Depression in patients with rheumatoid arthritis: description, causes and mechanisms

Two sets of contributory factors to depression among patients with rheumatoid arthritis (RA) are generally examined – the social context of the individual and the biologic disease state of that person's RA. This article will review the evidence for both. RA affects patients both physically and psychologically. Comorbid depression is common with RA and leads to worse health outcomes. Low socioeconomic status, gender, age, race/ethnicity, functional limitation, pain and poor clinical status have all been linked to depression among persons with RA. Systemic inflammation may also be associated with, cause, or contribute to depression in RA. Understanding the socioeconomic factors, individual patient characteristics and biologic causes of depression in RA can lead to a more comprehensive paradigm for targeting interventions to eliminate depression in RA.

KEYWORDS: depression ■ disability ■ pain ■ rheumatoid arthritis ■ socioeconomic status ■ systemic inflammation

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Health effects of depression in rheumatoid arthritis

Chronic medical conditions are associated with an increased risk of depression and suicide [1]. Rheumatoid arthritis (RA), a chronic illness that affects 1.3 million adults in the USA [2], is a systemic inflammatory disease that affects people both physically and psychologically. Major depressive disorder is common in patients with RA, with a prevalence of 13–42% [3–9], at least double to four-times that in the general population. The wide range in the prevalence of depression in clinical studies of RA is likely due to the different methods used for measuring depressive symptoms. In patients with RA, poor clinical characteristics and function are associated with subsequent depressive symptoms [10].

Depression affects patients with RA beyond the burden of mental illness itself. Patients with RA and comorbid depression have worse health outcomes. Depression, a treatable condition, increases the risk of mortality in RA [11]. Specifically, depression in patients with RA is an independent risk factor for cardiovascular disease [12] and myocardial infarction [13], suicidal ideation [14,15] and death [11,16–18] even after controlling for RA disease duration, disease activity, disability and pain. Also, patients with RA and associated depression have increased health service utilization [19] and are less likely to be adherent with their medications [20,21]. In addition to these negative health consequences, depression may contribute to unemployment, loss of work productivity and increased healthcare costs in persons with arthritis [22,23].

Comorbid depression in RA is especially troublesome because it often goes unrecognized and/or untreated [24,25]. Depression or depressive symptoms can be easily measured in RA using a variety of measures, from screening tools, such as the Center for Epidemiologic Studies Depression Scale, to diagnostic screening interviews [26], but rheumatologists rarely communicate about depression with their RA patients who have moderately severe-to-severe depressive symptoms [27]. The implication is that the burden of disease due to depression remains largely intact and is not adequately addressed by current health regimens. Addressing both the physical and psychological factors of RA during clinic visits is important because, as noted above, depression can impact mortality, health service utilization, and adherence to medications and self-care regimens. Regardless of whether rheumatologists refer RA patients to mental health professionals, communicate with the patient's primary care physician about the patient's depression or treat the depression themselves, it is important that rheumatologists are aware of the health impact of depression in RA.

As with most complex biologic systems, the relationship between depression and RA is multifactorial: in some cases it is likely that depression is mediated by the socioeconomic results of RA. In other cases, depression may be due to disability from RA, and/or the systemic inflammation from the proinflammatory cytokine milieu of RA. Regardless of the initiating factors, the contributory effect of the socioeconomic, functional

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and biologic consequences of RA can perpetuate depressive symptoms. Understanding the mechanistic components of depression in RA is critical for effective treatment (**Box 1**).

Socioeconomic factors related to depression in patients with RA

The terms 'socioeconomic status', 'social class' and 'socioeconomic position' (collectively known as SES) are broadly employed in health research, signaling the importance of socioeconomic factors for health outcomes. Low SES is generally associated with high psychiatric morbidity, depression [28] and mortality [29]. Poorer coping styles, ongoing life events, stress exposure and weaker social support are some examples of depression risk factors that are more prevalent in lower SES groups [30]. Regarding the direction of the association for SES and depression, results more consistently support the idea that causation (low SES increases risk of depression) outweighs selection (depression hinders social mobility), although both directions may operate simultaneously [28].

There is a substantial body of research linking SES, depression and RA [31,32]. However, despite expert consensus that SES is multifactorial, most health studies of SES in patients with depression and/or RA use a single socioeconomic variable measured at a single period and level [33]. Occupation is frequently used as a measure of SES in Europe [29,34,35] and education or income is more commonly used in the USA [36–38]. Yet, focusing on only one of these measures does not provide a complete picture. Standard occupational categories in the USA are inadequate measures of SES because categories include workers with diverse skills, earnings and/or prestige [39]. Education and income are not transposable and income can differ at similar education levels based on sex, age and racial/ethnic groups [33]. To illustrate this point, a recent US national survey found that multiple measures of SES, including both low educational obtainment and low income are independently associated with poor mental health and arthritis [40].

