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Causal Association between Anxiety and Inflammatory Bowel Disease (IBD)

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Abstract:

For the past few years, the prevalence rate of inflammatory bowel disease (IBD) has been continuously increasing. The situation becomes an important factor affecting individual and social development. Based on the traditional Chinese medicine model of "Earth deficiency leading to wood shaking", the paper utilizes the method of literature research to systematically demonstrate the bidirectional causal relationship between anxiety and IBD. The core conclusion reveals that anxiety is not only a common comorbidity of IBD but also an independent risk factor for its incidence. On the contrary, the disease burden of IBD directly leads to the occurrence and exacerbation of anxiety. This bidirectional relationship is mainly mediated through the "brain-gut axis" mechanism, including the activation of the HPA axis, dysbiosis of the gut microbiota, and abnormalities in neuroimmune regulation. Based on this, the study presents a bidirectional and comprehensive intervention strategy, emphasizing the need to pay attention to both the physical and mental health of patients in clinical practice. Furthermore, to accomplish better prevention and treatment outcomes, clinical practice use integrated traditional Chinese and Western medicine treatment, psychological intervention, and multidisciplinary collaboration.

Keywords: Anxiety; Inflammatory bowel disease; Earth deficiency leading to wood shaking; Gut-Brain axis.

1. Introduction

Inflammatory Bowel Disease (IBD) is a long-term inflammatory bowel disorder including Crohn's Disease (CD) and the Ulcerative Colitis (UC). It is thought that IBD disorders of innate and adaptive immune systems lead to abnormal inflammatory responses to commensal bacteria of genetically susceptible people.

The ECCO conference 2023 data showed that the disease burden of IBD varies greatly in terms of region. In Europe it stands at about 24-27.2 per 100, 000 person-years. The prevalence however differs greatly with ranges of 150 per 100, 000 in Lithuania to 405.6 per 100,000 in Catalonia, Spain. However, as contrasted to previous statistics, statistics of the

Chinese Center of Disease Control and Prevention showed that in China the number of IBD patients will rise to 1.5 million as opposed to 350, 000 cases between 2005 and 2014. It is prevalent in China at 107.1 per 100, 000. Comprehensively, as global industrialization and urbanization go on, the onset and prevalence of IBD could go on rising. Based on this, in recent years, the research on IBD has been continuously and deeply advanced. Drug R&D technologies have evolved. The scientific progress have improved the prognosis and life expectancy of IBD patients. However, the presence of chronic diseases and their prolonged course possibly jeopardize patients' quality of life. Patients are prone to develop emotional disorders. Recent studies have detected that the prevalence of anxiety in IBD patients is higher than that in the general population. Research discovers that 49% of IBD respondents suffer from anxiety, and 56% of the respondents have depression, while these rates in the general population are much lower, at 6% and 3% respectively [1]. Meanwhile, anxiety can interfere with the progression of IBD by affecting the patient's physiological status and treatment compliance. Furthermore, anxiety may also increase the incidence of IBD through multiple mechanisms such as the microbiota-gut-brain axis and neuroimmunity.

IBD is commonly comorbid with anxiety disorders. The two conditions exacerbate each other, but their causal relationship is complex. Currently, the study about the direct and indirect effects of anxiety on the first onset of IBD is less. Therefore, based on a review of the latest literature, this article aims to understand the deeper bidirectional relationship between anxiety disorders and IBD rather than to asserts a direct causal relationship. It emphasizes the overlapping mechanisms, converging biomarkers and shared pathways, with the aim of providing theoretical references for the clinical treatment of IBD patients and prevention of IBD in patients with anxiety disorders. Furthermore, the author offers a novel and comprehensive treatment strategy.

