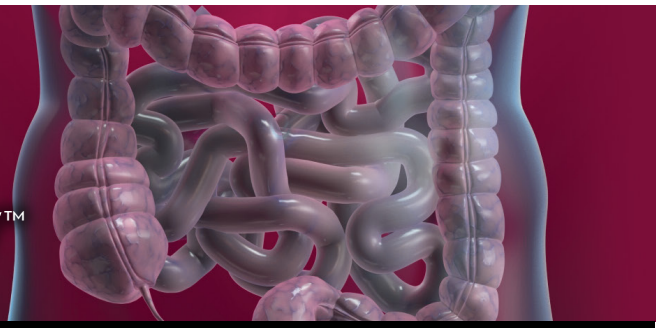
IBD RESEARCH REVIEW™



Making Education Easy

Issue 63 – 2023

In this issue:

Abbreviations used in this issue

aHR = adjusted hazard ratio
AUC = area under the receiver operating characteristic curve
BMI = body mass index
CD = Crohn's disease
CDAI = Crohn's Disease Activity Index
CI = confidence interval
CRP = C-reactive protein
FCP = faecal calprotectin
FODMAP = low fermentable oligosaccharides, disaccharides, monosaccharides and polyols
HBx = hepatitis B virus-encoded oncogene X protein
IBD = inflammatory bowel disease
IBS = irritable bowel syndrome
IL = interleukin
NS = not significant
NSAIDs = nonsteroidal anti-inflammatory drugs
OR = odds ratio
TNF = tumour necrosis factor
UC = ulcerative colitis

Welcome to Issue 63 of IBD Research Review.

A study from Japan reports that leucine-rich alpha 2 glycoprotein is superior to CRP in the prediction of mucosal healing in CD patients with ileal disease, but comparable to CRP in CD patients with colonic disease. Meanwhile in a nationwide population-based Swedish study, individuals with IBD, especially those with UC, exhibited an increased risk of neoplastic colorectal polyps, emphasising the importance of colonoscopic surveillance in this group of patients. In our Science Blog for this issue, Dr Srikantaiah Manjunatha discusses the role of hepatitis B virus-encoded oncogene X protein (HBx) in UC.

We hope you enjoy the latest issue of IBD Research Review and welcome your comments and feedback.

Kind regards,

Professor Michael Schultz
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Dr Srikantaiah Manjunatha
manju@researchreview.co.nz

Usefulness of serum leucine-rich alpha 2 glycoprotein in Crohn's disease: Is there any difference between small intestine and colonic lesions?

Authors: Matsumoto S & Mashima H

Summary: This study examined the association between endoscopic disease activity (Simple Endoscopic Score for Crohn's disease [SES-CD]) and leucine-rich alpha 2 glycoprotein (LRG) level in 141 CD patients with small intestinal and colonic lesions. LRG levels were elevated in patients without mucosal healing versus those with mucosal healing (15.9 vs 10.5 μg/mL; $p < 0.0001$). LRG cut-off for mucosal healing was 14.3 μg/mL (AUC 0.80; sensitivity 0.89; specificity 0.63); with an LRG cut-off for disease in the terminal ileum (type L1) of 14.3 μg/mL (sensitivity 0.91; specificity 0.53), and for colonic disease (type L2) of 14.0 μg/mL (sensitivity 0.95; specificity 0.73). The diagnostic performance of LRG and C-reactive protein (CRP) for mucosal healing was AUC 0.75 and AUC 0.60 ($p = 0.01$) for type L1 and AUC 0.80 and AUC 0.85 for type L2 (NS).

