APLICATION TO EULAR STANDING COMMITTEE FOR CLINICAL AFFAIRS (ESCCA)

EULAR RECOMMENDATIONS FOR TERMINOLOGY, DIAGNOSIS AND MANAGEMENT OF CALCIUM PYROPHOSPHATE CRYSTAL ASSOCIATED ARTHRITIS

Convenors:
Michael Doherty (UK), Thomas Bardin (France), Eliseo Pascual (Spain).

Background
Calcium pyrophosphate dihydrate (CPPD) crystal deposition occurs almost exclusively in articular tissues, most commonly fibro-and hyaline cartilage. CPPD deposition is the most common cause of cartilage calcification or chondrocalcinosis (CC). CC may occur as an isolated phenomenon in otherwise normal joints or in association with structural changes similar to osteoarthritis (OA). Hospital-based case series suggest that the arthropathy associated with CC is characterised by florid osteophytosis and a different pattern of joint involvement compared to OA without associated CPPD deposition (1-4). This hypertrophic “subset” of OA, which may also associate with more inflammatory symptoms (e.g. stiffness, effusion) than OA without CPPD deposition, has been termed by some as “pyrophosphate arthropathy” (PA) (4).

Isolated CC and PA may be [1] clinically occult and asymptomatic, or [2] associate with acute, self-limiting “attacks” of florid crystal-induced synovitis - so-called “pseudogout”. PA may also associate with intermittent or persistent symptoms of pain, stiffness and functional limitation. Rarely, atypical or periarticular deposition of CPPD may associate with clinical syndromes of tendinitis, tenosynovitis, bursitis or tophaceous “pseudo-tumours”.

Major risk factors for CPPD deposition are increasing age, OA and previous joint trauma/injury whereas less common risk factors are metabolic disease (haemochromatosis, hyperparathyroidism, hypomagnesaemia, hypophosphatasia) and rare monogenic familial predisposition (4, 5). Apparently sporadic CC and PA are both common. The unadjusted prevalence of CC and PA in adults aged between 40-
79 years is 4.5% and 2.4% respectively (6), although the prevalence of CC increases with age from 4% in those aged <65 to fully 27% in those aged >85 (6).

The complexity of CPPD deposition in terms of its variable clinical phenotypes and association with OA has been complicated further by the use of different terminologies and classification for CPPD deposition. For example, the umbrella term “CPPD deposition disease” is commonly used for all instances of CPPD deposition, (even though CPPD crystals usually cause no “disease”) with numerous suggested subsets under that umbrella including pseudogout, “pseudo-OA”, “pseudo-RA”, “pseudo-neuropathic”, “pseudo-ankylosing spondylitis”, “pseudo-polymyalgia” and “lanthanide deposition” (5). However, some clinicians and authors use the terms CC or pseudogout for any such phenotype, and others still restrict the term CC for radiographic calcification, pseudogout for acute synovitis, and PA for the combination of CPPD plus structural changes of OA (4,7).

Many members of the EULAR Task Force that developed recommendations for both diagnosis and management of gout (8,9) considered that it would be desirable to agree a uniform terminology, with clearly stated definitions. Furthermore, as with gout, there are clinical issues relating to the method of diagnosis of CPPD deposition (clinical, radiographic, crystal confirmation) and to the management of both the episodes of acute synovitis (pseudogout) and the chronic symptoms that may relate to PA. Given the high prevalence of CPPD deposition it seems appropriate for EULAR to consider the development of recommendations for this common disorder. Whether the project should be undertaken by EULAR alone, or in collaboration with the ACR, is a matter for ESCCA to decide.

**Objectives**
To produce evidence-based recommendations for the terminology, diagnosis and management of CPPD associated arthropathy.
Steering group Committee Members

The proposed convenors are Michael Doherty (UK), Thomas Bardin (France) and Eliseo Pascual (Spain), the convenors of the EULAR Recommendations for Gout (8,9). The proposed lead researcher is Dr Weiya Zhang (Associate Professor in Musculoskeletal Epidemiology, Nottingham UK) who again was the lead researcher for the Gout Recommendations. Dr Zhang will undertake the literature searches, analyses and first draft of the recommendations.

Other suggested members, all experts in crystal-associated arthropathies, include: Fernando Perez-Ruiz (Spain); Leonardo Punzi (Italy); Victoria Barskova (Russia); Paul Dieppe (UK); Tim Jansen (Netherlands); Pierre-Andre Guerne (Switzerland); Jose Pimentao (Portugal); Burkhard Leeb (Austria); Till Uhlig (Norway); Iain Watt (Netherlands/UK)

Target audience

The target audience for the recommendations are European Rheumatologists. It is hoped that this audience, which is readily accessible through EULAR, will have an established interest in CPPD and OA and that EULAR recommendations will stimulate further interest and debate and increase knowledge. This increased knowledge and improved standard of care may subsequently be disseminated to General Practitioners who are the other major target audience. We feel that targeting General Practitioners directly throughout Europe poses major logistical problems but that initial targeting of rheumatologists is feasible and likely to be effective.