2. Key Findings: Mechanisms and Evidence of Bidirectional Association

2.1 "Earth Deficiency Leading to Wood Shaking" As A Pathogenesis Model between Anxiety And IBD

The exact causes of IBD have not been not fully elucidated yet. It is generally believed that the disease results from an abnormal and persistent inflammatory response in the intestinal immune system triggered by environmental factors in genetically susceptible individuals. A Swedish cohort study has revealed that lower stress resilience may increase the risk of diagnosing IBD by affecting inflammation or intestinal barrier function [2]. A population-based cohort study in Denmark found that 161 out of 22,103 IBD patients (0.7%) and 572 out of 110,515 control patients (0.5%) had contact with hospitals due to anxiety within five years prior to the date of IBD diagnosis. Compared with the control population, the odds ratio (OR) for anxiety in IBD patients was 1.4 (95% CI 1.2-1.7). The probabilities within 0-2 years (OR 1.3; 95% CI 1.0-1.7) and 3-5 years (OR 1.5; 1.2-1.8) before IBD diagnosis both increased [3]. Therefore, it can be known that when the pressure in environmental factors exceeds the stress resistance capacity of the body, it may trigger and affect anxiety. Subsequently, this situation leads to IBD. From this, it can be inferred that anxiety has been confirmed as an independent risk factor for IBD.

The theory of the five elements' generation, control, mutual restriction, and transformation in traditional Chinese medicine (TCM) is the prerequisite and foudation for the smooth operation of the human body and even the nature. The introduction of the pathogenesis model into the disease-related cognitive system is helpful to deeply understand the prognosis and development of diseases.

Modern TCM has formed a systematic theory regarding the etiology and pathogenesis of IBD, believing that the onset of IBD is closely related to dampness, heat, stasis, and deficiency. Among these, "dampness-heat accumulating in the intestines" is the key pathogenesis in the active phase, "spleen deficiency" is the fundamental pathogenesis for the prolonged course of the disease, and "blood stasis obstructing the collaterals" is a key factor in the chronic and difficult-to-heal nature of the condition [4]. Starting from the TCM pathogenesis model of "Earth deficiency leading to wood shaking," "earth deficiency" refers to spleen and stomach weakness, which is an important internal basis for the onset of IBD, i.e., "genetic susceptibility." When the functions of the spleen and stomach are weak and abnormal, it leads to poor transformation and transportation of food and fluids. This directly manifests as loose stools or constipation in the digestive system; ingested food cannot be converted into nutrients, and the transformed essence of food and water cannot be transported throughout the body. Over time, the amount of nutrients absorbed by the zang-fu organs and limbs decreases, leading to a natural decline in their functions; insufficient generation of qi and blood, poor mental state, palpitations; and disorders in water metabolism, resulting in the accumulation of dampness-heat.

These are directly corresponding to the common symptoms of IBD patients, such as malnutrition, immune disorders, and intestinal inflammation. "Wood shaking"

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means the disorder of liver qi. In the TCM perspective, anxiety is often categorized as "depression syndrome" or "hysteria." Its core pathogenesis is closely related to the "heart," "liver," and "spleen." The liver rules flowing and spreading. Its functions include regulating the movement of qi, controlling mental and emotional states, promoting digestion and absorption, and maintaining the circulation of qi and blood. If liver qi becomes stagnant, excessive, or inadequately nourished, it will directly manifest as symptoms of anxiety such as tension and irritability. Among the five elements' generation, control, mutual restriction, and transformation relationships, the core relationship between spleen (earth) and liver (wood) is "liver wood over-restrains spleen earth." Long-term anxiety leads to stagnation of liver qi. When this stagnation persists for a long time, it transforms into fire (liver fire). The situation makes the liver qi rebellious and overactive, thereby over-exerting and consuming the functions of the spleen and stomach, and aggravating the deficiency of earth. On the contray, the long-term weakness of the spleen and stomache and the imbalance of body homeastasis cannot nourish the liver wood, which will further make the liver Qi stagnant and unstable, and the "wood shaking" will intensify. Together, they form a self-reinforcing vicious cycle of "the more the earth is deficient, the more the wood is shaking, and the more the wood is shaking, the more the earth is deficient."

