IBD RESEARCH REVIEW™

Making Education Easy

Issue 64 – 2024

In this issue:

- Epidemiology of IBD in Oceania
- Adalimumab and risk of serious infections in CD patients
- Childlessness in patients with IBD
- Post-operative infectious complications in IBD
- Serum levels of lipoprotein lipase in IBD
- Long-term risk of arrhythmias in IBD
- Risk of cardiovascular events with small molecule drugs
- Risk of acute coronary syndrome in IBD
- Science blog: IBD and cardiovascular disease

Abbreviations used in this issue

5-ASA = 5-amino salicylic acid
aHR = adjusted hazard ratio
CD = Crohn's disease
CI = confidence interval
CRP = C-reactive protein
CVD = cardiovascular disease
IBD = inflammatory bowel disease
IBDU = IBD unclassified
IFN-ϒ = interferon gamma
IL = interleukin
JAK = Janus kinase
LPL = lipoprotein lipase
S1P = sphingosine-1-phosphate receptor
RCT = randomised controlled trial
TNF = tumour necrosis factor
UC = ulcerative colitis

CLICK HERE
to read previous issues of IBD Research Review

Welcome to Issue 64 of IBD Research Review.

A systematic review and meta-analysis reports that the incidence and prevalence of IBD in Oceania is high. Meanwhile, and analysis of data from the PYRAMID Registry has found that patients with CD who respond to adalimumab have lower risk of developing serious infections, compared with non-responders. We also include four studies reporting on the association of IBD and cardiovascular disease and this is followed by our Science Blog by Dr Srikantaiah Manjunatha discussing this association.

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

Kind regards,

Professor Michael Schultz
michaelschultz@researchreview.co.nz

Dr Srikantaiah Manjunatha
manju@researchreview.co.nz

The epidemiology of inflammatory bowel disease in Oceania: A systematic review and meta-analysis of incidence and prevalence

Authors: Forbes AJ et al.

Summary: This systematic review and meta-analysis including 19 incidence and 11 prevalence studies assessed the epidemiology of IBD in Australia, New Zealand, and the surrounding region (Oceania). Pooled incidence rates were 19.8 per 100,000 person-years (95% CI 15.8-23.7) for IBD, 8.3 per 100,000 person-years (95% CI 6.9-9.8) for CD, and 7.4 per 100,000 person-years (95% CI 5.7-9.1) for UC. Pooled estimates from prevalence studies were 303.3 per 100,000 people (95% CI 128.1-478.4) for IBD, 149.8 per 100,000 people (95% CI 71.0-228.5) for CD, and 142.2 per 100,000 people (95% CI 63.1-221.4) for UC.

Comment (MS): This study, led by a research group in Canterbury pooled incidence and prevalence data from over 30 studies from across Oceania. Most studies were conducted in Australia and New Zealand, but two studies included were from Fiji and French Polynesia, respectively. The highest incidence was 39.8 per 100,000 person-years recorded in Canterbury, which had increased from 25.2 per 100,000 person-years over the preceding 10 years. A similarly high incidence was found in Barwon, Australia with 29.31 per 100,000 person-years. As expected, there was an even split between male and female and the disease affected predominantly people of European descent. The pooled prevalence rate for IBD was 303.3 per 100,000 persons (CD 149.8; UC 142.2; IBD unclassified [IBDU] 9.5). All-in-all, there was a significant heterogeneity observed amongst the studies, reflecting different geography, ethnicity and methodology. Great variations existed between the studies with hospital-based studies demonstrating lower levels of incidence and prevalence compared to population-based estimates. Although this review aimed to cover Oceania, only two studies from the Pacific were included.

Reference: Inflamm Bowel Dis. 2023;Dec 30 [Epub ahead of print]

Abstract

Impact of treatment response on risk of serious infections in patients with Crohn's Disease: Secondary analysis of the PYRAMID Registry

Authors: Ahuja D et al.

