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A theoretical framework to improve the construct for chronic pain disorders using fibromyalgia as an example

Dinesh Kumbhare and Luigi Tesio

***Abstract*:** Fibromyalgia (FM) is a frequent, complex condition of chronic musculoskeletal pain with no evidence for biological correlates. For this reason, despite many efforts from the medical community, its construct still appears ill defined. Promising candidate biomarkers are critically reviewed. A research agenda is proposed for developing a clearer construct of FM. The ideal theoretical framework is one of overcoming the illness–disease dichotomy and considering reciprocal interactions between biology and behaviour. This approach may foster research in other fields of pain medicine and of medicine in general.

Keywords: chronic pain disorders, fibromyalgia, rehabilitation

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Introduction

Fibromyalgia (FM) is a clinical condition characterised by widespread and persistent pain with insomnia, fatigue, morning stiffness, cognitive symptoms (memory, concentration, attentional problems, mental slowness) and emotional problems (depression and anxiety).[1,2] Its estimated prevalence is estimated at 2–4% of the general population.[2] FM is a complex syndrome that most likely originates from a multi-axial interaction between psychological, neurological, endocrine and immune systems. A detailed review of these is beyond the scope of this article but a brief summary can be found in the literature (2018).[3–6] Of interest here, FM shares with many forms of chronic pain an ill-defined construct. It has been described as an 'enigma' that has been under-, over- and mis-diagnosed.[7] Hauser *et al.* suggest the utilisation of evidence-based interdisciplinary guidelines that include a comprehensive clinical assessment to avoid the problem of inappropriate diagnosis.[7] Despite significant research over the past 30+ years, there exist issues of legitimacy of the condition, the diagnostic usefulness of the label, classification nosology, etiology and pathophysiology.[8] New diagnostic criteria have been proposed as well as recommendations for improved diagnosis by German,[9] European,[10] Canadian and International teams.[11,12] In the context of symptoms without the presence of any universally accepted biomarker, diagnostic criteria were proposed combined with excluding diseases already known for causing chronic widespread pain.[1] We suggest that the proper identification and management requires refocusing on the construct as a unitary disease–illness condition and developing appropriate content of the diagnostic criteria. These should merge into a unique diagnostic algorithm with both clinical features and the bio-markers of pathophysiology.[13]

The construct of FM: a historical perspective

The criteria for FM were originally developed in 1990 by the American College of Rheumatology (ACR) to reflect the prevalence of patients who presented to physicians complaining of chronic widespread pain and tender points.[1] These criteria reflected the fact that, at that time, the consensus opinion about the pathophysiology of fibromyalgia (i.e. the underlying 'disease') was that it was primarily a musculoskeletal disorder. These criteria focussed primarily on the pain. In 2010, the criteria were modified to reflect co-morbid symptoms that contribute to the global suffering (and had been neglected in the past)

Correspondence to:
Dinesh Kumbhare
Department of Medicine, Division of Physical Medicine and Rehabilitation, University of Toronto; Pain Research Institute, Toronto Rehabilitation Institute, University Health Network, 550 University Ave, Toronto, ON M5G 2A2, Canada
dinesh.kumbhare@uhn.ca

Luigi Tesio
Department of Biomedical Sciences for Health, Università degli Studi di Milano, Milano, Italy

Department of Neurorehabilitation Sciences, Istituto Auxologico Italiano, IRCCS, Milano, Italy

included secondary symptoms such as depression, poor sleep, cognitive symptoms, and a minimum of three tender regions.[2] In 2016 new criteria were introduced, which no longer required the clinician to examine the patient for tender points (the only clinically detectable feature suggesting possibly some underlying muscle abnormality or a feature of sensitisation). This was in response to the fact that most physicians in the United States (US) were making the diagnosis of FM without examining for tender points and thus inappropriately applying the 2010/2011 criteria to their patients.[14] Also, the tender point examination was not viewed as a consistent, objective test but having a subjectivity and dependent upon each individual examiner's opinions and abilities to detect them. The emphasis was on whether the patient had chronic widespread pain (using a scale) and on secondary symptom severity: a purely subjective approach. The results took into account aspects of the pain, impact of the condition on the person and severity. However, the evolution of criteria has not been 'anchored' to any pathophysiology or any biomarkers of disease mechanism. An evaluation of the validity of these criteria and the violations of validity analysis can be found in Figure 1 of Appendix A (taken from Kumbhare *et al.*[3]).

