

INFLAMMATORY BOWEL DISEASES AND RESILIENCE

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ABSTRACT

INTRODUCTION: Inflammatory bowel disease (IBD) comprising ulcerative colitis (UC) and Crohn disease (CD), affects >1 million individuals in the United States and 2.5 million in Europe. IBD is an immune-mediated chronic condition for which currently no definitive cure is available. The current study utilizes a positive psychology framework to understand the role of stress in IBD, seeks a proof of concept that stress resilience could be a protective factor in patients with IBD. Resilience is defined as the inherent and modifiable capacity of an individual to cope or recover from adversity.

OBJECTIVE: On the basis of previous knowledge, we want explain and bring closer the understanding of the resilience of patients with inflammatory bowel diseases.

METHODS: The PubMed database, and the Google scholar database were searched. The search was performed using keywords. This paper includes research dealing with resilience in patients with inflammatory bowel diseases within the last ten years.

RESULTS: Although IBD imposes a mental and physical toll on individuals, some individuals do report feeling stronger due to having IBD. Most studies included in this review investigated psychological resilience and trait resilience that promoted the ability to bounce back from IBD-related adversity. Conversely, higher levels of resilience were found to predict better quality of life among IBD patients. Higher levels of resilience predicted higher levels of adaptation to the ostomy; notably, perseverance—defined as a trait of resilience was the most reliable predictor. Resilience was not significantly affected by clinical characteristics in UC patients.

CONCLUSION: Many unmet needs still exist in the IBD research agenda, including a better understanding of its pathophysiology, reduction of diagnostic delays, discovery of more effective and safer drugs, optimization of existing therapies, improving patients' adherence to the treatment plan, improving patient's quality of life, management of extraintestinal manifestations, and prevention of complications. A multidimensional approach is necessary for delivering high-quality healthcare for IBD patients.

Key words: Inflammatory, bowel disease, resilience

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INTRODUCTION

The inflammatory bowel diseases (IBDs) are chronic intestinal disorders that are typically categorized as one of two subtypes: Crohn's disease and ulcerative colitis. Ulcerative colitis is limited to the colon, with superficial mucosal inflammation that extends proximally in a contiguous manner, and can lead to ulcerations, severe bleeding, toxic megacolon, and fulminant colitis. In contrast, Crohn's disease can affect any part of the digestive tract, often in a noncontiguous manner, and is characterized by transmural inflammation, which can lead to complications such as fibrotic strictures, fistulas, and abscesses (1).

Although potentially important differences between ulcerative colitis and Crohn's disease have been observed, such as immune-cell subpopulations differentially enriched(2) and genetic variants (e.g., *NOD* and *PTPN22*) that increase the risk of Crohn's disease but may be protective against ulcerative colitis (3), a comprehensive understanding of the underlying pathophysiological mechanisms resulting in these divergent clinical manifestations is still lacking. Moreover, additional heterogeneity beyond these two IBD subtypes is likely; for example, ileal and colonic Crohn's disease may represent distinct entities, and colonic Crohn's disease can be further classified into subtypes on the basis of gene expression profiles (4). The IBD armamentarium includes untargeted therapies, such as aminosalicylates, glucocorticoids, and immunomodulators, as well as targeted biologic therapies that act through one of the following mechanisms: neutralization of cytokines that promote inflammation (e.g., anti-tumor necrosis factor [TNF] antibodies) or drive the differentiation and function of specialized immune subsets (e.g., anti-interleukin-12 and anti-interleukin-23 antibodies), blockage of signal transduction cascades downstream of these pathways (e.g., Janus kinase [JAK] inhibitors), or modulation of lymphocyte trafficking (e.g., anti- $\alpha 4\beta 7$ integrin

antibodies). Biologic therapies are effective in many patients, but up to 30% of patients do not have a response to initial treatment, and in up to 50% of patients, the response is lost over time. Although inadequate drug levels and development of immunogenicity to drug treatments underlie some of these failures, additional heterogeneity of IBD beyond the classic Crohn's disease and ulcerative colitis subtypes is likely to be another important factor. The pathophysiology of IBD involves complex genetic, environmental, epithelial, microbial, and immune factors. This review does not cover all the breakthroughs in these diverse areas but instead highlights some recent advances.