Summary: This secondary analysis of data from the PYRAMID Registry assessed the impact of treatment response on the risk of serious infections in 1515 adalimumab-treated CD patients. Overall, 763 (50.4%) patients were classified as responders at 6 months; they were less likely than non-responders to have moderate-to-severe symptoms (55.6% vs 33%), or to require steroids (45.5% vs 17.3%) or opiates (6.6% vs 1.3%) at baseline. During 36 months of follow-up, responders were 34% less likely to experience serious infections (HR 0.66; 95% CI 0.46-0.96). The risk of gastrointestinal and extra-intestinal infections was also lower in responders than non-responders.

Comment (MS): According to generally accepted guidelines, risk factors for serious infections are being assessed prior to the initiation of immunomodulatory treatment, especially prior to initiating biological therapy. The authors aimed to analyse the impact of response to treatment on the risk of infection. Serious infections are thought to be the result of systemic immunosuppression, however, vedolizumab, a gut-specific agent, has a similar risk profile. The authors used the PYRAMID Registry for patients with moderately to severely active CD treated with adalimumab and followed over 6 years and stratified between responders (steroid-free remission) and non-responders. Of 5025 patients, 1515 patients were included in the analysis. 763 patients or 50.4% had responded to treatment at 6 months; 6.8% responders compared to 9.4% experienced serious infections between 6-36 months on treatment. Most infections were gastrointestinal. There were however significant differences between the cohorts which need to be taken into account when looking at this data. For example, responders had shorter mean disease duration (10.4 vs 8.6 years, $p < 0.01$), lower rates of diabetes (2.7% vs 1%; $p = 0.03$), less CD-related surgery (46.5% vs 35.1%; $p < 0.01$), opiate use (6.6% vs 1.3%; $p < 0.01$) and corticosteroid use (45.5% vs 17.3%; $p < 0.01$), but were more likely to be on immunomodulators, mostly azathioprine (34.2% vs 39.2%; $p = 0.05$). All these factors, especially steroid use, could play a role in complication susceptibility.

Reference: Clin Gastroenterol Hepatol. 2024;Jan 10 [Epub ahead of print]
Abstract

RACP MyCPD Program participants can claim the time spent reading and evaluating research reviews as CPD in the online **MyCPD program**.
Please contact **MyCPD@racp.edu.au** for any assistance.

New Zealand Research Review subscribers can claim CPD/CME points for time spent reading our reviews from a wide range of local medical and nursing colleges. Find out more on our **CPD page**.

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.

For more information, please go to http://www.medsafe.govt.nz

Childlessness in patients with inflammatory bowel disease – data from the prospective multi-center Swiss IBD Cohort Study

Authors: Sulz MC et al.

Summary: This analysis of data from the large prospective multicentre, nationwide Swiss Inflammatory Bowel Disease Cohort Study (SIBDCS) examined the rate of childlessness and the cumulative probability of reproduction in 3300 female and male IBD patients. Among 1412 female patients, 184 (70.1% CD and 29.9 % UC) were aged ≥40 years and were diagnosed with IBD before the 30 years of age, of whom 59 (32.1%) were childless. The proportion of childless females was higher in CD versus UC (36.4% vs 21.8%; p = 0.026), a relative risk of childlessness of 1.7 in CD versus UC, and higher than in the general Swiss general population (21%). The mean number of children was 1.32 per patient, with CD at 1.12 per female and UC/indeterminate colitis at 1.78 per patient (p = 0.001). A longitudinal analysis of IBD patients trying to conceive indicated that 50% of women were neither pregnant nor had born a child 5 years after trying to conceive.

Comment (LH): Infertility, childlessness and adverse pregnancy outcomes are significant issues for those with IBD and often cause substantial concern. The current literature has predominantly addressed pregnancy outcomes in IBD with less focus on infertility and rates of childlessness.[1] This prospective multi-centre Swiss cohort study looks specifically at childlessness rates in those with IBD and avoids the issue of infertility due to its associated lack of objectivity and complexity. Sulz et al., found that rates of childlessness in those with CD were higher than in both those with UC and the general population. For example, 36.4% of females ≥40 years with CD diagnosed before age 30 years were childless. This compared to 21.8% of those with UC and 21.0% of the general population. The difference in childlessness rates is speculated to be due to voluntary childlessness, with evidence showing the involuntary infertility rates in families with IBD do not differ from control populations.[2] Reasons for voluntary childlessness reported in the literature include issues surrounding fear of disease exacerbation, IBD inheritance, fear of drug interactions and an inability to care for the child.[3,4] Despite Sulz et al., speculating this may be a cause for the difference in childlessness rates between CD, UC, and the general population, ultimately one key issue in this study is that the use of childlessness implicates both voluntary and involuntary causes and therefore conclusions regarding the true cause for difference between groups cannot be determined. This study highlights the need for further research around childlessness and infertility in both CD and UC patients and that practitioners should actively address this topic during patient review.