Comment (SM): Mucosal healing is an important long-term therapeutic goal for patients with IBD and to achieve this the disease activity needs to be regularly assessed with clinical symptoms and laboratory markers such as CRP, faecal calprotectin (FCP) etc. CRP is an acute phase protein synthesised in the liver in response to IL-6 stimulation and is the most widely used surrogate marker for monitoring clinical disease activity. Its usefulness can be limited because the CRP cut-off value for predicting mucosal healing is low. LRG is a new acute phase protein with properties similar to CRP. There are important differences too, which include stimulation by various cytokines such as IL-1β, TNF-α, IL-22 in addition to IL-6 and it is synthesised not only in the liver but also from sites of inflammation. This study found an optimal cut-off value for estimating mucosal healing in CD of 14.3 μg/mL and was more useful than CRP in predicting mucosal healing in the ileum dominant group suggesting its utility differs according to the site of the disease. The search for an ideal non-invasive marker to monitor mucosal healing has gained importance. Even though CRP and albumin in combination can improve the prediction of mucosal healing, CRP has the limitation of being unlikely to reflect true disease activity of small intestinal lesions. FCP is another useful non-invasive marker, but it has significant diurnal variation and there are no established cut-off values for mucosal healing. Active small bowel lesions are associated with poor prognosis in CD. The current study showed that, in terms of accuracy in predicting mucosal healing, LRG was superior to CRP in patients with ileal disease, but comparable to CRP in patients with colonic disease. However, low specificity and high false positivity suggest that the change in LRG values (LRG delta) may be more useful in monitoring rather than cut-off value alone. There is a surge of interest with more publications on LRG, which are all encouraging, and its role in mucosal healing is likely to get clearer in the near future.

Reference: Crohn's Colitis 360 2023;5(3):otad028

Abstract

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Allogenic stem cells for Crohn's anal fistulas: Treating early improves the deep remission rate

Authors: Fathallah N et al.

Summary: This French after-market study assessed the real-life efficacy of darvadstrocel injection for complex perianal fistulas in 43 patients with CD (22 male; median age 37 years) whose fistulas were drained with seton(s) and were receiving biologic treatment. Over a median 383-day follow-up, 28 (65%) patients had a clinical response (22 complete) and 16 (37%) achieved deep remission (complete combined clinical-radiological response). Perineal Disease Activity Index (PDAI) decreased, with 39 (91%) patients experiencing symptomatic improvement (discharge, pain, induration) and 28 (65%) with no perineal symptoms. Deep remission was associated with a shorter history of CD; <3 years was associated with higher odds (OR 4.5; p = 0.04).

Comment (SM): Perianal fistulas severely affect the quality of life of CD patients. They worsen the prognosis and increase the health care costs. Even though the biologics, especially the anti-TNF agent infliximab, approximately doubled the healing rates over placebo, the primary failure of fistula closure remains high (40%) and recurrences are frequent, especially in complex fistulas. After drainage, simple removal of seton is less effective than surgical closure of the tract. Stem cells are a recent alternative treatment due to their immunomodulatory, anti-inflammatory, regenerative and reparative effects. The cure rates with stem cell therapy at 24 weeks and 52 weeks were significantly higher than the surgical closure of internal opening. Stem cells are now commercially available in Europe (darvadstrocel) and this study aimed to evaluate the real-world efficacy of darvadstrocel injection into complex fistulas in CD. The 'deep remission' was defined as the association of a complete clinical response with a complete radiological response. This was seen in only 37% of patients. Nevertheless, PDAI decreased markedly and 91% of patients reported significant improvement in discharge, pain and indentation. This could be due to the anti-inflammatory and immunomodulating effects rather than reparative and regenerative effect. The adverse events included pain (14%) and abscess formation (21%). A duration of CD of <3 years was associated with deep remission. This should encourage the consideration of this treatment earlier in the course of the disease and further studies are needed to confirm. The place of stem cell therapy in relation to surgical obturation techniques like glue injection, flap advancement, ligation of inter sphincteric fistula etc, whose failure can lead to problematic fibrosis, also needs further clarification. Stem cell therapy appears to be an optimistic and useful option in the management of this frustrating phenotype of CD with considerable morbidity.

Reference: Colorectal Dis. 2023;25(11):2170-2176
Abstract

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Independent commentary by Dr Srikantaiah Manjunatha (Manju) FRACP

Dr Srikantaiah Manjunatha (Manju) is a Consultant Gastroenterologist at Te Whatu Ora-Southern, Dunedin and Honorary Senior Clinical Lecturer at the University of Otago. After completing his MBBS from the University of Mysore in India and MD (Medicine) from the prestigious PGIMER (Post Graduate Institute of Medical Education & Research), Chandigarh, India, he moved to the UK in 1988. He completed advanced training in medicine and gastroenterology in the UK after obtaining his MRCP (UK) in 1989. He worked as a registrar, senior registrar and consultant in medicine and gastroenterology for 25 years in the NHS, UK. He also held honorary faculty positions in the universities of Wolverhampton and Birmingham. He was elected FRCP (London) in 2009 and served as a national assessor for the JAG (Joint Advisory Group) for GI endoscopy quality for four years before retiring from the NHS in September 2014 and moving to New Zealand. He was elected FRACP in January 2016. His special interests are therapeutic endoscopy, inflammatory bowel disease and molecular mechanisms of gastrointestinal disease.