At the same time, this TCM pathogenesis model is consistent with the modern medical theory of the "gut-brain axis." "Wood shaking" refers to anxiety disorder, corresponding to long-term imbalance of the central nervous system. "Earth deficiency" corresponds to the damage of the intestinal barrier function, microbial balance, and immune homeostasis. According to research, psychological stress can effect the gut-brain axis through neuroendocrine pathways. When the body is stressed and in an anxious state, the HPA axis (hypothalamic-pituitary-adrenal axis) releases cortisol. Cortisol can regulate the activity of intestinal immune cells and the release of cytokine, increase intestinal permeability and damage the barrier function, and alter the structure of the intestinal microbiota. Therefore, this shift affects the upward signaling transmission of the gut-brain axis, abnormally activates the intestinal immune response, and directly induces or aggravates intestinal inflammation. This is exactly the manifestation of the body's "dysfunction of spleen in transportation," resulting in the endogenous generation of dampness and turbidity, and finally the transformation of dampness into heat, leading to inflammation. Conversely, the gut microbiota can also regulate the activity of the HPA axis and effect brain activity. A majority of studies have found that the gut microbiota plays a significant role in maintaining the normal function of the HPA axis. The gut microbiota can rely on Toll-like receptors on enteroendocrine cells.to regulate its secretion activity. In addition, the gut microbiota can also alter the brain emotional activity. The gut microbiota stimulates enterochromaffin cells to produce the neurotransmitter serotonin (5-HT). The neurotransmitter transmits signals by paracrine and affects the emotional activities of the brain. In addition, the gut microbiota can send signals to promote the production of pro-inflammatory cytokines and cortisol. In that cases, it activates indoleamine 2, 3-dioxygenase (IDO) and affecting tryptophan metabolism. Ultimately, the change in tryptophan metabolism regulates the activity of the central nervous system [5].

The "Earth deficiency leading to wood shaking" model explains that anxiety is a potential trigger for the onset and recurrence of IBD. Also, it reveals the possibility that the proportion of secondary anxiety disorders in IBD patients is higher than normal people.

2.2 Thinking about the Impact of IBD on Anxiety Disorders

The patient's symptoms are the primary concern in the development of the disease. The core of IBD is chronic and recurrent intestinal inflammation. Gastrointestinal symptoms include persistent and recurrent diarrhea, abdominal pain, rectal bleeding, weight loss, and malnutrition (risk as high as 92%), fatigue [6]. These symptoms have severe effect on the normal life of the patient. Patients are deprived of energy to do social activities. Besides, they are also deprived of self-esteem and feel too anxious about judgments of other people. Patients have been in a low self-esteem and uncomfortable situation of malignancy. Consequently, patients find keeping regular and normal social activities difficult leading to patients being stressed about life. This case, in turn, increases the likelihood of the development of the symptoms of social alienation among the patients and results in their high anxiety concerning the engagement in any social interaction [7]. At the more practical level, patients that are lifelong on treatment are under heavy economic burden that also entails high direct medical costs. The costs that it may end up incurring annually may hit tens of thousands of yuan in extreme cases. Indirect economic burdens are also major. As an example, patients will lack the opportunity to work normally because of constant symptoms, leaving only a few possible work options or even leaving work altogether. Also, caring about them during work needs by their family members or nursing workers take extra time and financial expenses. This position puts the patients into a lower socioeconomic situation, undermines their social functions, exacerbates their feelings of powerlessness and

psychological pressure and predisposes them to anxiety disorders. In addition, it was confirmed that there is a strong hierarchical relationship between the quality of life and the severity of IBD symptoms. It illustrates that those with more intense aesthetics of IBD have reduced quality of existence. In addition to that, There is a significant negative relationship between pain and fatigue (−0.032 [SE 0.010]) and exhibiting the fact that the co-occurrence of symptoms has a higher impact on the reduction in quality of life [1]. Thus, the less favorable and more intricate the symptoms of IBD, the more the quality of life of patients will decrease, and the more realistic the development of anxiety disorders in patients.