1. *Hoffmann P et al. Pregnancy with inflammatory bowel disease: Outcomes for mothers and their children at a European tertiary care center. J Obstet Gynaecol Res. 2022;48(3):621-33*
2. *Tavernier N et al. Systematic review: fertility in non-surgically treated inflammatory bowel disease. Aliment Pharmacol Ther. 2013;38(8):847-53*
3. *Marri SR et al. Voluntary childlessness is increased in women with inflammatory bowel disease. Inflamm Bowel Dis. 2007;13(5):591-9*
4. *Mountifield R et al. Fear and fertility in inflammatory bowel disease: a mismatch of perception and reality affects family planning decisions. Inflamm Bowel Dis. 2009;15(5):720-5*

Reference: J Gastrointestin Liver Dis. 2023;32(4):460-468
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.

Risk and management of post-operative infectious complications in inflammatory bowel disease: A systematic review

Authors: Mowlah RK & Soldera J

Summary: This systematic review assessed evidence for risk factors in IBD patients associated with increased post-operative infectious complications and considered strategies to reduce morbidity and mortality based on 35 studies. Post-operative complication risk factors included malnutrition, obesity, hypoalbuminaemia, and preoperative abscesses. Increased infectious complications were associated with peri-operative blood transfusions. Post-operative complications were not affected by use of medications such as 5-aminosalicylates and immunomodulators, but an increased risk of complications was associated with corticosteroids. Ustekinumab and vedolizumab had similar infectious complication rates as other treatments.

Comment (LH): Post-operative infectious complications pose a significant concern in those with IBD. Despite the marked advance of medical therapy in IBD since the introduction of biologic therapy, surgery still remains an important strategy in both UC and CD with up to 20% of UC and 80% of CD patients undergoing surgery during their lifetime.[1] Mowlah et al., have highlighted hypoalbuminaemia, malnutrition, preoperative abscess, obesity, perioperative blood transfusion and corticosteroid use to be associated with increased risk of complications including post-operative infection. Anti-TNF therapy impact showed conflicting results, possibility influenced by timing and patient population. Several primary strategies have been highlighted to reduce these complications including pre-operative nutritional risk screening with the use of tools such as Onodera's Prognostic Nutritional Index and subsequent optimisation prior to surgery. Addressing peri-operative anaemia to minimise blood transfusion requirements with consideration of erythropoietin and iron may also be considered and aims made to taper and withdraw corticosteroids. However, thiopurines were deemed safe to use in patients with IBD, and while biological agents appear to be relatively safe, it is advised to plan the timing of surgery in relation to the last dose of the drug. This systematic review provides insight into the multiple factors that must be considered in the perioperative period of a patient with IBD. However, further investigations are required in terms of the role of emerging therapies such as ustekinumab and vedolizumab in the perioperative setting as well as more longitudinal studies exploring the influence of personalised nutritional strategies on surgical outcome.

1. *Lowe SC et al. Declining rates of surgery for inflammatory bowel disease in the era of biologic therapy. J Gastrointest Surg. 2021;25:211-9*

Reference: World J Gastrointest Surg. 2023;15(11):2579-2595
Abstract

IBD and Cardiovascular disease

Serum levels of lipoprotein lipase are increased in patients with inflammatory bowel disease

Authors: Rodríguez-Hernández O et al.

Summary: This cross-sectional study examined whether serum lipoprotein lipase (LPL) levels differ between 197 IBD patients and 208 age- and sex-matched controls and whether features of IBD are related to LPL levels. In a multivariate analysis, including cardiovascular risk factors and lipid profile changes caused by IBD, patients had a higher level of circulating LPL (beta coefficient 196 ng/mL; 95% CI 113-259; $p < 0.001$), LPL serum levels did not differ between CD and UC. Serum CRP levels, disease duration, and ileocolonic CD were positively related to LPL; however, LPL was not associated with subclinical carotid atherosclerosis.