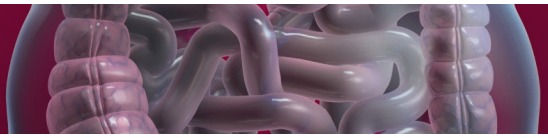
Inflammatory bowel disease and risk of colorectal polyps: A nationwide population-based cohort study from Sweden

Authors: Axelrad JE et al.

Summary: This Swedish study examined the types and risks of colorectal neoplasia (CRN) associated with specific polyp types in 41,880 patients with IBD (CD n = 12,850; UC n = 29,030) and 41,880 matched reference controls. During follow-up, 1648 IBD patients (3.9%; incidence rate 46.1 per 10,000 person-years) and 1143 controls (2.7%; 34.2 per 10,000 person-years) had an incident neoplastic colorectal polyp (aHR 1.23; 95% CI 1.12-1.35). The highest HR was associated with sessile serrated polyps (aHR 8.50; 95% CI 1.10-65.90) and traditional serrated adenomas (aHR 1.72; 95% CI 1.02-2.91). Risk of colorectal polyps were particularly elevated in those with IBD at a young age and 10 years after diagnosis. Absolute and relative colorectal polyp risks were greater with UC (aHRs 1.31) than CD (aHR 1.06); 20-year cumulative risk difference was 4.4% for UC and 1.5% for CD.

Comment (SM): IBD patients are at an increased risk of CRN, which includes colorectal dysplasia and colorectal cancer, due to chronic inflammation. Many disease- and patient-specific factors are attributed to the risk of CRN including disease extent, duration, degree of inflammation, concomitant primary sclerosing cholangitis (PSC), and prior CRN. It was generally believed that colorectal inflammation may suppress polyp formation and most of the neoplasia in IBD does not arise from typical adenomas. This was based on earlier studies which had heavy selection bias. The SCENIC consensus simplified the nomenclature of CRN in IBD. The distinction between IBD associated polypoid or visible dysplasia and sporadic adenomas was not deemed important, as endoscopic resection was recommended for all. There was scant information available characterising specific histological neoplastic architecture of colorectal lesions in IBD in comparison to the general population. This population-based study showed an increased risk of incident CRN polyps, particularly those of adenomatous, traditional serrated and tubule villous architecture, in patients with UC, compared to matched reference population. The incidence rate of neoplastic colorectal polyps and advanced polyps was 46.1 and 14.9 per 10,000 person-years, respectively, in IBD patients. In UC, a 1.3-fold risk of any neoplastic polyp, 1.4-fold increased risk of advanced polyps and 2.6-fold increased risk of traditional serrated adenomas, with the highest risk occurring after 20 years of follow-up, and in those with extensive colitis. The study is thought provoking, with the results different to our understanding of CRN in IBD for all these years. The endoscopists need to be even more vigilant in actively looking for all types of CRN in IBD. This also reinforces the need for closer endoscopic surveillance of UC patients, more so when the disease is extensive and has been present for over 20 years.

Reference: J Crohns Colitis 2023;17(9):1395-1409
Abstract



Systematic review with meta-analysis: Diagnostic performance of faecal calprotectin in distinguishing inflammatory bowel disease from irritable bowel syndrome in adults

Authors: Dajti E et al.

Summary: This systematic review and meta-analysis assessed the diagnostic performance of FCP in distinguishing patients with IBD from those with IBS based on 17 studies including 1956 patients. Random-effect bivariate modelling suggested the summary sensitivity was 85.8% (95% CI 78.3-91), with specificity of 91.7% (95% CI 84.5-95.7). With an IBD prevalence of 1%, the negative predictive value (NPV) was 99.8% and the positive predictive value (PPV) was 9%. Subgroup analyses suggested greater sensitivity at a cut-off of ≤50 µg/g versus >50 µg/g (87% vs 79%) and in Western versus Eastern countries (88% vs 73%), with similar specificity. All included studies had a "high" or "unclear" risk of bias.