Besides the psychosocial causes, biological processes such as alterations in the gut-brain axis, increased levels of inflammatory bio-markers and other drug side effects might also mediate the development or worsening of the anxiety disorders [8]. IBD patients experience chronic intestinal inflammation and it results in the dysfunction of intestinal vascular barrier. The bacteria toxins and inflammatory products in the intestinal cavity get into the blood, triggering the systemic inflammation. The imbalance of central neurotransmitters via the blood-brain barrier can be caused by the rise of proinflammatory cytokines in the blood. This directly cause anxiety. Moreover, such process causes the activation of microglia, which are the immune cells of the brain. The condition decelerates the brain-derived neurotrophic factor in the hippocampus leading to the atrophy of the hippocampal and a lack of equilibrium in the neurotransmitters. Hippocampus is one of the major parts of the brain to control emotions. These modifications are objectively connected to the added score of anxiety in patients. This is the biological account that substantiates the theory that fluctuations in the emotions of the brain are caused by intestinal inflammation.

3. Comprehensive Prevention and Treatment Strategy and Clinical Significance

Many overlapping biological pathways that affect the bidirectional interaction between the gut and the brain include genetic vulnerability, immune system maladaptations, hypothalamic-pituitary-adrenal (HPA) axis changes, and maladaptation of the gut microbiota [9]. The comorbidity of IBD and anxiety disorders induced by these mechanisms influences the gut inflammation and the activity of central nervous system. Consequently, according to the bidirectional model, the prevention and control interventions must be two-way and holistic.

The model of the deficiency of the Earth causing the shaking of wood can help the physician to rely on it in the process of treatment. IBD is a recurrent and challenging situation to heal the condition of its patients. The anxiety fluctuations are commonly experienced by IBD patients. The cause is the deficiency of Earth. “Wood shaking” is the symptoms. The thing is quite similar to the inability to recover the source of earth and easy flow of wood. According to this model, the best approach of managing diseases is to use an integrative approach whereby traditional western pharmaceuticals and traditional Chinese medicine are combined. Eventually, it is in clinical practice whereby the harmony of body and mind is achieved and only well followed by treatment of both the symptoms and the underlying cause. However, the treatment plan must include not only administering biologics that would directly suppress the inflammatory activity in the gut but also TCM techniques that would balance the liver and spleen. By soothing the liver and relieving depression, invigorating spleen and supplementing qi, and tonifying the kidney and consolidating the foundation, it can break the vicious cycle of “earth deficiency and wood shaking.” At the same time, psychological interventions such as cognitive behavioral therapy, mindfulness, qigong and other methods can also be applied to directly manage “wood shaking” and stabilize emotions. This comprehensive intervention, from emotional management to gut repair, aims to simultaneously stabilize the “earth” foundation and appease the “wood” disturbance. This kind of method aims to achieve more sustained and high-quality clinical remission. In addition, IBD patients can also positively intervene in the progression of their condition through probiotic supplementation and nutritional therapy.

From a societal perspective, pain may lead to increased help-seeking behavior in patients through health anxiety or increased cognitive load in coping with IBD, directly affecting healthcare utilization, and thus increasing social and economic costs [10]. Therefore, monitoring the physical and mental states of IBD patients synchronously can also help alleviate the societal burden.

For patients with anxiety disorders, it is essential to pay close attention to gut health and avoid becoming potential IBD patients.