Comment (SM): LPL is an extracellular enzyme crucial in the lipid metabolism, specifically in the breakdown of triglycerides (TG) in the circulating lipoproteins. LPL breaks down TG into free fatty acids and glycerol, which can then be utilised for energy or stored in adipose tissue. IBD is associated with a state of 'inflammatory dyslipidaemia' with a decrease in total cholesterol and low-density lipoprotein cholesterol (LDL-C) and an increase in TG and high-density lipoprotein cholesterol (HDL-C) compared to healthy controls. The combination of high risk of cardiovascular disease (CVD) with low levels of cholesterol is known as 'lipid paradox' and is consistently seen in other inflammatory diseases also. The main inhibitors of LPL are apolipoprotein-CIII (ApoC-III) and angiopoietin-like proteins. LPL has a significant role in the progression of atherosclerosis, and, for this reason, therapies aimed at increasing LPL mediated clearance of TG by decreasing the activity of LPL inhibitors like ApoC-III are emerging. In this study it was interesting to note the increase rather than decrease in LPL levels despite the lipid profile. This was also associated with disease duration, activity and phenotype suggesting LPL may have a role in inflammatory dyslipidaemia and CVD risk in IBD patients. LPL has differential effects on several inflammatory pathways that are relevant in atherosclerosis. It has been shown to regulate TNF-α and IFN-ϒ-mediated inflammatory cytokine signal transduction pathways in aortic endothelial cells and reverse TNF and very low-density lipoprotein cholesterol (VLDL) stimulated cell adhesion molecules. The upregulation of LPL disproportional to TG levels is probably a primary response to inflammation and exact reason is not clear. There are also reduced levels of ApoC III in inflammation that can result in raised LPL levels. The relationship between LPL and atherosclerosis is complex and multifactorial. On one hand it plays a protective role by clearing TG rich lipoproteins from blood stream and reduces the availability of TG to form atheromatous plaques. On the other hand, there are factors that can disrupt this balance and contribute to atherosclerosis. These include inflammatory dyslipidaemia, persistent inflammation, genetic factors, insulin resistance etc. LPL levels in IBD are independent and not a consequence of other changes in lipid profile caused by IBD. Further studies are needed to clarify the implications of these findings and the role of LPL in IBD and CVD.

Reference: Int J Mol Sci. 2023;24(6):5194
Abstract

Long-term risk of arrhythmias in patients with inflammatory bowel disease: A population-based, sibling-controlled cohort study

Authors: Sun J et al.

Summary: This analysis of a Swedish nationwide histopathology cohort assessed the long-term risk of arrhythmias in 24,954 CD patients (median age at diagnosis 38.4 years; 52.2% female), 46,856 UC patients (median age 42.1 years; 46.3% female), and 12,067 IBDU patients (median age 43.8 years; 49.6% female), and matched reference individuals and IBD-free full siblings. Over a median 10-year follow-up, 7.6% of CD patients, 8.9% of UC patients, and 8.2% of IBDU patients developed arrhythmias, compared with 6.7%, 7.5%, and 6.0% of matched reference individuals. Overall arrhythmias were increased in CD (54.6 vs 46.1 per 10,000 person-years; aHR 1.15; 95% CI 1.09-1.21; $p < 0.001$), UC (64.7 vs 53.3 per 10,000 person-years; aHR 1.14; 95% CI 1.10-1.18; $p < 0.001$), and IBDU (78.1 vs 53.5 per 10,000 person-years; aHR 1.30; 95% CI 1.20-1.41; $p < 0.001$), corresponding to one extra arrhythmia case per 80 CD, 58 UC, and 29 IBDU cases over 25 years. IBD patients also had an increased risk of specific arrhythmias, except for bradyarrhythmia.