Comment (SM): Calprotectin is a protein bound to calcium and is produced when neutrophils are activated in inflammatory process to protect the body. It is found in saliva, serum, spinal fluid, and faeces (FCP). FCP is used as a surrogate marker for intestinal inflammation and to monitor response to treatment and state of the disease in IBD. IBS symptoms can mimic symptoms of IBD, and a reliable non-invasive marker would help to distinguish and avoid significant costs and risk of invasive procedures. This systematic review and meta-analysis of 17 studies with 1956 patients looked at the diagnostic utility of FCP in identifying IBD in patients with symptoms of IBS. The pooled sensitivity of 85.8% and specificity of 91.7% applied to an IBD prevalence of 1% in primary care translated to a NPV of 98.8% and a PPV of only 9%. For a prevalence of 5% IBD in secondary care the NPV was still high at 99.2% and PPV was 34%. The pooled sensitivity and specificity for CD was 92% and 93% respectively and for UC 83% and 83% respectively. FCP also showed higher sensitivity in Western population than Eastern population (86% vs 73%) but NPV was not affected. These data clearly demonstrate the usefulness of FCP in ruling out IBD when the patients present with symptoms of IBS with low FCP. The same does not apply to making a positive diagnosis of IBD when FCP is high due to very low PPV. These findings are more meaningful when the cut-off value is set at 50 µg/g of faeces. Infection, malignancy, drugs like NSAIDs, food allergy, coeliac disease, and cirrhosis are some of the causes for false positive results. Abnormal FCP can cause the concern of IBD in patients and primary care referrers alike and the normal FCP can effectively rule out IBD. However, raised FCP is not diagnostic of IBD on its own and should be assessed in conjunction with other clinical features and investigations when appropriate.

Reference: Aliment Pharmacol Ther. 2023;58(11-12):1120-1131
Abstract

Induction and maintenance treatment with upadacitinib improves health-related quality of life in patients with moderately to severely active ulcerative colitis

Authors: Panés J et al.

Summary: This *post-hoc* analysis of a 52-week, placebo-controlled, phase III study assessed the Health-Related Quality of Life (HRQoL) benefits of upadacitinib in 988 UC patients across a range of patient-centred outcomes including the Ulcerative Colitis Symptoms Questionnaire (UCSQ), Inflammatory Bowel Disease Questionnaire (IBDQ), Work Productivity and Impairment Questionnaire (WPIQ), 36-Item Short Form survey (SF-36), and European Quality of Life-5 Dimension 5 Levels (EQ-5D-5L). Improvements with upadacitinib were observed in all HRQoL measures ($p < 0.001$) except WPIQ-absenteeism versus placebo as early as week 2 of induction, which were sustained until week 52, with more 15 mg or 30 mg upadacitinib than placebo recipients achieving meaningful within-person change in the UCSQ, IBDQ, overall work impairment, presenteeism, and activity impairment, SF-36 physical and mental component summaries; and EQ-5D-5L ($p < 0.001$).

Comment (SM): Patients with UC experience reduced HRQoL compared to the general population. UC may impact work productivity, off work activity and general wellbeing due to disease-related physical and psychological burden. Improvements in patient-reported outcomes (PRO) are often a target for UC therapy and it is recommended that the primary therapeutic goal in IBD is to limit the impact of disease on patients' quality of life. STRIDE (Selecting Therapeutic Targets in Inflammatory Bowel Disease) and SPIRIT (Selecting End Points for Disease-Modification Trials) consensus initiatives highlight the importance of PRO and impact of disease on patients' quality of life. Upadacitinib is a selective and reversible Janus kinase (JAK) inhibitor, and its efficacy has been demonstrated as an induction and maintenance treatment for adults with moderate-to-severe UC. The aim of this study was to establish the HRQoL of 8-week induction treatment with upadacitinib across a broad range of PRO (IBD symptoms, work productivity, physical and mental qualities of life and general wellbeing) in a *post hoc* analysis of phase III studies, and also to determine whether any demonstrated benefits are sustained with 52-week maintenance treatment for responders on induction. The benefits identified in HRQoL with upadacitinib treatment fulfil the recommendations of the STRIDE initiative that emphasises the restoration of HRQoL as an important long-term treatment goal for patients with IBD. HRQoL is increasingly recognised as an important factor influencing patient preferences regarding treatment options. Clinical, endoscopic, and histological remission notwithstanding, the PRO and HRQoL also play an equally important role in future clinical trials and treatment options for IBD.