4. Review of Existing Research

Over the past few years, it is a tendency to observe the growth of studies on the connection between IBD and anxiety, in general. As other fields have developed, and research on pertinent populations has been implemented, increasing evidence is emerging that anxiety frequently co-exists with gastrointestinal dysfunction. This comorbid psychosomatic comorbidity is a two-way process. Cyto-

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kines (IL-6 and TNF-a) that are the products of intestinal inflammation may enter the blood-brain barrier and influence the activity of amygdala and hippocampus [11]. Nevertheless, pathophysiological mechanisms of IBD as well as anxiety do not have an exhaustive explanation. It primarily deals with the knowledge of the general structure as it concerns neural-immune pathways, microbiota-gut-brain axis, and central nervous system alterations. Nevertheless, the absence of particular mechanisms is still limited. At present, numerous researches are at their exploratory stage of interrogative of whether and how psychosocial factors influence the pathogenesis of IBD. The level of anxiety can be mitigated through early screening of the anxiety and the use of psychotropic drugs and psychotherapy to enhance the quality of life of the patients. The future research ought to consider what type of intervention can be maximum beneficial in the case of treating psychological distress among the IBD. Later in the stage, nursing teams should collaborate with gastroenterologists and psychiatrists. When combined with the notion of patients, they ought to delve into developing standardized and unified treatment regimens of IBD complicated with psychological issues.

Namely, currently, the definition of the traits of body alterations during the initial phase of IBD is lacking. The aetiology of the disease is not clearly known. Research work and creation of the new technologies in order to diagnose earlier and more accurately should be considered in future technological advances. These practices through which there will be early detection of biological changes that precede the appearance of symptoms, detection of inflammation, and monitoring of the uptake of the inflammatory process using non-invasive techniques can be used to improve clinical practice. The research is not an easy but significant decision towards the advancement of social health and wellness [11]. Moreover, the shift in the mental health of patients can help to prevent the disease further development and outbreaks as well.

Moreover, the study is based on animal subjects, which are hard to replicate such intricate pathophysiological situations and psychosocial aspects of IBD. There should be more efforts done in the future to come up with a new model system that will be more related to the characteristics of the human diseases. Besides that, AI can be adopted to create environment simulation.

Simultaneously, individual sample heterogeneity and population-specific characteristics of IBD result in the presence of differences in the evaluation of the research outcomes of various countries. Considering the heterogeneity of IBD, multi-center and massive clinical trials have to be conducted in the future. The combination of the genetic background, the immunophenotype, and the disease subtype of the respective patients will enable the realization of the individualized monitoring of the physical and psychological condition of the individual patients. The clinical practice will respond to the results by developing the correct dietary intervention strategies. The dual-dimensional assessment (inflammation-anxiety) enables the treatment scheme to dynamically vary according to therapeutic outcome factors to enhance therapeutic outcomes and minimize the potential of complications [12].

In future, more long-term and population wide prospective cohort studies should be done and molecular mechanisms need to be further investigated into.

5. Conclusion

As this review remarks, anxiety and IBD have a bidirectional causal relationship and the two forms a vicious cycle. Based on the concept described in the TCM mechanism model; earth deficiency causes wood shaking, in conjunction with the findings of modern medical research, this paper acknowledges that the risk factor of IBD is probably anxiety, and that is the key contributing factor to encourage the development of its condition to be malignant. Moreover, the reason as to why the chances of secondary anxiety disorders in patients with IBD are greater than those of the general population can also be explained by this study. The paper immensely researches IBD and the special factor behind its condition, which is anxiety. This is useful in enhancing the treatment effect of patients with IBD and minimizing the possibility of complications. Patients with anxiety disorders should also be able to focus on their own gut health, which is also conductive. This ensures that anxiety patients act before it is too late and results to IBD patients.

Nevertheless, this analysis has considered only those studies written in English and Chinese, and they might not bring in all the developments in other language nations. Furthermore, the current study does not present actual cohort and experimental research but the analysis of the existing literature, which makes its conclusions less objective.

Hopefully, other researchers in the future can carry out more detailed and extensive studies. In the view of the alignment of traditional Chinese medicine and the western one, the research will help scientists in the enhancement of the quality of life of IBD patients and the creation of social health and welfare.

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