INTESTINAL EPITHELIUM

The intestinal epithelium comprises a single layer of epithelial cells linked by tight junctions and intercalated with immune cells (5). The small intestinal epithelium is a highly dynamic tissue organized as a series of protrusions (villi) and invaginations (crypts of Lieberkühn). Major functions include facilitating nutrient absorption, acting as a physical barrier against gut luminal contents, and responding to signals from the intestinal microbiota and immune system. Secretory cells include goblet cells, which produce mucus and such antimicrobial peptides as trefoil factor and resistin-like molecule beta that limit luminal microbes. Early studies suggested that the mucus layer was denuded in Crohn's disease owing to a reduction in goblet cells (6), and a recent single-cell RNA sequencing (scRNA-seq) study showed that down-regulation of a colonic goblet-cell-secreted protein, whey acidic protein four-disulfide core domain 2 (WFDC2), in active ulcerative colitis may lead to abnormalities in mucus layer formation, increased colonization and invasion of microbiota, and breakdown of the epithelial barrier (7). These findings suggest that WFDC2 and other molecules produced by goblet cells might be protective in ulcerative colitis.

Tromal cells, which are nonhematopoietic mesenchymal cells that include fibroblasts, myofibroblasts, and perivascular pericytes, reside below the epithelium in the lamina propria and play important roles in fibrosis and wound healing. A recent report suggested a role for a previously unknown subpopulation of fibroblasts in exacerbating ulcerative colitis, owing to increased expression of immune-cell-attractant chemokines CCL19 and CCL21, as well as interleukin-33, which induces certain immune-cell subsets to produce type 2 cytokines (8). Thus, approaches aimed at enhancing epithelial barrier function could lead to potential therapeutic strategies for IBD.

GENETICS, GENOMICS, AND EPIGENOMICS

Early studies suggested a heritable risk that is greater for Crohn's disease than for ulcerative colitis and a higher incidence of IBD in first-degree relatives of patients with IBD than in the general population (9). To date, genomewide association studies have identified more than 240 risk variants that affect intracellular pathways recognizing microbial products (e.g., *NOD2*); the autophagy pathway, which facilitates recycling of intracellular organelles and removal of intracellular microorganisms (e.g., *ATG16L1*); genes regulating epithelial barrier function (e.g., *ECM1*); and pathways regulating innate and adaptive immunity (e.g., *IL23R* and *IL10*). Only 8 to 13% of disease variance in Crohn's disease and 4 to 7% in ulcerative colitis can be explained by known IBD risk loci, but genetic factors, such as variants in the antiinflammatory interleukin-10 signaling pathway, may play a more important role in children with very-early-onset IBD (10). Moreover, genetic studies, recently reviewed in detail, have greatly accelerated the identification of genes and pathways that may be critical for mucosal homeostasis and the development of IBD.

Genomewide profiling studies have focused on identifying molecular features, such as gene expression and epigenetic modifications, that distinguish additional subtypes within the canonical Crohn's disease or ulcerative colitis classifications, differentiate Crohn's disease from ulcerative colitis, or discriminate between IBD and a healthy state. Analyses of gene expression and chromatin accessibility in samples of colonic tissue have been used to identify two molecular subtypes of Crohn's disease that have differences in cellular metabolism (e.g., glucose and lipid metabolism pathways) and immune signaling pathways (e.g., interleukin receptors, G protein-coupled receptors, and toll-like receptors) (5). Other studies have identified genes that are more highly expressed in tissue from patients with IBD; for example, increased expression of the cytokine oncostatin M was observed in inflamed intestinal tissue from patients with IBD and was predictive of the subsequent failure of anti-TNF therapy.¹² A potential limitation of analyses using whole intestinal tissue, however, is the substantial heterogeneity of cell types contained within; thus, gene expression measurements may preferentially detect the most highly expressed messenger RNA (mRNA) transcripts in the most abundant cells and cannot be unequivocally linked to a specific cell type.

Technological advances enabling transcriptional profiling (e.g., scRNA-seq) and high-dimensional protein analyses (e.g., mass cytometry) at the single-cell level have resulted in the identification of IBD-associated signatures and the discovery of new subpopulations of fibroblasts,⁹ epithelial cells,⁸ and immune cells that are enriched or depleted in IBD (11,12). For example, a cellular module termed GIMATS (IgG-producing plasma cells, inflammatory mononuclear phagocytes, activated T cells, and stromal cells) was shown to be enriched in a subgroup of patients with ileal Crohn's disease and was associated with the lack of a durable remission in response to anti-

TNF therapy. Thus, genetic, genomic, and epigenomic studies have the potential to identify genes and pathways in specific cell subtypes that could represent future therapeutic targets or serve as biomarkers to aid in clinical decision making.

RESILIENCE AND HOW TO MEASURE IT

Studies on resilience vary in their methodology and samples (13,14). Historically, most studies focused on difficult environmental circumstances and children's ability to thrive and withstand the risk factors in their surroundings (15,16).

