#### **Editorial comment**

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# Laboratory biomarkers of systemic inflammation — what can they tell us about chronic pain?

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### 1 Introduction

In this issue, the article by Gerdle et al. reports on the longterm changes in pro- and anti-inflammatory biomarkers in plasma after treatment in an interdisciplinary multimodal pain rehabilitation program (IMMRP) [1]. This commentary will also include a discussion of the complementary study by Hysing et al. published previously in this journal [2]. The two studies are similar in that they report on a small cohort of complicated patients with chronic pain, primarily functional syndromes that would be classified as Chronic Primary Pain under the new ICD-11 guidelines [3]. Both studies were exploratory without indicating a specific hypothesis other than by using an extensive panel of both pro- and anti-inflammatory biomarkers, elevations from the normal range might be seen pre-treatment and that treatment might affect these biomarkers. The implied assumption, although not stated, was that improvement in symptoms would be associated with a possible decrease in pro-inflammatory biomarkers.

There are some differences between the studies, however. The article by Gerdle et al. investigated a cohort of patients with the primary functional diagnosis of Fibromyalgia Syndrome (FM). Other possible comorbidities present in their population were not stated but FM is rarely an isolated pain problem [4]. The article by Hysing et al. consisted of patients with many comorbid functional diagnoses including FM and this patient cohort has been described in a previous study [5]. I would suspect that the populations were similar as to the presence of similar comorbidities. Both studies do have control populations of those without pain to use for normal values of the biomarkers measured.

The Gerdle et al. article also reports on the changes from before to after treatment using several variables

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including pain, daily activity, depression, anxiety etc., 12 months after treatment and the results were mixed – some were improved, some were worse and some were unchanged. The biomarker changes correlated marginally only with changes in depression and with sitting times despite being generally lower at the 12 month follow-up. The small numbers in each category may not be sufficient to produce reliable statistics.

The article by Hysing et al., unfortunately, does not comment on outcomes after treatment but just that certain biomarkers decreased at 12 months or longer after treatment.

## 2 Mini review

The plethora of studies on inflammatory biomarkers associated with chronic pain in the literature has a similar focus and they are primarily exploratory other than the study by Wang et al. [6] which focusses on IL-8 in fibromyalgia with the hypothesis that treatment would result in a decrease. Their hypothesis was proven correct in a limited cohort of FM patients.

The measurement of the anti-inflammatory biomarkers in most studies seems a bit by accident only because they are usually included in the wide selection of inflammatory biomarkers included in most screening panels [7, 8]. Little emphasis is placed on these which is surprising since they may be just as relevant as the pro-inflammatory biomarkers, especially in regard to improvement after treatment. More studies must be done to clarify, if possible, the relative importance of the pro-and anti-inflammatory biomarkers.

Both studies, Gerdle et al. and Hysing et al., appear to focus on pain as a primary objective of treatment. This ignores the history of IMMRP treatment which was founded by Fordyce [9] using behavioral modification as a base which specifically states that pain relief is not the goal in treatment. The focus is the disability related to pain. To quote Fordyce,

"You are more disabled than the medical evidence would indicate" [10].

Fordyce used this introduction to focus treatment of the pain behaviors, verbal, social, activity-related, that are commonly demonstrated by patients disabled with chronic pain. Changing the behaviors to improve function was the goal, not reduction in pain. Further development of IMMRP with the addition of Cognitive Behavioral Therapy (CBT), mindfulness, etc. has not changed the focus greatly. In the broader context of pain behavior, pain expressed by patients verbally is also just pain behavior and this may or not change with IMMRP even if other pain behaviors do change in a positive way. In the literature looking at outcomes of IMMRP, pain reduction is not too significant although other pain behaviors are usually modified to a somewhat greater extent [11–13].