Why the present construct of FM is unsatisfactory

One of the major threats to the present approach is that, when the criteria are applied, a highly heterogeneous sample can be obtained.[3] This also arises from using criteria that were based upon freely self-reported symptoms and are applied by healthcare practitioners in different countries, socioeconomic groups and, most important, the lack of a reference standard against which the criteria are developed. Kumbhare *et al.*[3] opined that the criteria rely too heavily upon expert opinion and, furthermore, that there was no specific technique to investigate any underlying pathophysiology. The results of Table 1 suggest that there is acceptable inter-criteria agreement between the 1990 and 2010 criteria but not with the newest 2016 criteria.

The construct of FM: cutting edge of research

To our knowledge, current research suggests that central sensitisation may be an important part of the syndrome's pathophysiology.[15–17] The pattern of expanding pain characterised by hyperalgesia (increased pain in response to normally painful stimuli) and allodynia (pain in response to normally non-painful stimuli) strongly suggested supraspinal rather than purely spinal dysfunction.[18] Moreover, in addition to widespread pain and tenderness, patients experience other symptoms suggestive of central nervous system (CNS) involvement, including fatigue, sleep, mood and memory difficulties, and hyper-sensitivity to sensory stimuli. Specific dynamic quantitative sensory testing (QST) has demonstrated other CNS pain processing abnormalities, including an increase in facilitatory activity (increased wind-up or temporal summation) and decreased descending analgesic activity [conditioned pain modulation (CPM)] as contributory mechanisms to CNS-mediated pain amplification.[19] Ideally, the criteria should include features of this construct.

Possible biomarkers for FM

In the ideal situation, a valid biomarker correlates, both in its level and changes, with clinical outcome. Validation of an outcome measure is far from a simple issue, and proper statistical techniques should be adopted.[20] The same holds for biomarkers. Their validation can be accomplished only by performing a number of therapies on a number of independent cohorts: an enormous work.[21]

To make things even more difficult, there are a number of candidate biomarkers for FM. These include blood-borne biomarkers, imaging, neurophysiology measures and polygenomics assessments. A detailed systematic review is beyond the scope of this article. Kumbhare *et al.* have published a scoping review of relevant biomarkers, which is summarized herein.[3] With regard to blood-borne biomarkers, the literature provides evidence for hypothalamic–pituitary axis perturbations including adrenocorticotropic releasing hormone and cortisol[21–28]; interleukin-6, -8 and -10[29–31]; tumor necrosis factor[30,32–34]; brain-derived neurotrophic factor[35]; and S100β.[35] Radiological assessments also provide biomarkers, such as advanced brain imaging that has shown changes in functional connectivity and blood flow.[36] Furthermore, recent advances in quantitative ultrasound of skeletal muscle have shown discriminative ability between healthy controls and persons with myofascial pain and FM.[37–40] Kumbhare *et al.* used texture feature analysis to examine the B-mode ultrasound images of the trapezius muscle of subjects with myofascial

Table 1. The inter-criteria agreements for the 1990 and 2010 FM criteria available in the literature.

Study	Sample size FM	Sample size controls	Criteria evaluated against 1990 criteria[32]	Inter-criteria agreement
Bidari *et al.*[34]	168	100	2010	0.79
Carrillo-de-la-Pena *et al.*[35]	80	59	2010	0.73
Usui *et al.*[36]	94	43	2010	0.82
Ahmed *et al.*[37]	79	67 (1990 criteria met)	2016	0.47

FM, fibromyalgia.