Resilience, from the Latin verb "resilire", means rebound or recoil (17). The most commonly used description for medical purposes involves the ability to adapt well in the face of adversity (18). Recently, Ungar recommended to standardisation of research on resilience by defining three distinct parts: (1) risk exposure, (2) desired outcome, and (3) protective factors (19). However, resilience is a dynamic process that grows over time (20).

Resilience among patients with a chronic illness is often defined as an individual's ability to cope well in the face of disease (21). Literature reviews on chronic illnesses and resilience revealed a paucity of articles including adults compared to children (22,23). However, resilience was either defined as a set of personal traits or as an outcome. In cancer patients undergoing treatment (24), higher levels of resilience were positively related to higher levels of activity and lower levels of psychological distress. In a study of the relation between self-silencing and resilience in women with HIV, higher rates of silencing were associated with lower levels of resilience (25). Furthermore, higher levels of income, education, and employment were significantly associated with resilience. A review of 12 cross-sectional studies on resilience and chronic illness showed that resilience was both a significant predictor and

outcome of recovery and quality of life in individuals living with a chronic condition (21). Hence, resilience can be considered as a part of a patient's clinical complexity (26).

There is a multitude of scales measuring resilience mostly unique to the sample or specific situation researched. A comprehensive review by Windle et al. concluded that of 15 original scales examined many lacked sufficient information regarding the psychometric ratings and theoretical underpinning of the scales (27). Three scales were regarded as having more robust psychometric properties, Connor-Davidson resilience scale (CD-RISC) (28), resilience scale for adults (RSA), and the brief resilience scale (BRS) (29,30).

The BRS contains six items of resilience with higher scores indicating higher levels of resilience (30). The BRS assesses individuals' traits of resilience and their ability to cope with stress. It was initially tested on samples of cardiac rehabilitated and fibromyalgia patients. Similarly, the RSA measured 5 domains of resilience with 37 items, namely personal competence, personal structure, social competence, social support, and family coherence (29). It was originally tested on a sample of psychiatric outpatients. The scale was later reduced to 33 items and used a semantic differential scale format for higher accuracy (31). Lastly, the CD-RISC comprises 25 items, also measuring trait resilience on a five-point Likert scale (28). Like the RSA, CD-RISC was first assessed among a sample of psychiatric patients. To this day, the CD-RISC has been translated into over 70 different languages and is by far the most widely used scale of resilience (32).

RESILIENCE DEFINITION

Resilience is not easy to define and there is no simple definition since the term covers a very wide range of features, is comprehensive and significant. The name comes from the English word „resilience“ which was adopted in Croatian

language (33). The word is translated in many ways, but most often means „the ability to recover“. It consists of personal qualities which enable the individual to thrive in the encounter of a problem (34). Resilience is a complicated interaction of risk factors and protective factors which leads to positive development results (35). It is a positive adaptation after stressful situations and represents confrontation and heaving above hard experiences, that is, represents the capacity of a person to successfully adapt to changes, to resist the negative influence of stressors and avoid the appearance of significant dysfunctions (war trauma, family issues, workplace issues and similar). This does not mean that there is no awareness of the problem, absence of pain, not putting any effort to avoid the aforementioned. Resilience actually represents the strength to handle and deal with a problem, and to continue normally through life (36). Resilience is a constant process of adjustment to newly created conditions which consists of acquiring a growing and broader competence for stress reaction. It is in significant connection with the general developmental processes, relationships with significant others and the specific life circumstances of a person. Resilience development is closely linked to personality development as a whole, and is deeply individual as personality development (37). In the context of comorbidity, it is important to bear in mind that there are different forms of resilience and that, in accordance with the cascade model, certain factors of resilience may contribute to development of others. It is useful to have in mind personal and group resilience (38,39), physiological, psychological, social and spiritual resilience (40), and primary, secondary and tertiary resilience (41). Psychological and spiritual resilience actually represent psychological and spiritual defense mechanisms in crisis states, stress states and trauma. Psychological and spiritual resilience include hope, activity, purpose and meaning,

community, gratitude and joy, which overcome vulnerability that includes despair, helplessness, absurdity, isolation, anger and sadness. In other words, resilience on a psychosocial level represents and includes different kinds of psychological, mental, social and spiritual capital. Primary resilience is linked to maintenance of balance, equilibrium and health, which ensure welfare and prevent stress-related diseases. Secondary resilience denotes the factors and processes which enable us to successfully cope with crises and illnesses and to re-establish health and psychosomatic harmony.