Reference: Inflamm Bowel Dis. 2023;29(9):1421-1430
Abstract

Anti-tumour necrosis factor-induced skin rashes in inflammatory bowel disease: A systematic review and evidence-based management algorithm

Authors: Au M et al.

Summary: This systematic review assessed cutaneous complications (including psoriasiform, eczematous and lupoid eruptions) of anti-TNF therapy in patients with IBD and the authors developed an algorithm for management based on 34 studies. Eczema may be managed with topical agents and anti-TNF therapy continued; however, immediate cessation of anti-TNF treatment and alternative immunomodulators are required for the development of lupus. Psoriasis and psoriasiform lesion management may follow a step-wise process with topical treatments in less severe cases, and a switch to an alternative anti-TNF or an alternative class of biological agent in more severe cases.

Comment (LH): Anti-TNF agents have changed the course of IBD and since their arrival on the market have become a mainstay in the therapeutic treatment of IBD. Although they have a relatively good safety profile, their use has been associated with a wide range of paradoxical autoimmune dermatological complications, some of these leading to treatment discontinuation. In this systematic review by Au et al., which looked at the four most common cutaneous complications, it was found that eczema, occurring in 6.6% of those reviewed, could generally be managed with topical agents and anti-TNF therapy continuation. Cutaneous lupus reactions on the other hand, which overall occurred in 2.4% of those on infliximab and 1.8% of those on adalimumab, required immediate therapy cessation with, in some cases, the addition of systemic steroids and steroid sparing agents as well as alternative immunomodulator consideration. This review is limited by the lack of robust evidence, largely consisting of retrospective studies and case series/reports with significant heterogeneity in diagnostic criteria regarding dermatologic diagnosis and a lack of dermatologist involvement and histological confirmation of the diagnosis in several studies. The burden of skin involvement must be balanced against the risk of relapse and additional therapy in each individual patient with more high-quality data to guide management is required in this field. However, it is encouraging that we now have two new agents available in New Zealand for the treatment of IBD. There is no evidence to date that adverse events caused by anti-TNF agents give rise to a higher adverse event profile with other agents.

Reference: Intern Med J. 2023;53(10):1854-1865
Abstract

Combined use of CDAI and blood indices for assessing endoscopic activity in ileocolic Crohn's disease

Authors: Hu X et al.

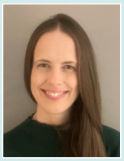
Summary: This retrospective multicentre study was conducted to develop a convenient, non-invasive tool to assess endoscopic activity in 300 patients with ileocolic CD (training cohort 210 patients; test cohort 90 patients) using independent risk factors (CDAI, CRP, platelet-to-lymphocyte percentage ratio [PLpR]) associated with endoscopic activity combined into a comprehensive index. The index achieved good discrimination and was better than CDAI in the area under the receiver operating characteristic curve in the training cohort (AUC 0.849 vs 0.769; $p < 0.05$), which was confirmed in the test cohort (AUC 0.84; 95% CI 0.744-0.936). Intra-individual comparison also suggested the comprehensive index was superior in the prediction of endoscopic activity. Subgroup analyses suggested that the AUC of the comprehensive index was higher than CDAI especially in the inflammatory phenotype (0.824 vs 0.751; $p < 0.05$).

