The emerging role of mood disorders in inflammatory bowel diseases

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Abstract

Inflammatory bowel diseases (IBD) are chronic, devastating conditions of the gastrointestinal tract characterized by a complex pathogenesis, increasing worldwide prevalence, a wide spectrum of extraintestinal manifestations, and a reduced health-related quality of life (HRQoL). Furthermore, mood disorders, specifically anxiety and depression, are more prevalent among IBD patients compared to the general population. The connection between mental disorders and IBD is compound, bidirectional and still not fully understood. The IBD may impact psychological health, whereas anxiety and depression are associated with a more aggressive course of IBD. The inflammation process, gut microbiota alterations and drug side effects are factors that influence the mental state of patients with IBD. Importantly, despite the high prevalence of depression and anxiety in IBD, many of the current guidelines do not include clear recommendation for assessment of mental problems in patients and further management. Therefore, monitoring for mood disorders should become a part of the multi-disciplinary and holistic approach to patients with IBD. This review is based on current literature searched in PubMed, mainly considering publications from the last 10 years.

Key words: depression, anxiety, inflammatory bowel disease, ulcerative colitis, Crohn’s disease

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Introduction

Inflammatory bowel diseases (IBD), encompassing ulcerative colitis (UC) and Crohn’s disease (CD), are chronic, devastating conditions of the gastrointestinal tract, characterized by a relapsing course with periods of flares and remissions and the presence of the wide spectrum of extraintestinal manifestations (EMs). The prevalence of IBD is increasing worldwide, especially in highly developed countries, where about 0.3% of the population is already suffering from them, and in newly industrialized regions of the world. For instance, in Canada, one of the countries with the highest incidence of IBD, it is estimated that 0.9% of the population will be affected in 2025, whereas in China there will be over 1.5 million cases of IBD by that time. Furthermore, the etiopathogenesis of IBD has not been fully elucidated. The key role in the development of the disease is played by the interaction of genetic, immunological, microbiological, and environmental factors. Consequently, there are no single diagnostic tests, and despite the introduction of novel biological treatment strategies, effective therapy remains unavailable. Additionally, it has repeatedly been demonstrated that the health-related quality of life (HRQoL) of IBD patients is significantly reduced. For example, a recently published meta-analysis, which encompassed 7154 patients, demonstrated that in all 19 studies included, the QoL levels in IBD patients compared to healthy controls were poorer in at least 1 aspect. Furthermore, almost 40% of IBD patients in remission suffer from fatigue, which has a negative impact on HRQoL independently of disease activity. Last of all, anxiety and depression disorders are more prevalent in IBD patients compared to the general population, and the interrelation between the conditions is unclear. The gut–brain axis and interference of numerous agents in communication between the gut and the brain seem to play a crucial role. Among the suggested mechanisms are activation of the inflammatory response in the brain, compromised blood–brain barrier integrity and the impact of gut microbiota. The results of studies on the impact of mental disorders on IBD onset and course are inconclusive. Additionally, in a recently published study it was demonstrated that patients with anxiety, depression and immune-mediated disorders (including IBD, multiple sclerosis and rheumatoid arthritis) had reduced cognitive function. Moreover, ½ of IBD patients with depression and ⅓ of those with anxiety remained undiagnosed. It also has to be emphasized that all the aforementioned factors, along with the fact that the onset of IBD is associated with young age, indicate not only the necessity of further research, but above all the importance of including the mental aspects in IBD patients’ care.

Epidemiology of depression and anxiety disorders in patients with IBD

Patients with IBD have a 2- to 4-fold greater risk of developing depressive disorders and a 3- to 5-fold of greater risk of developing anxiety disorders than the general population. Many cases of psychiatric disorders remain undiagnosed. Many studies have repeatedly demonstrated that psychological problems are more common in patients with active disease compared to those in remission; that patients with CD are at higher risk than those with UC; and that women are affected more often than men. However, the occurrence of depression and anxiety in IBD is similar or even less frequent than their occurrence with other chronic disorders (Table 1).

Furthermore, in a large study conducted in Canada, the prevalence and incidence of depression, anxiety, bipolar disorders, and schizophrenia were higher in IBD individuals than in a matched cohort of the general population. The study, comprising more than 6000 IBD patients, showed that women were more often affected by depression and anxiety than men. However, the authors also observed that the incidence of psychiatric disorders was higher in individuals aged 18–24 years, in urbanites and in individuals of lower socioeconomic status. There is a growing body of evidence that the prevalence of mental health problems in IBD patients is increasing. For instance, in a cohort of more than 60,000 US veterans with IBD, the annual age-standardized prevalence rates of depression and anxiety increased respectively 3.75-fold and 5-fold in the years 2001–2015.

Selected studies evaluating the prevalence of anxiety and depression disorders and associated factors among IBD patients are presented in Table 2.