Box 1. Characteristics associated with depression in rheumatoid arthritis.

- Socioeconomic factors
  - Income
  - Education
  - Employment
  - Race/ethnicity
  - Neighborhood conditions
- Patient factors
  - Gender
  - Age
  - Race/ethnicity
  - Comorbidities
  - Coping mechanisms/social support
- Rheumatoid arthritis disease factors
  - Inflammation
  - Disease activity
  - Pain
  - Functional status/disability
  - Clinical remission

With notable exceptions [32,40–43], few studies of SES and depression in patients with RA have measured multiple indicators of SES. Future studies need more complete and better markers of SES. The importance of race/ethnicity in regard to SES is reflected in bias, culture, access to care, environmental and genetic factors, and should be included as a marker of SES [44]. For instance, arthritis affects some racial/ethnic populations disproportionately [45], and in fact, race/ethnicity has been shown to directly influence differences in depression scores in patients with RA [46]; yet few studies of depression in patients with RA include race/ethnicity as a covariate. When evaluating SES in the context of depression in patients with RA, future studies should acknowledge that socioeconomic factors interact with other social characteristics, such as race/ethnicity, to produce different health effects across groups. Not assessing SES differences that occur by income, education, race/ethnicity and geographic location ignores health disparities [47].

Another frequent omission in evaluating SES in patients with RA is neighborhood socioeconomic conditions. Despite increasing recognition that both individual and neighborhood level SES can influence health, few studies of depression in patients with RA measure neighborhood features. One prominent exception is a study by Harrison *et al.* that found significant relationships between area of residence and measures of health in patients with RA. Results suggested that patients from more socially deprived areas are more likely to experience more depression and poorer emotional health [41]. We recommend that future studies include measures of individual income, education, occupation, race/ethnicity and neighborhood socioeconomic conditions. If these variables are not included, then the missing measures should be identified as absent when stating conclusions.

Patient & RA disease factors related to depression

Female gender and younger age have well-known associations with depression and confound the

SES-depression relationship in RA [4,5,36,48]. As women have a higher prevalence of RA and depression, ignoring gender will falsely increase the magnitude of other variables associated with depression. Conversely, overlooking age tends to suppress other covariate effects because age has a U-shaped relation with depression [49]. As mentioned above, race/ethnicity is an important factor to include in measures of SES but is also a patient characteristic independently associated with depression in RA. Specifically, Asians with RA report less depression [46] while Hispanics with RA, particularly those who are not fully acculturated to mainstream Anglo society, report more depression [50].

Comorbidities and pain are commonly associated with both RA and depression [51,52]. Not surprisingly, pain has been indicated as a mechanism along the causal pathway for depression in those with RA [53–56]. Furthermore, depression may confound self-reports of pain [57]. Alternatively, pain in a patient with RA and comorbid depression could be diagnostic overshadowing – a process where the physical symptoms of RA are misattributed to depression [58].

There is conflicting evidence as to whether or not RA disease activity measured by rheumatologist-documented swollen, tender joints affects depression. Some studies show a positive correlation between depression and RA disease activity scores [59–61] while others do not [32,46]. Regardless of acute disease activity measures, there is no doubt that limited function, as measured by the Health Assessment Questionnaire, is a strong predictor of depression in patients with RA [5,10,11,54,56,59,62,63]. Taking this one step further, loss of valued activities beyond functional decline has been shown to lead to depression [10,63]. This suggests that depression in RA may not be caused by the acute clinical manifestations of RA disease activity but instead caused by the long-term disability and joint damage associated with arthritis that results in the loss of valued activities.

With regard to RA disease treatment, it is not unexpected that patients who achieve clinical remission are less likely to remain depressed compared with those who do not achieve RA remission [59]. The converse is true as well – patients who exhibit persistent depressive symptoms have poorer response to treatment and smaller reductions in their DAS28 scores [64]. A common element in the proposed mechanisms linking patient and RA disease characteristics to depression is the ability to adapt to the burden of RA disease and its treatment [62]. Positive coping mechanisms, social support (i.e., being married) [3,19] and having a sense of control over one's RA are also associated with decreased depressive symptoms [31].

Inflammation & depression in patients with RA

More recent studies have shown that systemic inflammation, measured by acute-phase reactants and proinflammatory cytokines, are often associated with the development of depression [65–67], and it has been suggested that systemic inflammation may be associated with, cause, or contribute to depressive symptoms during disorders of chronic inflammation [68–70]. In patients with RA, there is conflicting evidence regarding the association of the acute-phase reactant, high-sensitivity C-reactive protein, with depression [54,71]. The hypothesis that systemic inflammation contributes to the high prevalence of depressive symptoms in patients with RA is supported by the following observations.

