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Review Article

Inflammatory Bowel Disease and Cardiovascular Disease (Review)

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Abstract

Inflammatory bowel diseases (IBDs) are immune-mediated inflammatory conditions causing inflammation of the gastrointestinal tract. A range of medical treatment options are used to treat IBD-related inflammation including biologic tumor necrosis factor (TNF) antagonists. IBD prevalence is growing with patients increasingly older and more comorbid. Globally, cardiovascular diseases remain the leading cause of morbidity and mortality. IBD patients are at higher risk of cardiovascular disease, but this does not appear to be conferred by traditional risk factors such as hyperlipidemia and obesity. Appreciation of the relationship between IBD, cardiovascular disease, and inflammation is, therefore, of clinical importance. TNF-α is a key pro-inflammatory cytokine in the development of IBD-related inflammation, hypertension, and cardiovascular disease. Data suggest that commonly prescribed TNF antagonists may mitigate the increased cardiovascular risk in IBD patients. It is unclear if this is a direct effect of TNF antagonism or reflects better control of inflammation. Future research should focus on an improved understanding of the cardiovascular impact of IBD-related inflammation, the risk of adverse outcomes, and the potential effects of IBD treatment on cardiovascular risk profiles. This knowledge should allow better risk stratification when selecting treatment options, contributing to our goal of personalizing the approach to IBD treatment.

Key words: Inflammatory bowel disease, cardiovascular disease, tumor necrosis factor antagonists

Introduction

The inflammatory bowel diseases (IBDs), Crohn's disease, and ulcerative colitis are chronic inflammatory conditions of the intestinal tract. The exact etiology of IBD is unclear but considered to be multifactorial involving environmental and dietary triggers in an individual with a susceptible genetic profile and immune system.[1] Symptoms vary, but often include diarrhoea, abdominal pain, and fatigue. Medical management options have expanded to include biologic drugs for moderate-to-severe disease, significantly improving outcomes and quality of life for IBD patients.[2] The most commonly used biologics for IBD are the tumor necrosis factor (TNF) antagonists infliximab and adalimumab. The prevalence of IBD has grown globally.[3] With evolving and improving pharmacological management, and an aging population, it is predicted that the prevalence of IBD will continue to grow,[4] with the highest prevalence currently seen in the most developed nations.[5] The global burden of cardiovascular disease remains very high, necessitating a good understanding of its impact and interaction with other disease states and their treatment.[6] Gastroenterologists are increasingly caring for an older and more comorbid patient group, making treatment selection more challenging. Here, we discuss current evidence for the relationship between cardiovascular disease, IBD, and chronic inflammation, and review the role of TNF antagonists.

The clinical trajectory of IBD varies, often unpredictably, from mild disease with infrequent symptomatic exacerbations, to more severe phenotypes with significant, treatment refractory symptoms. Conditions resulting in chronic, persistent states of inflammation, as well as diseases characterized by discrete and self-limiting episodes of inflammation, may precipitate vascular

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Received: 07-01-2022; Accepted: 11-01-2022
doi: 10.15713/ins.johtn.0233

endothelial dysfunction and a resultant rise in arterial stiffness; a recognized risk factor for cardiovascular disease and cause of elevated systolic blood pressure.[7] Changes in endothelial function as a result of inflammation can arise through a number of mechanisms; primarily the presence of inflammatory cytokines, resulting in oxidative stress and the relaxation, or hyperplasia, of vascular smooth muscle cells. Cardiovascular disease is thought to be more prevalent within the IBD population, but traditional risk factors for cardiovascular disease, for example, obesity and hyperlipidemia, are not.[8] Some studies have suggested that the observed increased risk of cardiovascular disease in individuals with IBD is not related to disease severity.[9] As such, in individuals with chronic inflammatory conditions such as IBD, there may not simply be a direct relationship between increased risk of cardiovascular disease and burden of inflammation.[10]

