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MEDICINE

Rheumatoid Arthritis, Depression, and the Role of Celecoxib

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Abstract

Rheumatoid arthritis (RA) is a chronic autoimmune disease, causing joint destruction and associated physical, mental, and financial distress. Depression is not uncommonly found in patients with RA as both disorders share sociodemographic, functional, and biologic factors. There is growing evidence on the role of anti-inflammatory agents in managing depression, particularly celecoxib, which has been shown to significantly alleviate depressive symptoms as an augmenting agent. Compared with traditional nonsteroidal anti-inflammatory drugs (tNSAIDs), however, celecoxib offers modest improvement in clinical symptoms, with uncertain results for pain management, physical function, and adverse effects in patients with RA. Further research is needed to assess the effectiveness of celecoxib in the management of RA, particularly in patients suffering from comorbid depression.

Keywords Rheumatoid arthritis · Depression · Inflammation · Celecoxib

Abbreviations

BSRBR	British Society for Rheumatology Biologics Register
CBT	Cognitive behavioral therapy
DALY	Disability adjusted life years
DMARDS	Disease-modifying antirheumatic drugs
HAM-D	Hamilton Depression Rating Scale
HRQOL	Health-related quality of life
IL	Interleukin
RA	Rheumatoid arthritis
RCT	Randomized controlled trial
SNRIs	Serotonin-norepinephrine reuptake inhibitors
SSRIs	Selective serotonin reuptake inhibitors
T1DM	Type 1 diabetes mellitus
TCAs	Tricyclic antidepressants
TNF-α	Tumor necrosis factor-alpha
tNSAIDs	Traditional nonsteroidal anti-inflammatory drugs
US	United States

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Introduction

Rheumatoid arthritis (RA) is a chronic, autoimmune disease that causes joint destruction and affects patients physically, mentally, and financially [1–3]. It is a multifactorial disease, with a sequela of genetic and environmental interactions [2]. About 1.3 million adults suffer from RA in the United States (US) [4], and studies in Northern Europe and North America estimate a prevalence of 0.5–1% [2]. In a 15-year prospective study in the Netherlands, the mortality rate in patients with RA was 54% higher compared with the general population, with a standardized mortality ratio of 1.54 (95% CI 1.41–1.67) [5].

Patients with RA are more likely to suffer from depression and anxiety, with onset of psychological distress associated with RA-related disability [6]. The British Society for Rheumatology Biologics Register (BSRBR) found 1491 (19%) out of 7818 patients receiving disease-modifying antirheumatic drugs (DMARDs) to suffer from depression [7]. Abdul Rahim et al. reported 23.3% depression rate in patients who attended the RA clinic in Malaysia [8], and a 2013 systematic review by Matcham et al. including 72 studies (13,189 patients) found the prevalence of depression 16.8% (95% CI 10%, 24%) in patients with RA [9]. Abdel-Ahad et al.'s more

recent literature review of 47 references revealed a 13–48% prevalence of anxiety and depressive disorders in patients with RA [10]. After adjusting for covariates, Marrie et al.'s cohort study found a higher incidence of depression (incidence rate ratio [IRR] 1.46 [95% confidence interval (95% CI) 1.35–1.58]) in patients with RA compared with matched controls [11]. These rates approximate and sometimes exceed the prevalence of major depression in other illnesses. For instance, the estimated rate of major depression in type 1 diabetes mellitus (T1DM) is 12.0% [12], 17% in Parkinson's disease [13], and 16.5% among patients in palliative care [14]. Vallerand et al.'s review underlined the role of depression as a significant risk factor with unfavorable disease course and prognosis in patients with RA, highlighting the bidirectional relationship between both disorders [15]. Several sociodemographic and biological factors contribute to the increased prevalence of depression in patients with RA.