First, inflammatory cytokines and acute-phase reactants are increased in depressive symptoms in patients without RA. Compared with nondepressed individuals, depressed patients have activated inflammatory pathways, including increased expression of chemokines, adhesion molecules and cytokines [72–74]. Patients with major depression have increased serum and/or plasma concentrations of C-reactive protein [75,76], IL-6 [77,78] and proinflammatory TNF-α [79–82]. Elevations of these cytokines and acute-phase reactants exist in both serum and cerebrospinal fluid in depressed patients [83–86]. Furthermore, experimental human studies have demonstrated development of depressive symptoms following infusions of cytokines such as IFN-α [87,88].

Second, elevated levels of cytokines such as IL-6 and TNF-α may predict nonresponse to treatment for depressive symptoms. Prior data show that depressed patients with increased inflammatory biomarkers may be less likely to respond to conventional antidepressant treatments [89]. Also, patients with a history of poor response to traditional antidepressants have increased plasma levels of IL-6, TNF-α and acute-phase reactants [90–92]. In addition, depressed patients with higher levels of TNF-α experience a decrease to normal control values after antidepressant treatment [81].

Third, there is evidence that anti-inflammatory therapies have clinical benefit in reducing depressive symptoms. Acetylsalicylic acid, which blocks COX-1, COX-2 and the production of

prostaglandins, when combined with fluoxetine led to higher remission rates in an open-label study of depressed patients previously nonresponsive to fluoxetine alone [93]. Also, in a randomized trial, depressed patients who received the selective COX-2 inhibitor, celecoxib, in combination with reboxetine demonstrated fewer depressive symptoms compared with patients receiving reboxetine and placebo [94].

Fourth, it has been suggested that medications such as traditional disease modifying antirheumatic drugs and biologics influence the relationship between inflammation and depression in patients with RA. Randomized placebo-controlled trials have demonstrated that prednisone, disease modifying antirheumatic drugs and TNF-α antagonist medications have improved quality of life and functional outcomes in patients with RA, but few have specifically evaluated their effect on depressive symptoms. One study has shown that patients with persistent depressive symptoms tended to respond less well to anti-TNF, with smaller reductions in RA disease activity [64]. A randomized trial of etanercept for the treatment of another autoimmune disease, psoriasis, showed that participants receiving the TNF-α antagonist medication had significant improvement in depressive symptoms independent of improvement in disease activity [95].

The interactions between predictors of depression in patients with RA

None of the factors associated with depression in patients with RA exist in a vacuum. For example, a significant interaction exists between socioeconomic status and disability [43] for patients with RA and comorbid depression. The association of disability with depression was stronger for persons of lower SES compared with those with higher SES. The tacit assumption that disability and socioeconomic status have independent consequences on depression in patients with RA does not hold. One potential explanation is that at every level of functioning, persons from lower SES may not have the support or coping resources to perform as well as those from higher SES, leading to even higher rates of depression. RA affects people both physically and psychologically, and by focusing on the interactions between societal, individual, contextual and biologic causes of depression in RA, rheumatologists can consider a more comprehensive paradigm. This is true for other autoimmune diseases as well, such as systemic lupus erythematosus, where low SES is associated with health disparities in patient traits, levels of systemic disease/inflammation and a high prevalence of depression all coexist [96–98].

Future perspective

With the current national goals of public health research, we should anticipate effective policy development and interventions for reducing health disparities associated with SES, depression and RA. In addition, the rapid advances in immunology may lead to more persuasive data that systemic inflammation contributes to depression in RA. The first step has been made of acknowledging the high prevalence of depression in RA and its serious negative health outcomes. Now, rheumatologists must consider depression as a consequence of both social context and biologic RA disease factors in order to assess which aspects contribute the most to depression in patients with RA. In the next 10 years, rheumatologists can substantially decrease depressive symptoms in their patients by addressing the root causes of depression: preventing pain and disability, decreasing systemic inflammation and designing and implementing evidence-based programs to mitigate the effects of depression in RA [99,100]. This entails moving beyond associations to establish causal relationships that in turn can lead to new and targeted therapies for depression in patients with RA.

Executive summary

- Rheumatoid arthritis (RA) affects people both physically and psychologically and comorbid depression is common with a prevalence of 13–42%.
- Patients with RA and depression have worse health outcomes, including poor medication adherence, increased health service utilization, pain, disability and death.
- Low socioeconomic status is associated with depression in RA and should include measures of income, education, occupation, race/ethnicity and neighborhood conditions.
- Patient characteristics associated with depression in RA are female gender, younger age, race/ethnicity, poor coping mechanisms and decreased social support.
- Rheumatoid arthritis disease factors associated with depression in RA include pain, functional status and clinical remission.
- Systemic inflammation may contribute to depression in patients with RA.

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▪ **Discusses how to identify patients in clinical practice with depression and rheumatoid arthritis.**

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