Biology of subjectivity in chronic diseases

You can’t see the wood for the trees

This editorial refers to The temporal relationship between depression and rheumatoid arthritis disease activity, treatment persistence and response: a systematic review, by Alan M. Rathbun et al., on pages 1785-94.

To define outcomes in heterogeneous chronic conditions with multiple medical, psychological, social, environmental, phenotypic and epigenetic confounders is complex. This is further complicated when the phenotype is based on a plethora of subjective clinical assessments, i.e. pain, tenderness, fatigue, disability and mood, and observer reliability. RA and depression are both such examples. The complex interrelationship between subjectivity and clinical expression of a disease has led to evolving diagnostic criteria and measurement assessments that get refined, validated and then redefined as a better understanding of the disease process, new biomarkers and newer interventions emerge, and the natural history of disease evolves again.

In this issue of the journal, there is a meta-analysis that examines the relationship between depression and disease activity in RA, suggesting that there is a temporal relationship [1]. Is this due to a correlation of pain, disability, etc. with mood, or is there a fundamental biological cause-and-effect relationship? Anxiety and depression feature in many other musculoskeletal conditions, even in those without significant systemic inflammation [2]. Conditions such as FM, along with other somatoform disorders, have no demonstrable pathological process accounting for the array of subjective symptoms, including change in mood, pain, fatigue and disability. The diagnosis is then based on an accepted pattern that often overlaps within the diagnostic nomenclatures and the diagnosis can change and evolve over time, i.e. often patients seen for the first time with predominant periarticular joint tenderness diagnosed as FM may have a history of irritable bowel syndrome when spasmodic abdominal pain predominated. Yet both conditions can commonly overlap in terms of many other symptoms, i.e. fatigue.

The classification of biologically active compounds produced by cells, e.g. hormones, cytokines, chemokines, neurotrophins and metalloproteinases, causes confusion when relating cellular mechanisms and biochemical endpoints to the clinical expression of a disease process. Thus for the purpose of conceptual simplicity, we summarize these biologically active substances as biokines.

Abnormalities in the neuroendocrine system are well recognized in both depression and RA. Inflammatory biokines are established in the clinical expression of RA. These biokines have also been found to affect various substrates important in the aetiopathogenesis of major depression, including monoamines and glutamate. These are involved in neurotransmission, as well as affecting glucocorticoid receptors, and adult hippocampal neurogenesis. A case–control proteomic examination of controls and patients with severe depression and schizophrenia demonstrated multiple biokine abnormalities [3]. The relationship between depression, inflammatory cytokines IL-1 and IL-6, and CRP has been specifically investigated across a wide range of individuals with chronic disease. Howren et al. [4] concluded that the association between biokines and the degree of depression seemed reliable, but they were unable to determine the direction of the association, i.e. depression influencing biokines, biokines causing depression, or bidirectional. In a further, more detailed review it has been suggested that one-third of patients with major depression show elevated inflammatory markers [5].

There are other pointers to imply that biokines can directly influence mood. It is well established that therapeutic anti-inflammatory compounds such as corticosteroids and therapeutic cytokines such as interferon can have profound effects on a patient’s mood. There are also anecdotal reports of other traditional psychiatric conditions responding inexplicably to therapies that directly affect inflammatory biokines, e.g. anti-TNF therapy in anorexia nervosa [6]. Rheumatologists often observe that in some patients with chronic inflammation, i.e. RA or AS, their mood improves before more objective features of their condition—and who hasn’t felt fed up when laid up with an infection?

This direct and indirect relationship between biokines and mood has naturally led to researchers undertaking pilot studies of therapies targeted at the inflammatory process in patients with depression. A small-scale proof-of-concept study using infliximab in patients with resistant depression demonstrated benefit in those with elevated inflammatory biomarkers [7]. Interestingly our group and others have shown that, along with smoking, depression affects the response to anti-TNF agents, suggesting perhaps a need to alter dosages [8].

Even if the relationship between depression and musculoskeletal disease is a pure correlation and not
biologically linked, it still supports the educational need for the multidisciplinary rheumatology team to include an understanding of psychological assessments and interventions. It is well established that psychosocial counseling is important in musculoskeletal, psychiatric and many other chronically disabling diseases. Do these non-pharmacological interventions also influence biokines and is this as effective as the targeted pharmacological treatments? Can current research and trial methodology really give us a definitive answer?

More than a century ago, Koch postulated four criteria to establish a causal relationship between a causative microbe and disease. These postulates have evolved but have stood the test of time, and although imperfect, e.g. prions not fulfilling the second postulate of in vitro culture, they have proved an invaluable foundation on which our understanding of infectious processes and hence effective treatments became established. The explosion of molecular medicine and the spiralling number of biokines along with a better understanding of disease pathogenesis, newer imaging techniques and epigenetics means orthodox medical scientific methodology is at a crossroads and newer imaging techniques and epigenetics means orthodoxy, perception and silo thinking. Clinical medicine is nearing the zenith of a technological era where a modified clinical construct is justified to improve the patient journey. This will enable the scientist, researcher, clinician, patient and society to move away from understanding a clinical problem traditionally based on a clinician’s diagnosis and assessment to an understanding that also incorporates molecular (biokine) phenotypes, which will then improve the future objectivity of clinical care.

Disclosure statement: The authors have declared no conflicts of interest.

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Accepted 4 March 2013

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References