Demographics

Depression is the leading cause of disease-related disability among women [16]. Worldwide, women are more likely to suffer from depression, with significant gender disparity in adolescence [17]. The median age of onset for depression is mid to late 20s [18], and results from the National Comorbidity Survey Replication of over 9000 US adults found the prevalence of depression less common in those aged 65 years or older [19]. RA is similarly more prevalent in women, with 3:1 female to male ratio [20]. Although the incidence of RA increases with age [21], a cross-sectional study by Dargham et al. showed that patients diagnosed with RA in Qatar, Jordan, Lebanon, Saudi Arabia, and United Arab Emirates are around 10 years younger compared with the RA population studied in Northern Europe and North America, raising the hypothesis of genetic anticipation as a possible interpretation of the younger onset in this region [22].

Depression, Functionality, and Disease Severity in RA

Depression is projected to contribute the highest disease burden in 2020 as measured by disability-adjusted life years (DALY) [23] and is associated with poor medication compliance in RA [24]. Similarly, patients suffering from arthritis report poorer health-related quality of life (HRQOL) and are more emotionally unwell compared with persons without [25]. A 2013 cross-sectional study in Brazil found an association between moderate-severe RA and major functional disability and morbidity, with work and activity impairment increasing with disease severity [26]. This could affect patients' socioeconomic status, inversely associated with higher rates of depression [27]. Patients with RA report lower scores for social relationships and close attachment [28], found by The National Population Health Survey to almost double the risk of depression [29].

Pro-inflammatory Cytokines in Depression and RA

Inflammation, chronic stress, and infection activate microglia, releasing pro-inflammatory cytokines and activating the hypothalamic-pituitary axis. The resultant imbalance in serotonergic and noradrenergic pathways contributes to the onset and recurrence of depression. Elevated cytokines such as interleukin-6 (IL-6), tumor necrosis factor TNF-α, and IL-1β enhance indoleamine-2,3-dioxygenase activity, catalyzing the breakdown of tryptophan and depleting serotonin [30]. It has also been hypothesized that inflammatory cytokines activate different structures in the brain such as the medial prefrontal cortex, hippocampus, anterior cingulate cortex, and basal ganglia which are associated with behavior and known to function differently in patients with depressive disorders [31]. Depression is associated with increased pro-inflammatory cytokines, and patients not responding to antidepressant treatment are more likely to have elevated cortisol and pro-inflammatory markers [32, 33]. A longitudinal study of 4500 individuals found subjects with higher levels of IL-6 at age 9 years more likely to develop depression (adjusted odds ratio [OR], 1.55; 95% CI, 1.13–2.14), psychotic experiences, and psychotic disorder (adjusted OR, 1.81; 95% CI, 1.01–3.28; and adjusted OR, 2.40; 95% CI, 0.88–6.22, respectively) at 18 years of age [34]. Likewise, RA patients are in a chronic state of inflammation, with C-reactive protein (CRP) levels correlated with disease severity [35] and pro-inflammatory cytokines such as IL-17, IL-18, TNF-α, and RANK ligand involved in pathophysiology [36]. Risk factors related to increased oxidative stress and inflammation, such as obesity and smoking, can hence increase the prevalence and worsen both depression and RA [37–40].

Management

Updated guidelines aim for prompt recognition of RA among patients with inflammatory arthritides [41], earlier referrals to rheumatology services, more consistent use of DMARDs, with subsequent reduction in joint pain and swelling and increased likelihood of achieving DMARD-free remission [42, 43]. Pharmacological interventions involve the use of synthetic and biologic DMARDS, tNSAIDs, and glucocorticoids, with drug choice depending on disease stage and severity, medical comorbidities, and prior response to treatment regimens [44]. Alleviating comorbid depression involves patient

education about the role of stress, smoking, and obesity in accentuating oxidative stress, guidance towards healthier lifestyle choices, management of mood symptoms, and referral to psychiatry services as indicated [37–40]. Despite its efficacy with mood disorders [45], cognitive behavioral therapy (CBT) has weak and non-sustainable effect in improving pain and disability [46]. Psychopharmacological intervention involves different classes of antidepressants such as selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and tricyclic antidepressants (TCAs) and, in cases of treatment resistance, combination of more than one antidepressant or augmentation with lithium, thyroid hormone, and antipsychotics, among other agents [47].