Comment (SM): Although previous studies had explored the association between IBD and cardiac arrhythmias, the results were unclear and inconclusive, and the focus was mainly on atrial fibrillation which is the commonest arrhythmia. Systemic inflammation driven aetiology for cardiac arrhythmias has been attributed through various mechanisms including structural remodelling (accelerated atherosclerosis, myocardial injury, and fibrosis), electrical changes (termed inflammatory channelopathies) as well as other indirect effects like altered central and peripheral sympathetic effects. This nationwide population-based study found that patients with IBD were at a high risk of developing overall and specific arrhythmias (atrial fibrillation/flutter, supraventricular and ventricular arrhythmias/cardiac arrest) than reference individuals and their IBD free full siblings. The increased risk persisted over 25 years after IBD diagnosis and was higher in patients diagnosed between 18-39 years of age. No significant association was noted for bradyarrhythmia. Although the link between IBD and arrhythmias is intricate chronic systemic inflammation seems to be the key component. Inflammatory cytokines, particularly, TNF, IL-1 and IL-6, exert arrhythmogenic effects through directly affecting cardiac structural and electrical changes and indirectly through affecting other organ systems. Other contributors, as suggested in other CVD studies, include platelet and endothelial dysfunction, oxidative stress, hypercoagulability, and gut microbiome. Some medications like steroids may lead to increased risk of adverse CVD events while others like 5-ASA and anti-TNF agents may have cardioprotective effects. The optimisation of therapy while not triggering arrhythmias in those IBD patients with established CVD risk factors should be considered. Clinicians should be aware of long-term risk of arrhythmias in IBD. A risk assessment of modifiable and established CVD risk factors should be carried out and there is still need for establishing relevant guidelines for management of CVD in patients with IBD.

Reference: PLoS Med. 2023;20(10):e1004305
Abstract

Research Review publications, videos and e-Learning modules have been endorsed by The Royal New Zealand College of General Practitioners (RNZCGP) and have been approved for up to **1 CME** credit per learning hour for Continuing Professional Development (CPD) purposes.
Please **CLICK HERE** to download RNZCGP Dashboard.

Time spent reading this publication has been approved for CNE by The College of Nurses Aotearoa (NZ) for RNs and NPs. For more information on how to claim CNE hours please **CLICK HERE**.

Review article: Risk of cardiovascular events in patients with inflammatory bowel disease receiving small molecule drugs

Authors: Olivera PA et al.

Summary: This review of the incidence of cardiovascular events in patients with IBD associated with the use of small molecule drugs (SMDs) including JAK inhibitors and sphingosine-1-phosphate receptor (S1P) modulators sought to provide recommendations on mitigation strategies. Evidence suggested no increase in risk of cardiovascular events with tofacitinib and other JAK inhibitors. Risk was higher in IBD patients with an intermediate to high cardiovascular risk. S1P modulators were found to have a dose-dependent, first-dose, transient risk of conduction abnormalities (bradycardia and atrioventricular [AV] block). Cardiovascular risk factor screening and monitoring is recommended for all IBD patients and risk stratification should be performed before starting SMD treatment.

Comment (SM): SMDs are novel, targeted, oral drugs for the treatment of moderate-to-severe IBD with the benefits of overcoming the limitations of biologics including limited efficacy, immunogenicity, and parenteral administration. Targeting downstream cytokine signalling with JAK inhibitors and blocking lymphocyte traffic from lymph nodes and spleen with S1P modulators are the basis of novel mechanisms of action. There is a potential risk of major adverse cardiac event (MACE) and thrombotic events with the use of JAK inhibitors and there are safety warnings and recommendations about their use. These recommendations were applied to IBD from extrapolated data from rheumatoid arthritis (RA) and the same outcome has not been repeated in IBD. It is considered that the extrapolated data may not be appropriate for IBD patients. IBD patients are younger than RA patients and have a lower prevalence of CVD risk factors. IBD patients also have lower risk of CVD than other patients with immune mediated inflammatory disorders though their risk is higher than in general population. The risk of CV events has been associated intrinsically with systemic inflammation and IBD disease activity. Hence the risk of CV events associated with JAK inhibitors may be outweighed by systemic inflammation. Established CV risk factors should be actively investigated and controlled in IBD patients especially when JAK inhibitors are used. Age over 50, male sex, family history of CVD, hypertension, dyslipidaemia, diabetes, smoking, obesity, sedentary habits etc. are the risk factors to be kept in mind while using these drugs. The lipid profile should be monitored at baseline, induction, and every 6 months thereafter and dyslipidaemia should be treated with statins. The lowest possible dose of JAK inhibitors should be used to maintain remission. As far as the cardiac conduction abnormalities with S1P modulators are concerned the risk of bradycardia and AV block is high during first day of exposure and negligible after 8 days. The risk factors to identify patients at high risk are not much different from those stated above but may also include the use of drugs like beta blockers and calcium blockers. In essence, available evidence from RCTs indicates a reassuring safety profile of SMDs from the CVD perspective. Real-world data may differ and unless the safety is established from real-world studies, it seems prudent to adhere to safety and regulatory recommendations.