Evidence-Based Structure and Methods

The Task Force will have an initial meeting in Zurich where the objectives, structure, activity and logistics will be fully explained and discussed. In advance of the meeting a systematic review (1962-present) of terms and definitions that have been used for CPPD deposition (CPPD crystal deposition disease, CC, PA, pseudogout etc) will be undertaken and circulated to Task Force members. This will then be presented at the meeting, and the pro’s and cons of the various terms fully discussed. A consensus agreement for an appropriate glossary of terms and definitions, representing the
majority view of the Task Force, will be determined (analogous to the system used in
the Recommendations for diagnosis and management of hand OA for the terminology
and definitions that were employed).

At the first meeting the Task Force will discuss various issues relating to the diagnosis
and management of CPPD associated arthropathy and agree domains in which
propositions will be sought. For example, for diagnosis, possible domains may be
clinical features, synovial fluid analysis or imaging characteristics, whereas for
management possible domains may be general aspects, acute attacks, chronic PA,
management of predisposing risk factors or surgery. Following the first meeting the
Task Force will determine, using a Delphi technique conducted via email, a specified
number (approximately 10 or more for each) of key propositions relating to the
diagnosis and management of CPPD associated arthropathy. This process will be
conducted in identical fashion to that undertaken for the Gout Recommendations (8,9).

A literature search with specified timelines will be undertaken to determine the
strength of research evidence relating to the specific content of each proposition. The
same search strategy as that used for the EULAR Recommendations for Diagnosis
and Management of Gout (8,9) will be used. The research evidence for diagnostic
issues will be categorised as 1 to 4 [4]. Wherever possible the sensitivity, specificity
and likelihood ratio will be estimated for diagnostic issues, and effect size, number
needed to treat, relative risk or odds ratio will be estimated for management issues.
Cost per adjusted quality of life year gained will be calculated for both if available.

A first draft of the Recommendations (containing Introduction, Methods and Results)
will be circulated to Task Force members and a second meeting in Zurich will be held
to discuss and finalise [1] the final wording of each proposition (changing wording, but
not content, if required to reduce any ambiguity) and [2] the summary discussion to
accompany each proposition. The strength of recommendation for each will then be
assessed using the EULAR visual analogue scale that takes into account both the
research evidence and expert opinion consensus (8,9). After the second meeting, a
further Delphi round will be undertaken by email to develop up to 10 key
recommendations for future research. The final document will be submitted for publication to the Annals of the Rheumatic Diseases.

**Presentation of recommendations**
The recommendations will be presented and published as a list of specific key propositions (approximately 10 each for diagnosis and management). In addition the Task force will consider development of algorithms, both for diagnosis and management. However, this will only be undertaken if the Task Force finds sufficient evidence to justify an agreed algorithm for either diagnosis or management.

**Relevance of the recommendations**
The recommendations should be relevant to all practising rheumatologists and general practitioners. It is hoped that they will improve the profile and interest in CPPD deposition and lead to improvements both in management and research into CPPD associated arthropathy.

**Dissemination of the Recommendations**
It is proposed that the recommendations are presented at the EULAR Congress in 2010 and subsequently at other national meetings within Europe by the individual members of the Task Force.

The main manuscript will be submitted to Annals of the Rheumatic Diseases. In addition all Taskforce members will be asked to write editorials and summaries of the recommendations in other national rheumatology and general practice journals. It will be explained to the Task Force members that dissemination of the recommendations is as important a responsibility as the initial production of the recommendations.

**Implementation of the recommendations**
The possibility of undertaking an audit of current practice with respect to management of acute pseudogout and chronic symptomatic PA in several countries in Europe will be discussed at the first meeting. Following production and dissemination of the recommendations a second audit could investigate the success of the
Recommendations and their role in any change in standard of care. Such projects would be examined and costed separately from the recommendations themselves.

**Update policy of the recommendations**

The recommendations will need updating, depending on the rate, quality and importance of new studies and trials in CPPD. It is hoped that through development of the recommendations a number of areas will be highlighted where more research evidence is required. It seems likely that an update will not be required until 5-10 years after their initial publication.

**Practical and financial aspects of the project**

Two one day meetings in Zurich will be required:

1. An initial meeting to discuss and confirm the objectives, structure, activity and logistics of the project. This will be in February 2009 (date to be confirmed).

2. A second meeting to discuss and edit the draft recommendations, to determine strength of recommendations, and (if feasible) to design algorithms for diagnosis or management. This will be in Zurich in November 2009 (date to be confirmed). The costs of both these meetings will need to be covered by EULAR.

The recommendations will be finished by February 2010 in time for presentation at the EULAR Congress in June 2010.

The costs of the literature searches, data entry, database compilation, duplicate extractions (to determine reproducibility and accuracy of extraction process), translations and drafting by the lead researcher, Dr Weiya Zhang PhD will be 20,000 Euro. This is to cover essential infrastructure costs (including part-time data enterers, photocopying, library retrieval costs etc) without any contribution to the salaries of either Dr Zhang or our academic co-ordinator (Mrs Helen Richardson) who assists Dr Zhang. This cost estimate is based on our Unit’s experience with the recent EULAR recommendations on diagnosis of hand OA (10) and current recommendations on
diagnosis of knee OA, in which the Nottingham Unit undertook the literature searches and initial drafting of manuscripts. Both Dr Zhang and Mrs Richardson have essential, complimentary infrastructure roles. Dr Zhang is lead researcher and author, whereas Mrs Richardson is an experienced research assistant, co-ordinator and compiler of email Delphi rounds, key liaison person for Task Force members and the key meeting organiser (including personal attendance throughout the meetings to handle logistics relating to the project and unforeseen occurrences).

References