Gut microbiota

Gut microbiota is involved in IBD pathogenesis and is simultaneously among the crucial factors interfering with the gut–brain axis. Therefore, the gut microbiome can be a link between IBD and mental disorders. Characteristic
differences in the abundance of individual microbiota species in IBD patients with associated anxiety and depression disorders as well as reduced HRQoL have been identified. Dysbiosis is associated with abnormal metabolism of tryptophan, which under normal conditions passes through the blood–brain barrier and becomes a precursor of serotonin. In an alternative pathway, especially intensified in the case of intestinal inflammation, tryptophan can be metabolized to kynurenine and its derivatives, leading to the development of depressive disorders both by the direct action of these substances on neuronal transmission and indirectly by decreasing serotonin levels. In addition, through fermentation of dietary fibers, gut microbiota is responsible for the production of short chain fatty acids (SCFAs), which control the inflammation process of the intestines. In IBD, the amount of SCFAs is reduced, so the concentration of some of their metabolites is also reduced. One of them, gamma-aminobutyric acid, is inhibitory neurotransmitter involved in the development of anxiety and depression. This connection may be the starting point for creating a future therapeutic strategy based on selective manipulation of microbiota species to modify the course of both IBD and associated mental disorders. However, even if the results of preliminary studies on the influence of gut microbiota modulation on depression and anxiety in IBD patients are promising, there is not enough evidence to apply it in clinical practice.

Ingesting certain microorganisms can influence human brain activity in specific regions modifying behavior, emotions and cognition. Additionally, it can lead to decreases in the concentration of stress hormones. These findings mean that some probiotic species, which in this context are termed ‘psychobiotics’, may be usable as a treatment option. Interestingly, microbiome alterations may be significant in psychiatric pharmacotherapy, because some drugs currently prescribed by psychiatrists or neurologists were used as antibacterial agents in the past. However, as already mentioned, scientific evidence is still insufficient to recommend psychobiotics as a form of therapy.

### The impact of depression and anxiety disorders on IBD onset

The influence of mental disorders on the development of IBD remains unclear. It is suggested that abnormalities in mental functioning may occur several years before the diagnosis of intestinal disease. For instance, a Canadian study demonstrated that anxiety disorders and mood disorders were diagnosed in respectively 80% and 54% of patients with IBD on average 2 years before the IBD diagnosis. Additionally, patients with depression and anxiety disorders were diagnosed with the disease earlier (34.9 years on average) than those without these disorders (37.8 years on average). In subsequent studies, it was found that the interval between the deterioration of mental functioning and the diagnosis of intestinal disease may be even longer, and could be up to 5 years.

### Impact of anxiety and depression disorders on the course of IBD

Depression and anxiety associated with IBD may directly affect its course. The correlation between intestinal disease activity and worsened mental condition is particularly evident in patients who believe that psychological stress contributes to exacerbations. It was observed that IBD patients with accompanying mental disorders have increased likelihoods of surgical interventions, extended diagnostics with additional examinations, such as computer tomography (CT) or multiple colonoscopies, as well as a need for

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**Table 2. Prevalence of anxiety and depression disorders in IBD patients**

| Author, year          | Number of IBD patients | Prevalence of anxiety | Prevalence of depression | Associated factors                                                                 |
|-----------------------|------------------------|-----------------------|--------------------------|-----------------------------------------------------------------------------------|
| van den Brink et al., 2020  
18                          | 374                    | 28.3%                 | 2.9%                     | female sex, disease activity, disease duration                                      |
| Choi et al., 2019  
19                          | 15569                  | CD – 11.5%*           | UC – 16.7%*              | medication use, comorbid medical conditions                                         |
| Lewis et al., 2019  
20                          | 242                    | 40.1%                 | 30.6%                    | female sex for depression                                                          |
| Bhamre et al., 2018  
21                          | 70                     | 18.6%                 | 34.3%                    | disease activity                                                                   |
| Navabi et al., 2018  
22                          | 432                    | 39.4%                 | 25%                      | female sex, extra-intestinal manifestations of IBD, prior IBD-related surgery, tobacco use in CD |
| Byrne et al., 2017  
23                          | 327                    | 21.2%                 | 25.8%                    | female sex, disease activity                                                       |
| Chan et al., 2017  
24                          | 200                    | 27%                   |                          |                                                                                  |
| Bennebroek Evertsz' et al., 2012  
25                          | 231                    | 42.6%                 |                          | disease activity                                                                   |

*6 years after diagnosis; IBD – inflammatory bowel diseases; CD – Crohn’s disease.*
corticosteroids, immunomodulators or anti-tumor necrosis factor (TNF) therapy. The presence of depressive symptoms can worsen the course of IBD and may be considered a predictor of aggressive, recurrent disease.