Reference: Aliment Pharmacol Ther. 2023;57(11):1231-1248
Abstract

Inflammatory bowel disease patients have an increased risk of acute coronary syndrome: A systematic review and meta-analysis

Authors: Zaka A et al.

Summary: This systematic review and meta-analysis examined the risk of acute coronary syndrome (ACS) in IBD patients based on 12 retrospective cohort studies (n = 225,248). IBD patients had an increased risk of ACS in adjusted (HR 1.23; 95% CI 1.08-1.41) and unadjusted analyses (HR 1.50; 95% CI 1.16-1.92), but there was substantial heterogeneity among studies. Subgroup analysis suggested a greater association with ACS in IBD patients <40 years of age (relative HR 1.50; 95 CI 1.15-1.96).

Comment (SM): The risk of ACS in IBD patients has been unclear with differing results in earlier studies. These studies were not prospective and had included all patients with ischemic heart disease rather than ACS. ACS is a term used to describe a range of conditions resulting from sudden reduction or blockage of blood flow to cardiac muscle. It includes unstable angina, non-ST elevation myocardial infarction and ST elevation myocardial infarction. ACS is commonly caused by rupture of atherosclerotic plaque in coronary arteries leading to formation of clots that can partially or completely block the blood flow to heart muscle. The aetiology of ACS in IBD patients comprises of two distinct but potentially overlapping pathophysiological entities. The first is the ACS due to rupture of atheromatous plaque in the context of established atherosclerosis. The second is the ACS due to acute intracoronary thrombosis. Chronic inflammation in IBD contributes to a systemic inflammatory state potentially affecting blood vessels and accelerating atherosclerotic process. In addition, some risk factors for IBD like smoking, obesity etc. are also risk factors for ACS. Medications used to manage IBD such as steroids may have adverse events (hypertension, insulin resistance etc) contributing further to the risk of ACS. Chronic systemic inflammation can initiate proatherogenic changes via the circulating pro-inflammatory cytokines like TNF, IL-6 etc. The changes include endothelial dysfunction, dyslipidaemia, insulin resistance, homocysteinaemia and oxidative stress which leads to atheroma formation. Acute inflammation is also associated with instability of established plaques leading to ACS. The hyper-coagulable state associated with acute flares of IBD also contributes to both venous and arterial thromboembolic events. The hypothesis that patients with high inflammatory burden i.e., severe disease, longer duration, more extensive intestinal involvement, recurrent flares etc., may be at higher risk of ACS compared to patients with mild disease is plausible. Nevertheless, ACS secondary to acute thrombosis of coronary arteries in the absence of atheromatous plaques is rare. Even though this large meta-analysis demonstrates approximately 23% increase in risk of ACS in IBD patients, adjusted analysis showed diminished association compared to unadjusted analysis, suggesting the association is partly explained by mediating variables including traditional CVD risk factors like hypertension, smoking, diabetes etc. The potential risk of ACS should be considered by clinicians treating IBD patients and strict control of systemic inflammation and management of modifiable risk factors to reduce further morbidity and mortality is critical.

Reference: Open Heart 2023;10(2):e002483
Abstract

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.