RESILIENCE IN INFLAMMATORY BOWEL DISEASE

Although IBD imposes a mental and physical toll on individuals (42), some individuals do report feeling stronger due to having IBD (43). Most studies included in this review investigated psychological resilience and trait resilience that promoted the ability to bounce back from IBD-related adversity (44,45). Some demographic characteristics found to be relevant to individuals with IBD included being optimistic, older, male, employed, not religious, and nulliparous (46). Women with IBD more commonly reported resilience to be an essential determinant of health and both genders mentioned self-efficacy, social support, occupational balance, and job satisfaction as the main determinants of health (47). Women with IBD and high resilience showed changes in brain-behavioural patterns, whereas the results were not conclusive for male participants (48). Individuals whose onset of CD occurred later in life (after 30 years of age) and who performed complimentary activities appeared to be more resilient (46). These findings were corroborated by Taylor et al.'s study, which compared level of physical activity, resilience, and health-related quality of life (HRQOL) among IBD participants (49). A higher intensity of physical activity independently and significantly predicted a higher level of physical HRQOL, but not mental

HRQOL. Resilience, on the other hand, was a significant and positive impact on mental HRQOL. Sehgal et al. found that lower levels of resilience were associated with significantly higher levels of anxiety and clinical depression (50). Conversely, higher levels of resilience were found to predict better quality of life among IBD patients. Higher levels of resilience predicted higher levels of adaptation to the ostomy; notably, perseverance—defined as a trait of resilience was the most reliable predictor (51). Moreover, lower income, sleep disturbances and being unmarried negatively impacted the level of resilience and depression among CD patients with an ostomy. Resilience was not significantly affected by clinical characteristics in UC patients. Overall, there was a slightly higher resilience level among UC patients compared to CD patients (52).

Contrarily to the previous studies, Sirois and Hirsch drew a distinction and defined resilience as a set of traits that only promote the ability to recover from an illness (53). The authors contrasted the concept of resilience with one's ability to thrive, the latter entailed growth above and beyond the recovery. The study examined illness acceptance, coping efficacy, depressive symptoms, and perceived social support differences among IBD patients who experienced loss, resilience, and thriving. At baseline, results indicated that across the four outcomes coping efficacy significantly distinguished those who thrived versus those who were resilient. 6 months later, this difference was no longer statistically significant. However, both resilient and thriving IBD groups were consistently reporting better psychological outcomes compared to the individuals experiencing loss from their illness. Stress resilience was investigated in two studies (54,55).

Melinder et al. examined prospectively a large cohort of young men from the general Swedish population speculating that low-stress resilience would predict the onset of IBD. Three quarters

of subsequently diagnosed individuals had low to moderate levels of stress resilience. Skrautvol and Naden examined qualitatively stress resilience through integrative care (55). The highly select interviewees dealt with IBD using complementary and alternative medicine (CAM) and dietary supplements stressing the perceived importance of individualising treatment plans and making changes in their lifestyle. These findings go in line with Sirois' findings that 46% of individuals with IBD used CAM as a complementary treatment to conventional medicine (56). Although the magnitude of the relation was small, individuals with IBD who reported high perception of health and high levels of resilience had greater odds of using CAM.

During transition from juvenile to adult-centred care, both self-efficacy (SE) and resiliency were found to independently and significantly predict better transition (57). In response, Carlsen et al. developed an e-health transfer concept to assess patient-reported outcomes, including self-efficacy, resilience, stress response among adolescents with IBD transitioning to healthcare (58). Resiliency and IBD only began to be investigated during the last 5 years. In most studies, resiliency was perceived as a series of traits or psychological resilience, only one study defined resiliency as a dynamic process, and two others looked at stress resilience (54, 55). There also seemed to be some disagreement on whether the definition entails to thrive or restore former health (53). Moreover, the dominance of cross-sectional data, small size, and purposive samples, as well as the near absence of longitudinal studies, are some of the shared limitations across the reviewed articles (59).