Why is this point important? There is some indication and an implication that improvement in function has been accomplished in the two programs. Perhaps the association of pro- and anti-inflammatory biomarkers should be tested against improvement in function, mentally and physically, as was attempted by Gerdle et al. This would change entirely the focus of the many studies underway that state that chronic inflammation is associated with chronic pain and too often the studies imply a causative relationship which is yet to be proven. The fact that antiinflammatory biomarkers as well as pro-inflammatory biomarkers have been identified in studies and both change over time, muddies the waters somewhat. Are the pro- and anti- inflammatory biomarkers inter-related? Is this inflammation or are the biomarkers non-specific and just indicators of inflammation on the one hand (acute injury or infection) and stress on the other hand? There is literature that associates an increase in inflammatory biomarkers in subjects/patients with stress (PTSD) [14] and depression [15] Depression is now proposed to be caused by neuroinflammation but, again, cause and affect cannot be interpreted when only associations have been shown.

These two studies present a small window on the biomarkers being investigated in the field of pain, both acute and chronic, and the biomarker research we see here is in its infancy. Other areas researching biomarkers have progressed further, especially brain imaging which has also found predictors for "chronification" after an acute back pain episode [16]. This brings us to the issue of how to go forward with the pro- and anti-inflammatory biomarker research in chronic pain. As Gerdle et al. point out, most studies are small, often uncontrolled and with several other criticisms as to the reliability of the results although the trend is supportive. Hypothesis testing is one step forward instead of testing for a wide variety of pro- and anti-inflammatory biomarkers in the hopes that something positive will be found.

There is limited translation from animal models to human illnesses with chronic pain and this should also go forward. The search for the "holy grail", the key to transitioning from acute to chronic pain is another focus. A recent article from the IMMPACT group [17] addresses this issue. The IMMPACT consortium focusses on the interaction of brain imaging, QST and skin biopsies in neuropathic pain and they "assume that the bulk of the risk for chronic pain is based on brain properties". Where do plasma, cerebrospinal fluid and other tissue sources documenting inflammatory biomarkers fit in this picture? Is neuro-inflammation, another exploding area of research, the key? Why does IMMPACT focus on brain function, skin biopsies, peripheral QST, stress indicators and lifestyle where these areas are usually not parameters considered in the inflammatory biomarker studies? Could it be that the production of inflammatory biomarkers is part of a top down phenomenon where brain changes are primary and the effects (biomarkers of inflammation) are seen in the periphery? Is the presence of inflammatory biomarkers a secondary process just reflecting the central changes in brain function and not the driver of chronic pain as implied in most studies?

Another point lost in many of the chronic pain studies addressing the association of inflammatory biomarkers with chronic pain, exemplified by the Wang et al. study, is the focus on a single pain diagnosis, in this case FM. As can be seen from the data included in the Hysing et al. study, these complicated patients often have more than one diagnosis, not just low back pain, headache, FM, etc. The psychiatric comorbidities were frequent in both studies commented on here. It is clear that stress, depression and anxiety are also associated with elevation of inflammatory biomarkers. To disentangle these associations and then focus on cause and effect as suggested by the IMMPACT group is a daunting challenge.

A final question which all of the aforementioned studies brings up is "what are we looking at"? The focus is on "inflammation" but the classical signs of inflammation other than pain (tumor, calor, rubor) are wanting. Standard measures of sedimentation rates and C-reactive protein levels used to assess systemic inflammation clinically are normal [2]. The exception may be in the significant group of patients with rheumatologic disease where the presence of biomarkers for inflammation may be due to the rheumatic comorbidity, not FM [4]. Perhaps this is not inflammation at all but these biomarkers are associated with both inflammation and chronic pain, restricted activity and psychiatric disorders where evidence for inflammation in the classical sense is lacking. The converse may be that we need a new definition for inflammation that

would include subjects with FM, stress, depression and other functional diagnoses where biomarkers for "inflammation" are present.

## 3 Conclusion

There is a strong need for collaboration between all these research areas to put the whole picture in perspective. Gerdle et al. and Hysing et al. provide information that expands our thoughts about chronic pain but these and similar studies are only beginning to chip away at a very large and polymorphic block of stone that holds many secrets to both acute and chronic pain.

Conflict of interest: The author declares no conflict of interest.

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