Comment (LH): Endoscopic healing is a recommended treatment target in IBD associated with improved long-term clinical outcomes. Evidence of endoscopic remission has been shown to be associated with lower relapse and hospitalisation rates as well as reduced need for surgery.[1] Although mucosal healing has emerged as a primary treatment target, significant limitations exist in terms of routine adoption due to expense and feasibility of this approach. A study by Yang et al., for example showed a low uptake of treat-to-target colonoscopy for the assessment of mucosal healing in a study of a prospective adult research cohort with IBD (SPARC IBD), showing only half received a colonoscopy in the 3-15 months after starting a new IBD treatment.[2] This has led to numerous non-invasive tools to evaluate endoscopic activity in patients with IBD. In this retrospective multicentre study by Hu et al., it was found that combining CDAI, CRP and PLpR had the best performance characteristic in predicting endoscopic disease activity in ileocolic CD with the sensitivity, positive predictive value, negative predictive value and accuracy all superior to any of the individual index components alone. Despite the promising results, the retrospective design and relatively small number of participants means that further studies are required. Additionally, recent studies have shown that additional biomarkers including FCP, vitamin D and albumin may also be used to assess endoscopic activity providing areas for future research.[3-4] Furthermore, intestinal ultrasound is being adopted in a number of IBD centres as a sensitive, specific, low-cost and non-invasive modality to investigate for disease activity.

1) De Cruz et al. Mucosal healing in Crohn's disease: a systematic review. Inflamm Bowel Dis. 2013:19(2): 429-44
2) Yang et al. Utilization of treat-to-target monitoring colonoscopy after treatment initiation in the US-based study of a prospective adult research cohort with inflammatory bowel disease. Am J Gastroenterol. 2023;118(9):1638-1647
3) Mosli et al. C-reactive protein, fecal calprotectin, and stool lactoferrin for detection of endoscopic activity in symptomatic inflammatory bowel disease patients: a systematic review and meta-analysis. Am J Gastroenterol. 2015;110(6):802-19
4) Yang et al. Clinical evaluation of vitamin D status and its relationship with disease activity and changes of intestinal immune function in patients with Crohn's disease in the Chinese population. Scand J Gastroenterol. 2021;56(1):20-29

Reference: BMC Gastroenterol. 2023;23(1):337
Abstract

Independent commentary by Dr Laura Hollingsworth



Laura graduated from the University of Tasmania Medical School in 2017. She has since worked as a junior doctor at the Royal Hobart Hospital in Tasmania and has completed a year of Advanced Training in General and Acute Care Medicine with 6 months in Gastroenterology before starting as an advanced gastroenterology trainee at Dunedin Hospital in 2023. Laura has a keen interest in inflammatory bowel disease and has been involved in several research projects in the field.

Independent commentary by Professor Michael Schultz MD, PhD, FRACP

Michael studied in Erlangen-Nuremberg and trained in Manchester, London and Regensburg, Germany. He went to Chapel Hill, NC at the University of North Carolina for his postdoctoral fellowship. Michael joined the Department of Medicine at the University of Otago in 2005, taking up a joint clinical position as a Senior Lecturer and Gastroenterologist with the Southern District Health Board. He was Head of the Department of Medicine from 2016 to 2021. He was promoted to Professor in 2018. Michael's research expertise is focused on clinical and basic scientific aspects of inflammatory bowel diseases, with an emphasis on host-microbe interactions. He has several years of experience working with animal models of experimental colitis, and with the administration of clinical trials in patients with IBD. Michael is Director of the Gut Health Network which was established in 2011, and was elected as the President of the New Zealand Society of Gastroenterology in November 2016. Since early 2023, Michael is the Clinical Director for the Te Whatu Ora Southern Gastroenterology Department.

Avoidant restrictive food intake disorder prevalent among patients with inflammatory bowel disease

Authors: Yelencich E et al.

Summary: This cross-sectional study recruited 161 adult patients with IBD (CD 45.3%; UC 51.6%; IBD-unclassified 3.1%) from an ambulatory clinic in order to estimate the prevalence of avoidant/restrictive food intake disorder (ARFID), evaluate risk factors, and examine the association with risk of malnutrition associated with IBD. The Nine-Item ARFID Screen tool was used to determine ARFID risk, while nutritional risk was assessed with the Patient Generated-Subjective Global Assessment. Overall, 28 (17%) of patients exhibited a positive ARFID risk score (≥24). The majority of patients avoided ≥1 foods when they were experiencing a flare of their IBD, and as many as 74% continued to do so while asymptomatic. The risk of active symptoms and inflammation were associated with ARFID; ORs 5.35 (95% CI 1.91-15.01) and 3.31 (95% CI 1.06-10.29), respectively. Furthermore, a positive ARFID risk screen was associated with the risk of malnutrition (60.7% vs 15.8%; $p < 0.01$).

