disease spectrum, and early fibrosis is amenable to physiotherapy, whereas established fibrosis, which usually occurs after between three and six months is refractory to physiotherapy and manipulation runs the risk of iatrogenic fracture and should be avoided. There was considerable debate over the timing of MUA. A consensus was reached that MUA more than six months post-operatively is not indicated. There is limited evidence that MUA is most effective less than three months after surgery. Consensus agreement over the timing of MUA was challenging due to the lack of clear evidence and the risk of iatrogenic injury. Consensus was reached on MUA being an appropriate intervention between three and six months post-operatively.

Patients resistant to non-operative treatment require arthroscopic or open surgical procedures to excise and remove the soft-tissue contractures. Arthroscopic release may be used as an initial approach of choice. Kim, Gill and Millett provided an algorithm for this procedure following ACL reconstruction involving capsular distension with fluid, medial and lateral retinacular releases, graft debridement and posterior joint release. Open surgery for fibrosis is reserved for knees resistant to arthroscopic procedures (2% of cases) and often requires large incisions with extensive exploration of the joint and surrounding extra-capsular soft tissues. The outcomes of surgically treated post-traumatic fibrosis of the knee are poor, with most patients unable to return to pre-injury level of function. Currently, available treatments work by stretching or surgically removing the fibrotic tissue; they do not address the biological basis of disease. This may contribute to recurrence of post-traumatic fibrosis, which is a frequent problem.

The role of arthroplasty registries in research into fibrosis was considered. Population level studies of patients with fibrosis would allow identification of risk factors, provide more precise data about the incidence, and inform management strategies. Currently, the identification of patients with fibrosis in National Registries is difficult; as a reason for revision it forms one group in the Australian registry, while the England, Wales and Northern Ireland registry uses stiffness, despite the range of different pathologies that this encompasses. Furthermore, only patients having a formal revision procedure involving the exchange, removal or introduction of components are captured by registries, significantly underestimating the number of patients with fibrosis who are treated with non-operative measures or debridement only. A way forward for registries might be to use this consensus statement as a definition and include fibrosis after TKA as an indication for revision and also include open revision procedures not involving exchange of components and closed procedures such as MUA.

This consensus process has provided a definition, classification and diagnostic criteria for fibrosis of the knee after surgery. The aim was not to provide clinical guidelines on
the management of these patients. An international, multidisciplinary working group reviewed the existing literature on fibrosis of the knee and further research into the prevention and management of this condition is required. A major challenge is the accurate diagnosis and stratification of patients with fibrosis of the knee to allow robust clinical studies. The definition of the disease and diagnostic criteria presented here may be used to diagnose, select and stratify patients accurately in future clinical studies for this poorly understood condition. These statements should now undergo a period of validation to allow the definition and classification to be improved upon and modified.

Take home message:
This definition will be used to identify patients and stratify them accurately in future clinical investigations, and ultimately improve our understanding and treatment of this challenging clinical problem.

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D. A. Mann: Data collection, Writing the paper.
L. A. Bothwick: Data collection, Writing the paper.
D. J. Deehan: Study conception, Data collection, Writing the paper.

All authors were involved in the consensus forming process through contribution to three Delphi rounds. Draft consensus statements were written by N. S. Kalson and then revised and re-written by all authors during the consensus process. The draft manuscript was prepared by N. S. Kalson. All authors edited and approved the manuscript. The consensus process was coordinated by N. S. Kalson and D. J. Deehan.

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

This article was primarily edited by J. Scott and first proof edited by G. Scott.

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