There has been growing evidence on the role of anti-inflammatory agents in the management of depressive symptoms, particularly celecoxib. Chronic treatment with celecoxib attenuated depressive-like behavior and significantly reversed biochemical alterations associated with obesity in mice [48]. It has also been shown to protect against depressive states in mice injected with beta amyloid peptide and prevent the reduction in prefrontal serotonin content [49]. In 2006, the addition of celecoxib to reboxetine for the treatment of depression yielded significantly lower HAM-D (Hamilton Depression Rating Score) scores compared with controls [50]. These findings were replicated by two other randomized controlled trials (RCTs) which found the augmentation of fluoxetine or sertraline with 400 mg of celecoxib significantly superior to antidepressants alone in the management of depression [51, 52]. Halaris et al.'s recent RCT emphasized celecoxib's role as a safe and efficacious augmenting agent in the management of anxiety and depressive symptoms in patients with treatment-resistant bipolar depression [49]. The antidepressant effect of celecoxib has been correlated with reductions in inflammatory markers such as IL-6 and CRP, further supporting the role of inflammation in the biological etiology of depressive symptoms [49, 52]. Celecoxib has also shown efficacy in alleviating depressive symptoms in brucellosis and colorectal cancer patients [53, 54] and superiority to diclofenac in managing depressive symptoms in breast cancer patients [55]. A RCT protocol has been recently published aiming to assess the efficacy of augmenting vortioxetine with celecoxib in managing depression, with stratification based on inflammatory state at baseline [56]. Celecoxib however does not seem to possess similar antidepressant effect in older adults, as Fields et al.'s RCT in 2011 of 2528 subjects aged 70 or above showed no significant improvement of depressive symptoms after receiving naproxen or celecoxib for 12 months [57]. Other anti-inflammatory agents, such as aspirin yielded conflicting results in ameliorating and preventing depressive symptoms [58–60].

Celecoxib is approved for RA treatment as an anti-inflammatory and analgesic agent. Fidahic et al.'s meta-analysis of eight RCTs found celecoxib superior to placebo in clinical improvement (15% absolute improvement; 95% CI 7% to 25%; RR 1.53, 95% CI 1.25 to 1.86) and pain relief (11% absolute improvement; 95% CI 8% to 14%), with trivial difference in physical function. Compared with tNSAIDs, however, celecoxib offered a small difference in clinical symptoms (4% absolute improvement; 95% CI 0% less improvement to 8% more improvement; RR 1.10, 95% CI 0.99 to 1.23), with inconclusive findings in pain management and physical function. There is uncertainty in the risk for cardiovascular events and short-term serious adverse events, with small sample size, short duration of RCTs, and risk of bias standing as possible contributors to the inconclusive findings [61]. Nevertheless, the use of celecoxib seems beneficial compared with tNSAIDs due to reduced gastrointestinal events, and further research is needed to assess its safety in higher doses and in patients with cardiovascular comorbidities [62]. No studies currently exist assessing the efficacy and tolerability of celecoxib in the treatment of RA patients suffering from depressive symptoms.

Conclusion

The comorbidity of depression in rheumatoid arthritis surpasses that of other illnesses such as T1DM and Parkinson's, with higher prevalence in women owing to common sociodemographic, functional, and pathophysiologic factors. A biopsychosocial approach should be adopted in managing RA with comorbid depression, emphasizing the role of healthier diet, smoking cessation, and other measures in reducing oxidative stress. Celecoxib has been shown to possess antidepressant effect as an augmenting agent in managing depression, and further research is needed to assess its effectiveness in managing clinical symptoms, pain, and physical function in RA compared with tNSAIDs. There are currently no studies assessing the efficacy and safety of using celecoxib in RA patients with comorbid depression, and efforts should be directed towards examining the cost-effectiveness and utility of screening RA patients for depressive symptoms and the subsequent use of celecoxib as an analgesic, anti-inflammatory, and antidepressant agent in this population.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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Informed Consent N/A

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