pain,[41] with latent and active myofascial trigger points, and compared them with asymptomatic healthy controls, finding significant differences. A similar analysis was performed for FM.[42] Neurophysiological assessments have also been developed in chronic pain conditions like FM, headache and osteoarthritis. Current research suggests that central sensitisation may be an important part of the syndrome's pathophysiology, to be included among the features of this construct.[16] The Nociceptive Flexion Reflex (NFR) threshold has been proposed as a potential biomarker candidate that may assist uncovering the neurophysiological pain mechanism that could ultimately play an important role in a more homogeneous diagnostic categorization and an accurate treatment,[43–47] despite its well-known between-subject variability.[48] The NFR threshold has been described to be a marker not only of pain,[49] but also of the neuroanatomical reorganization at the spinal cord segments, specifically laminae II, III and IV of the dorsal horns.[49] The NFR threshold may vary between genders (threshold is lower in women).[50] The neurophysiologic mechanisms of this difference have been investigated.[51] For sure, inclusion of unbalanced sample size of males and females may introduce a biased effect size in the NFR threshold difference between fibromyalgic and healthy individuals.[51,52]

Potential methodology against current shortcomings

For a better understanding of the FM construct, the key to success is perhaps overcoming the old-established dichotomy between disease and illness. A disease refers to an abnormal biological condition that negatively impacts an organism's structure or function,[53] whereas illness usually refers to a patient's personal experience of symptoms or disability.[54,55] In chronic pain disorders, the clinical presentation can be an individual combination of manifestations attributable to the 'disease' as well as the 'illness'. However, the prevalent causal flow is not always straightforward. Often, any evidence for a 'disease' is missing, so that pain is wrongly considered as 'all in the mind' and therefore as non-existing. Recently, however, illness and disease have been claimed to represent the two sides of the same coin: a disease is defined as such (rather than an anomaly) because soon or later, in at least some of the patients, it will lead to an unwanted status of illness; on the other side of the same coin, any psychological states is associated to a specific biological reality, to the least at the level of neural circuitries (the substrate of the recent concept of 'nociplastic' pain).[56] A spiraliform, rather than unidirectional causal flow has been advocated in all health conditions, providing the rationale for treatments acting on the biological as well as on the psycho-behavioural sides of the coin. It is left to empirical research discovering which approaches are most effective in the various conditions.[57]

In agreement with this perspective, and in order to obtain diagnostic criteria based both on reliable biomarker and a reliable subjective-clinical representation, the following methodology is suggested:

a) Define carefully the construct for each syndrome. This is done by first establishing the content validity required within the construct. Measures of symptoms should comply with the highest metric standards for questionnaires.[58] In any case, for FM the ACR-established clinically based subjective criteria do not adequately consider the current understanding of the pathophysiology for FM. In order to do this with methodological rigor, the development of objective, reliable and clinically feasible biomarkers

is necessary. The biomarkers should be a combination of blood-borne biomarkers, neurophysiologic and imaging to appropriately reflect the complexities of the disorder. We would suggest as a start including measures of central sensitisation.

b) Employ the Delphi technique using the existing literature as well as the input from recognised experts would to establish the content validity.

c) Perform analyses on independent cohorts to measure the convergent and discriminant characteristics of the factors associated with the content as identified by the Delphi process described above.

d) Use (a) and (b) to develop the construct. This should be performed by a group of recognised experts and should represent basic science researchers, clinician scientists, clinical epidemiologists.

e) Using the newly agreed upon construct for the disorder a new diagnostic definition and criteria should be created.

f) Diagnostic criteria should then be applied clinically on independent cohorts to assess their impact upon important clinical care outcomes. Once this has been achieved the researchers and academic clinicians may accept it.

g) A decision-tree diagnostic algorithm should be developed, based on the established criteria, and tested with respect to its predictive capacity.