Stigmatisation and resilience share many common features (Fig. 2), some of which are IBD specific, and it is reasonable to assume that they mutually influence each other, as shown for psychiatric illnesses (60) and patients living with HIV (61). Disappointingly, only one study involving 40 community-based adult patients

with self-reported IBD has investigated this issue in the IBD population so far. In that study, the authors showed that individuals who seemed more resilient were also more positive, used humour as a coping mechanism, and placed their IBD in a wider life perspective (62). Also, stigma was more evident in patients with weak resilience, especially in those suffering from mental health disorders and in those lacking support networks (63). Several studies have been conducted in the territory of Bosnia and Herzegovina that show the connection between resilience and various mental and somatic diseases. Babić et al state that resilience is important for maintaining an individual's mental health in the fight against any disease (64). Boškailo et al state that a higher level of resilience affects a higher level of quality of life for breast cancer patients (65). Franjić et al state that people with a higher level of resilience are more likely to cope better with the disease and that such individuals have a faster recovery and healing process from colon cancer (66). Certain studies indicate the existence of a positive correlation between resilience and quality of life in colon cancer patients.

CONCLUSION

Many unmet needs still exist in the IBD research agenda, including a better understanding of its pathophysiology, reduction of diagnostic delays, discovery of more effective and safer drugs, optimisation of existing therapies, improving patients' adherence to the treatment plan, improving patient's quality of life, management of extraintestinal manifestations, and prevention of complications. A multidimensional approach is necessary for delivering high-quality healthcare for IBD patients, but we are still far from optimal management in real life. Psychosocial aspects of IBD still receive less attention than the more physical aspects of the illness. According to current evidence, stigmatisation and resilience in IBD patients are not adequately addressed in day-by-day clinical

practice, even if they have a great impact in terms of quality of life and coping with the stress of a chronic illness. More holistic approaches to IBD care are required that incorporate physical, psychological, and social aspects of living with IBD. Further research is required to better understand how stigma and resilience influence patient engagement with medical services, adherence to treatment, attitude towards healthy living, and longer-term disease outcomes. Future work to establish if and how stigmatisation can be reduced and resilience improved is urgently needed. In the authors' opinion, the combination of better medical treatments and comprehensive approaches addressing psychosocial aspects, including stigma and resilience, will lead to a better quality of life for patients with IBD.

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UPALNE BOLESTI CRIJEVA I REZILIJENCIJA

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SAŽETAK

UVOD: Upalna bolest crijeva (IBD) koja uključuje ulcerozni kolitis (UC) i Crohnovu bolest (CD), pogađa >1 milijun pojedinaca u Sjedinjenim Državama i 2,5 milijuna u Europi. IBD je imunološki posredovano kronično stanje za koje trenutno nije dostupan definitivan lijek. Trenutna studija koristi okvir pozitivne psihologije za razumijevanje uloge stresa u IBD-u, traži dokaz koncepta da bi otpornost na stres mogla biti zaštitni čimbenik kod bolesnika s IBD-om. Rezilijencija se definira kao sposobnost pojedinca da zadrži ili obnovi relativno stabilno psihološko i fizičko funkcioniranje kada se suoči sa stresnim životnim događajima i nedaćama.

CILJ: objasniti i približiti razumijevanje rezilijencije oboljelih od upalnih bolesti crijeva.

METODE: Provedena je elektronska pretraga baze podataka PubMed, te pretraga u bazi podataka Google znalac. Pretraga je obavljena korištenjem ključnih riječi. U ovaj rad uključena su istraživanja koja su se unutar pet godina bavila ispitivanjem rezilijencije kod oboljelih od upalnih bolesti crijeva.

REZULTATI: Niže razine otpornosti bile su povezane sa značajno višim razinama anksioznosti i kliničke depresije. Suprotno tome, utvrđeno je da više razine otpornosti predviđaju bolju kvalitetu života pacijenata s IBD-om. Više razine otpornosti predviđale su više razine prilagodbe na stomu. Na otpornost nisu značajno utjecale kliničke karakteristike bolesnika s UC. Općenito, postojala je nešto viša razina otpornosti među pacijentima s UC-om u usporedbi s pacijentima s CD-om.

ZAKLJUČAK: Sve nezadovoljene potrebe i dalje postoje u istraživačkom programu IBD-a, uključujući bolje razumijevanje njegove fiziopatologije, smanjenje kašnjenja u dijagnostici, otkrivanje učinkovitijih i sigurnijih lijekova, optimizaciju postojećih terapija, poboljšanje pridržavanja pacijenata planu liječenja, poboljšanje pacijentove kvalitete život, upravljanje izvanintestinalnim manifestacijama i prevencija komplikacija. Potreban je višedimenzionalni pristup za pružanje visokokvalitetne zdravstvene skrbi za pacijente s IBD-om, ali još smo daleko od optimalnog upravljanja u stvarnom životu. Potreban je holistički pristupi njezi IBD-a koji uključuju fizičke, psihološke i socijalne aspekte života s IBD-om.

Ključne riječi: upalne bolesti crijeva, rezilijencija

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