Comment (MS): ARFID is applicable to individuals of any age whose eating behaviours lead to insufficient caloric and/or nutrient intake. Studies have shown that the prevalence of ARFID in patients with various gastrointestinal disorders lies between 12-21%. This study, conducted in California on 161 outpatients, showed that approximately 17% of patients with IBD (approximately half/half CD and UC) could be classified as having ARFID according to the scoring tool. As expected, patients with symptoms were more likely to avoid certain foods than those without symptoms, however, even the latter continued to avoid foods. From all patients with a positive ARFID risk score, over 60% were at risk of malnutrition. 54% had a normal range BMI, while 5.6% were underweight and 40.4% overweight/obese. Foods that were most likely avoided were lactose containing, spicy, alcohol, wheat, deep-fried and caffeine. Patients mostly at risk were those with symptoms, active inflammation and recent corticosteroid use. Patients with IBD who are malnourished are more likely to have emergency surgeries, hospital admissions and active flares. These findings are likely applicable to the New Zealand situation, however, as recently demonstrated (McCarthy NE et al., Nutr Diet 2023), there are not enough dietitians with experience in dietary management of IBD.

Reference: Clin Gastroenterol Hepatol. 2022;20(6):1282-1289.e1
Abstract

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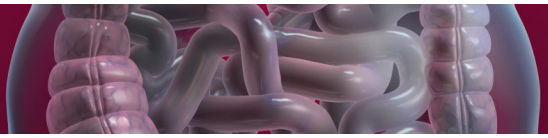

Current nutritional therapies in inflammatory bowel disease: Improving clinical remission rates and sustainability of long-term dietary therapies

Authors: Reznikov EA & Suskind DL

Summary: These authors undertook a literature review with an aim to increasing the understanding of diet and its effect in CD and UC. They stress that the contribution of diet to the development and treatment of IBD in both adults and children cannot be overstated. The evidence suggests that nutritional interventions improve both clinical symptoms and inflammatory burden in these groups of patients. The authors conclude that the current clinical literature supports the incorporation of low processed whole foods in the diet and the elimination of detrimental components. They suggest that prospective and longitudinal dietary studies are warranted to determine sustainable and long-term dietary options, and to gain a deeper understanding of the mechanisms involved.

Comment (MS): Dietary intervention in IBD can be aimed at different targets. For one, as outlined in the previous study, to allow for a balanced diet to avoid malnutrition, on the other hand nutrition can be used as therapy to ideally reduce the inflammatory burden of disease, induce remission and prolong symptom-free periods. The authors reviewed the available literature concerning Exclusive Enteral Nutrition (EEN), Partial Enteral Nutrition (PEN) with and without an Exclusion Diet, Whole Foods and Exclusion Diets, Specific Carbohydrate Diet (SCD), FODMAP, and Mediterranean Diet (MD). There is no doubt that integration of nutritional strategies improves the life of patients with IBD. EEN is a fully accepted treatment regime in CD for both paediatric and adult patients, however, compliance issues make EEN in adults less effective. No data supports the use of EEN in UC. Comparison between PEN, in which patients receive at least 50% of their energy intake from formula, and EEN showed that EEN is superior in the induction of remission, and laboratory parameter normalisation. However, when combining PEN with the CD Exclusion Diet compared to EEN, there was little difference. Promising is the SCD for both children and adults with remission rates of approximately 36%. The low FODMAP diet was seen as mainly effective in the treatment of remaining IBS-like symptoms in patients with IBD, while the MD was shown to improve disease severity scores.

Reference: Nutrients 2023;15(3):668
Abstract

SCIENCE BLOG

Dr Srikantaiah Manjunatha BSc, MBBS, MD(Med), FRCP(Lond), FRACP Consultant Gastroenterologist

Protein HBx from HepB virus family – The elusive X factor in ulcerative colitis pathogenesis

The role of intestinal bacterial dysbiosis in the pathogenesis of IBD is well established. Besides bacteria, the gut microbiota includes yeasts, archaea and viruses whose role was ill defined due to limitations in studying their composition and significance. New cutting edge technologies in nucleic acid sequencing, -omics and bioinformatics have made possible more sensitive metagenomics, identifying the role of these less understood players, including prokaryotic and eukaryotic viruses, in intestinal inflammation.