Why solving the FM puzzle might be useful for pain medicine, and medicine in general

Many of the prevalent chronic pain syndromes do not have a reference or 'gold' diagnostic standard (either clinical, biological or both) and are classified according to mostly self-standing, subjective 'criteria'. For example, the International Association for the Study of Pain (IASP)/World Health Organisation (WHO) definition for chronic pain is that of a symptom complex that has been present for at least 3 months. The pain could be characterised as nociceptive, neuropathic or nociplastic (see above). They combine together within a chronic pain patient to result in poor functioning causing disability.[59] Rigorous definition of the 'illness' syndromes and valid measures of the constituent variables would steer research efforts towards specific biomarkers, thus fostering the construction of effective diagnostic algorithms. Syndromes of 'illnesses without disease' extend well beyond the domain of pain, encompassing most psychiatric conditions, 'neurofunctional' motor disorder,[60] dizziness and visceral 'psychosomatic' disorders, and other. A better understanding of FM might thus help treating all of these conditions.

Conclusion

Chronic pain conditions are multifactorial and can involve many body systems and their manifestations blur the disease–illness distinction. Furthermore, the construct for most has yet to be appropriately defined and universally accepted. We use FM – a prevalent nociplastic pain syndrome – to demonstrate some of the shortcomings of the past and current methods of diagnosis. We have set out a potential pathway for future research that defines the construct and establishes its content and through the use of Delphi technique develops new criteria which add physiological markers to the current diagnostic methodology. The critical question remains in choosing the correct biomarker. Ideally, this should reflect underlying disease mechanism or critical pathophysiology, be objective, reliable and feasible.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

Ethical statement

Our study did not require an ethical board approval because this manuscript does not involve an intervention to a human or animal population.

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ORCID iD

Dinesh Kumbhare https://orcid.org/0000-0003-3889-7557

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Appendix A

Table 1. Validity measures for the fibromyalgia American College of Rheumatology (ACR) diagnostic criteria, adapted from Lijmer and colleagues (1999)[20] and Reid and colleagues (1995)[21].

Validity of diagnostic criteria	Accomplished by 1990 criteria	Accomplished by 2010 criteria	Accomplished by 2011 modification	Accomplished by 2016 criteria	Effect on accuracy and generalizability
Specify spectrum of evaluated patients	Yes	Yes	Yes	NA	Limits generalizability of studied sample to the stated demographics
Report test indexes for clinical subgroups	Yes	Yes	Yes	Yes	Indexes of accuracy provided represent the clinical error with the subgroup
Avoid verification bias	Yes	Yes	Yes	NA	Distorts indexes of accuracy
Provide numerical precision for indexes	No	No	No	No	Sensitivity and specificity values are numerically unstable with few or nonrepresentative patients
Specify test reproducibility	No	No	No	No	Limits the capability for the criteria to diagnose outside of the experimental setting
Avoided different reference tests	No	Yes	No	No	Adds variability to reported indexes
Avoided partial verification	Yes	Yes	Yes	NA	Adds variability to reported indexes
Blinded study	Yes	Yes	NA	NA	Prevents bias when determining whether index or reference tests are positive
Consecutive enrolment of patients	Yes	Yes	Yes	NA	If participants are not enrolled randomly or in a consecutive manner then there is a biased sample
Prospective	No	No	No	NA	Overestimation of diagnostic accuracy if test is evaluated in a group of patients already known to have the disease
Description of index test	Yes	Yes	Yes	Yes	Description of tests should be described with sufficient detail to allow for replication, validation, and generalization
Description of reference test	No	Yes	No	Yes	Description of tests should be described with sufficient detail to allow for replication, validation, and generalization

NA, not applicable.

Figure 1. Table from Kumbhare *et al.* evaluating the diagnostic criteria methodologically.[3]

Appendix B: validation of a construct

Construct validation has a number of steps: development of the content of the instrument, composition of the instrument, response characteristics, the relationship of the scores and independent measurements of the same construct and the consequences of using the instrument. Therefore, validity measures the instrument's performance and interpretations. Validity is divided into the following: content, criterion and construct validity. Cronbach defined content validity as 'the extent to which the items of an instrument are sampled adequately from a specified domain of content'.[1] Usually, demonstration of adequate content validity is the first step and deemed necessary prior to the study of other types of validity.[2] This is because, if there is poor content validity, then, according to Norbeck *et al.*, there is 'no sense' in testing the reliability of the instrument. In developing content validity there are three steps.[3] The first is labelled 'development stage', which encompasses domain identification, item generation and instrument (or tool, questionnaire, risk score) formation. Implicit in this process is that the precise definition of the construct has been established. The second or judgement stage entails asking a group of experts to determine whether the relevant content has been included and the adequacy of these domains as well as the extent to which the instrument measures them.[2]

