Exploring the link between depression and rheumatoid arthritis: prospects for optimal therapeutic success

"Should rheumatologists be responsible for the management of depressive symptoms of their patients? The answer is definitely yes."

Masayo Kojima
Author for correspondence:
Department of Public Health, Nagoya City University Graduate School of Medical Sciences, Mizuho, Nagoya, 467–8601, Japan
Tel.: +81 52 853 8176
Fax: +81 52 842 3830
masayok@med.nagoya-cu.ac.jp

Toshihisa Kojima
Department of Orthopedic Surgery, Nagoya University, School of Medicine

Naoki Ishiguro
Department of Orthopedic Surgery, Nagoya University, School of Medicine

Toshiaki A Furukawa
Department of Psychiatry and Cognitive-Behavioral Medicine, Nagoya City University Graduate School of Medical Sciences

According to the guidelines by the American College of Rheumatology, the goals of managing rheumatoid arthritis (RA) are to prevent joint damage and loss of function, and to decrease pain [1]. Should rheumatologists be responsible for the management of depressive symptoms of their patients? The answer is definitely yes.

Depression is a common comorbidity in patients with RA, with a prevalence of 13–20% [2,3]. Patients with RA are twice as likely to be depressed as people in the general population [4]. Depression is commonly associated with pain [5], which is a chief complaint of RA, along with poor prognosis [4]. The importance of assessing depression among RA patients has been repeatedly proposed [3,6]. However, according to a recent article by Sleath *et al.*, rheumatologists rarely discuss depression with their patients during medical visits [7].

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We examined the association between pain and depression in 218 outpatients with RA [8,9]. The level of inflammation was measured by C-reactive protein (CRP), and depression was assessed using the Beck Depression Inventory (BDI-II), a validated self-report scale of depression [10]. Data indicated that both inflammation and depression severity were significantly associated with pain, even after adjustment for clinical covariates in regression analyses. In logistic analysis, the combined effects of inflammation and depression in the presence of severe pain were linearly increased by the CRP level and depression severity, independently.

Two different kinds of persistent pain are known to exist: nociceptive/inflammatory pain and neuropathic pain [11]. While nociceptive/inflammatory pain is caused by injury or inflammation-stimulating nociceptive receptors at the periphery of the nervous system, neuropathic pain occurs as a result of lesion or dysfunction of the peripheral or central nervous system [12]. Our findings support the coexistence of the two kinds of pain in RA patients. Nociceptive pain is responsive to anti-inflammatory therapy, whereas neuropathic pain is complicated and difficult to treat. Antidepressant and antiepileptic drugs are commonly prescribed for neuropathic pain [13]. Also, nonpharmacological treatments, such as cognitive-behavioral therapy, are solely or additionally available. However, there is no sovereign remedy for neuropathic pain. Patients should be treated physically and mentally, based on the formulation of each patient's problems [5].

Rheumatoid arthritis is a chronic inflammatory disease, the etiology of which is not fully understood. There has been no fundamentally curative therapy for RA for a long time. Currently, dramatic improvements in biologic and nonbiologic disease-modifying antirheumatic drugs (DMARDs) enable us to achieve remission in most cases. When treatment is started at an early stage, an increasing number of RA patients can obtain disease control without joint damage. If DMARD therapy is started without delay, the prevalence of depression among RA patients might be decreased and the impact of depression on RA prognosis could be minimized. However, DMARDs have their side effects. Due to their toxicities, they cannot be prescribed for patients who have liver and/or kidney dysfunctions. Patients suffering from infectious diseases are also unable to take DMARDs. Some patients must discontinue DMARD therapy due to severe side effects or cost constraints.

We are at the next stage of considering ways to support those patients who cannot benefit from DMARDs. Support for the psychological

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problems for such patients is essential. Moreover, since depression is known to be associated with poor adherence to drug treatment, patients who were experiencing depressive symptoms before the initiation of therapy, are more likely to have problems. Therefore, to achieve the best RA management, psychological assessment and support are equally necessary for all patients.

It is argued that rheumatologists do not have enough time to assess their patients' depressive symptoms in the clinic [6]. However, simple questionnaires such as the Primary Care Evaluation of Mental Health Disorders Patient Health Questionaire (PHQ-9) [14], Hospital Anxiety and Depression Scale (HADS) [15] and BDI-II [10] exist, which are validated depression screening tools and take only 2–5 min to be completed in the primary care setting [16]. Additionally, two specific questions are commonly used to screen for depression [17]. First, for example, a patient can be asked, 'during the past month, have you often been bothered by feeling down, depressed, or hopeless?', or 'during the past month, have you often been bothered by little interest or pleasure in doing things?' If patients endorse any of the two questions, they may at least have mild depression and should be assessed further.

> *"The association between systemic inflammation and depression has attracted attention because they share some physiological process and may have some common role in the development of cardiovascular disease."*

According to the consensus statement of the UK experts in the management of depression in general practice [18], patients who have moderate-to-severe depression should take antidepressant medication. It is not conclusively known whether patients with mild depression should be treated with antidepressants. Counselling and psychosocial approaches are necessary for all patients who endorse depressive symptomatology.

Some small clinical trials have reported the benefits of tricyclic antidepressants in the management of depression and pain control among RA patients, and most selective serotonin reuptake inhibitors (SSRIs) and serotonin–noradrenaline reuptake inhibitors are suggested for the treatment of fibromyalgia syndrome [19]. Compared with traditional tricyclic antidepressants, SSRIs and serotonin–noradrenaline reuptake inhibitorss are less toxic and have fewer side effects; therefore, they are popular among elderly and physically ill patients. However, there is little evidence regarding treatment of RA patients using these medications. Further controlled studies are required to determine the optimal use of antidepressants for the management of depression and pain control among RA patients.

The association between systemic inflammation and depression has attracted attention because they share some physiological processes and may have some common role in the development of cardiovascular disease (CVD) [20]. Experimental studies support the bidirectional associations between depression and inflammation involving the neuroendocrine and autonomic nervous systems [21]. RA patients commonly experience both depression and inflammation. Moreover, CVD is a common comorbidity among RA patients and is the leading cause of premature death among RA patients. Although the mechanism of increased CVD risk among RA patients has not been fully disclosed, it is suggested that chronic systemic inflammation plays a major role [22]. Depression is an established risk factor for the development and prognosis of CVD. Even though depression and CVD are both common comorbidities in RA patients, depression has rarely been discussed in relation to the increased risk of CVD in RA. A recent empirical study suggests a possibility of SSRIs as anti-inflammatory drugs for RA patients [23]. RA patients may experience additional benefits from antidepressants in decreasing depressive symptoms that may prevent premature CVD mortality.

In conclusion, rheumatologists must pay attention to their patients' depressive symptoms and provide appropriate guidance, including referrals to specialists, if necessary. Future studies should help clarify the best way to manage depression associated with RA and the extent to which such treatment may benefit RA patients.

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