The GI tract harbours nearly 10^9 virus-like particles (VLP) per gram of tissue, with a majority of prokaryotic viruses (bacteriophages infecting bacteria) and a minority of eukaryotic viruses, which can infect the host cells directly. In IBD, bacteriophages are the 'predators' in the gut ecosystem altering their bacterial 'prey' resulting in 'dysbiosis' of the bacterial population initiating the IBD. The eukaryotic viruses interact directly with the host's innate immune system leading to chronic inflammation. This 'viral dysbiosis' could well be the triggering event in the inflammation cascade of IBD. The alterations in the faecal virome is characterised by a high abundance of *Caudovirales* and a low abundance of *Microviridae* members. One of the most abundant viral groups in the human gut, *Crassviridae* comprising of CrAss-like phages, have also been shown to be depleted in IBD. Some of these phages could exist in symbiosis with their bacterial host, and even drive bacterial diversity through a process called phase variation. Viral community typing might help to understand, differentiate and stratify a complex disease like IBD. Different novel phages associated with treatment success have also been identified.

Another novel association of viruses and IBD was reported by the identification of upregulation of hepatitis B virus (HBV)-encoded oncogene X protein (HBx), belonging to the *Orthohepadnavirus* genus, in the gut virome of early diagnosed, treatment-naïve paediatric patients with UC, but not CD. Further studies confirmed the HBx positivity in the biopsies of two cohorts of patients ranging from 47% to 57%. Previous exposure or current infection with hepatitis B, the only human virus of *Orthohepadna* genus, had been ruled out. This was intriguing as to how HBx protein could find its way to the gut mucosa as most viruses in this genus are predominantly hepatotrophic. Even though HBV is known to persist in extrahepatic tissues without evidence of systemic disease, this seemed unlikely in these patients with UC. The alternative explanation could be that there are hitherto unknown members of *Orthohepadnavirus* genus, possibly zoonotic, which are acquired through contaminated food or water leading to chronic exposure of the gut.

There is compelling evidence for the putative role of HBx in the aetiopathogenesis of UC. Mice exposed to HBx protein developed colitis with an altered immune milieu. The inflammation was reversed by treatment with HBx targeting siRNA. The pro-inflammatory effect of HBx was independent of the gut bacteria as pre-treatment of mice with an antibiotic cocktail did not reverse the colitis.

HBx is a small protein of 154 amino acids encoded by an open reading frame X (X-ORF) of the HBV genome which is highly conserved in the Hepadna virus family. Its importance in liver cancer was recognised by the fact that avian Hepadna virus infection, where X-ORF is absent, is not associated with liver cancer. HBx protein seems to affect numerous functions like cell signalling, cytochrome calcium regulation, cell proliferation, DNA repair, apoptosis etc., which are all implicated in its oncogenic potential. It is even speculated that a similar effect driven by HBx protein may be related to colorectal carcinogenesis in patients with UC. Further studies are needed to understand the importance of HBx in carcinogenesis and to use it as a potential target for preventing cancer in patients with UC. HBx is an initial trigger for inflammation in UC and not an epiphenomenon in later years due to chronic inflammation or immune modulatory treatment. In parallel with chronic hepatitis B the 'chronic carrier state' may be a deceptive state of harmony between host and virus with the risks of flares of inflammation and even cancer lurking in the background. Is HBx protein indeed the elusive X factor in the pathogenesis of UC and a potential new therapeutic target? Only time and further research may reveal the truth, but right now, the Hepadna virus family seem to be still guarding the family secret!

Further reading:

Massimino L et al. Gut virome-colonising Orthohepadnavirus genus is associated with ulcerative colitis pathogenesis and induces intestinal inflammation in vivo. Gut 2023;72(10):1838-1847

Mukhopadhya I et al. The gut virome: the 'missing link' between gut bacteria and host immunity? Therap Adv Gastroenterol. 2019;12:1756284819836620

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