Once content validity has been established then construct validity can be assessed. Construct validity has two parts, convergent and discriminant validity. A common methodological approach to establishing convergent and discriminant validity is to demonstrate that multiple measures of a construct are related or more related to one another than to measures that represent another construct.[4] When interval data are available there are three approaches that can be utilized: multi-trait-multimethod matrix, factor analysis or LISREL (linear structural relations).[5] The first approach uses an analysis of variance to decompose the observed data based upon person, trait and methods variables.[6] A key assumption is that the traits are uncorrelated, which is not necessarily correct. Furthermore, the method has been criticised as being qualitative.[7] For these reasons, most researchers opt not to use this technique. Another approach is to use factor analysis to assess validity. In this approach principal component analysis is performed. This methodology requires 'big data' and provides components which represent the various constructs that are embedded within the dataset.[8] Ideally, many independent large datasets are used and provide similar conclusions with regards to the eigenvalues associated each component. The third (LISREL) approach utilises features of measurement (convergent and discriminant validity) and structural models (nomological validity).[9,10]

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Appendix C

Biomarker Definition

A biomarker is 'A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes or responses to an exposure or intervention'.[1] This National Institutes of Health (NIH) definition covers

molecular, histologic, radiographic or other physiological characteristics and not direct measures of how a person feels or functions. The latter are designated as 'clinical outcome assessments' and represent outcomes of importance to patients. A biomarker represents a scientific or technological concept which may be difficult to measure experimentally. Thus an 'endpoint' variable should be defined to reflect the outcome of interest *and* can be measured reliably, reproducibly *and* be analysed using statistical techniques and modelling.[2] When assessing our example syndrome of FM, it becomes clear that the criteria are not biomarkers, but are in the category of clinical outcome assessment without a defined endpoint variable. There are a number of different biomarkers described by the FDA/NIH BEST working group (Table 2).[3,4]

Table 2. Biomarker type and purpose described by FDA/NIH BEST.

Biomarker type	Purpose
Diagnostic	To detect (or confirm the presence of) a disease or identifies an individual with a subtype of disease. Thus, when evaluating a diagnostic biomarker the key issues are: is there proof that it adds to the diagnosis? And whether the information provided by the biomarker results in a change in clinical decision making?
Monitoring	To assess the status of a disease and is designed to be measured serially. This type of biomarker is used to detect the effect of an intervention and characterise it.
Pharmacodynamic/ response	Changes in response to exposure of a medical product or environmental agent.
Predictive	Predicts the response that an individual or group of individuals may have when exposure to a medical product or environmental agent. The proof that a biomarker can achieve this is provided by an experimental protocol that randomises patients with or without the biomarker to one or more treatments and the differences in outcome as a function of treatment are compared with the presence, absence or level of the biomarker.
Prognostic	To identify the likelihood of a clinical event, disease recurrence or disease progression in patients who have the disease or medical condition of interest. Thus this biomarker is associated with different disease outcomes but a predictive biomarker would provide information about who will or will not respond to a therapy.
Safety	Provides a measure of the likelihood, presence or extent of toxicity when exposure to a medical intervention or environmental agent occurs. It is important to note that this biomarker type does not provide information about the safety and potential benefit of the therapy but only provides a measure of likelihood of occurrence.

BEST, Broadening Experience in Scientific Training; FDA, United States Food and Drug Administration; NIH, National Institutes of Health.

References

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3. Fleming TR and DeMets DL. Surrogate endpoints in clinical trials: are we being misled? *Ann Intern Med* 1996; 125: 605–613.
4. de Abreu Freitas RP, Lemos TM, Spyrides MH, *et al.* Influence of cortisol and DHEA-S on pain and other symptoms in post menopausal women with fibromyalgia. *J Back Musculoskelet Rehabil* 2012; 25: 245–252.