One of the suggested mechanisms explaining how depression can influence the activity and severity of IBD is its impact on the inflammatory process. For instance, in about 80% of severely depressed patients, hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis is observed. The resulting chronic hypercortisolism leads to elevation of pro-inflammatory mediators. Moreover, depression is associated with decreased parasympathetic activity of the autonomic nervous system (ANS), which causes inhibition of macrophage activation through the cholinergic anti-inflammatory pathway. As a result, depression clearly influences the Crohn’s Disease Activity Index score in CD patients, can lead to exacerbations of IBD and increases the rate of failure during infliximab treatment. In a study of 100 people with CD, it turned out that patients with major depressive disorder (MDD) found it harder to achieve remission. Persistent MDD after adequate treatment of CD with infliximab is a risk factor for the need of early retreatment.

Interestingly, a study of a small group of women with depression showed that treating them with behavioral-cognitive therapy resulted in a decrease in the concentration of interleukin 6 (IL-6), which is one of the major pro-inflammatory cytokines in IBD. According to another meta-analysis, behavioral-cognitive therapy in patients with IBD has limited and short-term effectiveness in treating depressive symptoms and improving HRQoL, without affecting anxiety, stress levels or disease activity.

Regarding pharmacotherapy of depression and anxiety disorders in IBD, although antidepressants are commonly used by these patients with (based on previous research) apparent beneficial effects, it is not possible to determine conclusively whether pharmacotherapy affects the course of IBD. Central neuromodulators may be used in painful IBD as supplements to peripheral agents, like in the management of functional disorders. In cases of major psychiatric problems, consulting with a psychiatrist to optimize therapy is recommended. The previously described potential benefits of using antidepressants may be associated with a reduction in inflammatory processes or simply with mood improvement. For now, it is only known that the use of certain antidepressants reduces the risk of intestinal disease in the future. Properly conducted randomized controlled trials are necessary to accurately define their efficacy.

**The impact of IBD on anxiety and mental disorders**

Depressive disorders are accompanied by elevated concentrations of pro-inflammatory mediators such as C-reactive protein (CRP), IL-6, IL-1, IL-12, and TNF-α. It has been suggested that CRP levels might be used to predict the severity and recurrence of depression. Consequently, patients with CD who received anti-inflammatory therapy with anti-TNF agents (infliximab or adalimumab) reported rapid improvement in depressive disorders. Most importantly, this was not associated solely with clinical improvement of their IBD.

Sleep disorders observed in patients with IBD, which are closely related to depression, may be a marker of subclinical inflammation or persistent histologic disease activity. It has been suggested that elevated levels of circulating cytokines contribute to sleep disturbances, even in clinical remission. Injection of pro-inflammatory IL-1 or TNF in animal models suppresses rapid-eye movement (REM) sleep and alters sleep patterns. Additionally, administration of IL-6 increases non-rapid eye movement (NREM) sleep and reduces slow-wave sleep during the first half of the sleep cycle. Interestingly, some studies have shown that CD patients who have impaired sleep quality while in clinical remission have a greater risk of disease flare-ups. This is why sleep disturbances, potentially modifiable risk factors for IBD relapse, should be considered for routine assessment in patients.

**Depression as a side effect of IBD treatment**

Drugs used in the treatment of IBD may also influence the occurrence of depression and anxiety disorders. It is known that long-term use of glucocorticosteroids negatively affects the mood of patients. Interestingly, in previous randomized clinical trials and observational studies, adverse psychiatric effects (APE) during biological treatment were very rare or absent. However, the exact frequency of them among biologically treated patients is difficult to assess, because many studies do not consider adverse effects of the drug on the patient’s psychological state. It is not known whether the authors did not observe such effects or whether they did not collect data related to this aspect.

**Depression and anxiety disorders in the guidelines**

In the recent guidelines of the European Crohn’s and Colitis Organization (ECCO) regarding the management of CD (2019) and UC (2017), there are no recommendations concerning assessment of the patients’ mental state and possible therapeutic interventions. Such recommendations appeared in the 2018 Nurses’ European Crohn's and Colitis Organization (N-ECCO) consensus regarding the role of nurses in caring for patients with IBD. According to this document, nurses should be aware of more frequent depression and anxiety disorders among...
the patients than in the general population, and, if necessary, should refer selected patients to a specialist. The British Gastroenterology Association also took a position on this matter in guidelines issued in 2019. The British recommendations suggest supportive behavioral therapy, hypnotherapy or mindfulness meditation for interested patients. Similarly, the German Clinical Practice Guideline on IBD emphasizes the significance of accompanying psychiatric symptoms. So far, no reliable studies have been conducted in patients with IBD and depression or anxiety disorders that may provide a basis for recommending antidepressants.

Conclusions

The risk of depression and anxiety disorders in patients with IBD is significantly higher than in the general population, so both family physicians and gastroenterologists should consider them in patients under their care, as they can negatively impact the course of the disease. Nevertheless, the current guidelines refer to this problem only to a limited extent at best. Considering the close relationship between depression and anxiety and the degree of disease activity, optimization of IBD treatment should include psychiatric, psychological and social support. Due to the steadily increasing incidence of IBD, a holistic approach is needed, both to avoid the development of depression-related disabilities and to improve HRQoL and patient–doctor compliance.

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