SCIENCE BLOG

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

Inflammatory bowel disease and cardiovascular disease: The *heart* of mechanistic link

The increased risk of developing CVD in IBD patients is well established. Patients with IBD are 2-4-fold more likely to experience a CV event, particularly in younger age (<45), female sex and active disease. The specific mechanistic link between IBD and CVD is evolving, but there are still some gaps in our knowledge. Some important relevant aspects are summarised below:

- The role of proinflammatory cytokines in the pathogenesis of CVD is well known with markers like CRP, TNF-α, IL-6, and IL-1β playing a major role in the atherosclerotic process, increasing the odds for CVD. Chronic inflammation in IBD has increased concentrations of same markers and negatively affects the endothelium whose dysfunction is common to both diseases. Chronic inflammation in IBD is also known to stiffen the aorta.
- The drugs used in the treatment of IBD influence CVD risk. The cumulative dose of glucocorticoids has a more significant effect on CVD risk than the activity and inflammatory burden of underlying disease. It can also affect the other CVD risk factors like hypertension, diabetes, and lipid profile. 5-ASA and TNF blockers may be cardioprotective due to anti-inflammatory effects. New classes of drugs like JAK inhibitors and S1P modulators have the potential to increase the CVD risk by their affect on lipids, hypertension and cardiac conduction.
- The gut microbiome is integral to the pathogenesis of IBD. A decrease both in the diversity and the ratio of firmicutes/bacteroides is the essence of 'dysbiosis' in IBD. This is also associated with development of atherosclerosis and increased arterial stiffness. The dysbiosis also results in increased intestinal permeability to bacterial endotoxins and lipopolysaccharides, which enter the circulation to cause chronic systemic inflammation through proinflammatory cytokines. Some bacterial degradation products also have an important role in the progression of CVD.
- The chronic inflammatory state in both CVD and IBD perpetuates endothelial dysfunction, platelet dysfunction and thrombogenesis. Increased homocysteine levels in IBD contributes to endothelial dysfunction and thrombosis. The activated endothelial cells produce adhesion molecules that capture monocytes and lymphocytes, resulting in damage and increased permeability. The process of both IBD and CVD are driven by series of events described above, which in turn are propagated by chronic inflammation and pro-inflammatory cytokines.
- Patients with IBD are 2-3-fold more likely to have a thromboembolic event than general population. A hyper coagulable and prothrombotic state exists in active phase of IBD. Increased platelet activation and aggregation is common in IBD. An elevation of coagulation factors and decreased levels of coagulation inhibitors also contributes to prothrombotic state. The risk of both venous and arterial thrombosis is increased in IBD.
- Nearly 200 IBD associated gene loci have been identified and over 100 of them are common to both UC and CD. *NOD2* was the first altered gene identified in CD and extensively studied. *NOD2* deficiency has been implicated in CVD pathogenesis also. *NLRP3* inflammasome is vital in regulating innate and adaptive immunity and its activation is implicated in the pathogenesis of both CVD and IBD. Polymorphisms of some of these genes seem to influence both diseases.
- Nutrients, microbiota, and the immune system regulate gut homeostasis. The gut microbiome can change rapidly with diet and influence the physiological response of the host. The 'Western diet' rich in processed food is associated with dysbiosis increasing susceptibility to IBD and CVD. On the contrary, the 'Mediterranean diet' has been found to be beneficial. Obesity is a traditional risk factor for CVD and is also a risk factor for CD. The expression of highly pro-inflammatory cytokines like IL-1β is considerably higher in the visceral adipose tissue confirming its important role as 'cytokine sink' in obesity. The chronic low-grade inflammation in obesity is called 'Metaflammation'. There is evidence that visceral adipose tissue in IBD patients is highly inflamed even without co-existing obesity.

IBD and CVD share many pathophysiological processes which collectively contribute to development and progression of both diseases. Not all patients with CVD present with traditional CVD risk factors and the existing CVD risk stratifying models may not apply to these IBD patients. This treatment gap for IBD patients who lack traditional risk factors needs to be addressed. Clinicians treating IBD patients should be aware of the increased CVD risk and should monitor the patients with periodic assessment of risk factors, some of which are dynamic, with timely intervention to prevent additional morbidity and mortality due to CVD.

Further reading:
Kumarapperuma H et al. Mechanistic insight: Linking cardiovascular complications of inflammatory bowel disease. Trends Cardiovasc Med. 2023;Jan 24 [Epub ahead of print]
Gabbiadini R et al. Atherosclerotic cardiovascular diseases in inflammatory bowel diseases: to the heart of the issue. Trends Cardiovasc Med. 2023; May 16;10:1143293
Tilg H et al. Does cardiovascular risk matter in IBD patients? J Int Med. 2023:294;708-720