TNF-α is a key pro-inflammatory cytokine involved in the development and ongoing activity of IBD. It's role in activating the adaptive and innate immune system can lead to both acute and chronic states of inflammation.[11] As such, antagonism of TNF-α using monoclonal antibodies is a primary target in IBD treatment.[12] The expression of TNF-α has also been identified as a contributor to hypertension and cardiovascular disease by increased oxidative stress, triggered by the activation of polymorphonuclear leukocyte NADPH oxidase.[13,14] Inhibition of TNF-α has been shown to improve endothelial function[15] and markers of vascular function such as common carotid intima–media thickness and flow-mediated vasodilation.[16] Alongside this, it has been shown to have a positive blood pressure-lowering impact.[14]

Despite these theoretical benefits, the evidence for the association between TNF-α inhibition, inflammation, and cardiovascular disease risk in IBD is limited. A 2017 nationwide French study of 178,360 patients with IBD supported the hypothesis that there is increased risk of cardiovascular disease in this population. However, treatment with a TNF antagonist appeared to mitigate this risk as better cardiovascular outcomes was observed in this subgroup of patients. This improvement only reached statistical significance when dual therapy with a thiopurine was used.[17] Higher levels of serum infliximab and better IBD treatment outcomes are seen for patients treated with combination azathioprine and infliximab therapy compared to infliximab monotherapy.[18] This suggests that the lower risk of cardiovascular disease seen in the French cohort above could relate to thiopurine treatment, higher infliximab levels, or better control of inflammation. However, the relative contribution or any or all of these effects remains unclear. In addition, a long-term follow-up study of 145 IBD patients demonstrated a deterioration in cardiovascular risk over time, but this risk was reduced by treatment with an anti-TNF-α therapy to control IBD symptoms.[19]

An interesting observation was made in a 2019 abstract examining the prevalence of hypertension in a Greek population of IBD patients. This study showed that in the 29.9% of patients with hypertension, the use of an antihypertensive, particularly an angiotensin receptor blocker, was independently associated with a milder IBD phenotype.[20] Recent evidence suggests that angiotensin II has a role in driving colonic mucosal inflammation,[21] with a 2020 study highlighting the renin angiotensin system as a potential, novel therapeutic target in IBD treatment.[22]

However, a wider body of evidence exists looking at cardiovascular risk, TNF antagonists, and chronic inflammation for rheumatology and dermatology conditions. While the phenotype of disease and patient populations are different to IBD, the common issue is acute and chronic inflammation, with TNF antagonists providing a core treatment option. A 2015 meta-analysis of 6321 patients from 11 studies demonstrated a significantly increased risk of developing hypertension in patients with rheumatoid arthritis.[10] A small study of 16 infliximab-treated, rheumatoid arthritis patients showed a significant drop in morning ambulatory blood pressure following the initiation of infliximab therapy. This finding was associated with a reduction in norepinephrine, but was independent of changes in disease activity.[23] Similarly, a 2011 study of 23 rheumatoid arthritis patients treated with the TNF antagonists adalimumab, etanercept, or infliximab and 17 control patients treated only with a disease-modifying antirheumatic drug (DMARD), demonstrated reduced systolic blood pressure, and improved endothelial function in the TNF antagonist group versus DMARD group.[24] A more recent double-blind, placebo-controlled, randomized, crossover trial of 10 patients with rheumatoid arthritis evaluated the immediate impact of a single infusion of infliximab. Following a single infusion of infliximab, a significant reduction in mean blood pressure was seen, but with no change to endothelial function as measured by flow-mediated vasodilation.[25]

Another 2015 meta-analysis, this time of 34 studies examined the cardiovascular risk in patients with rheumatoid, arthritis, psoriatic arthritis, and psoriasis. This analysis suggested an overall reduction in cardiovascular events, including myocardial infarction, heart failure, and ischemic stroke, in patients treated with TNF-α antagonists.[26] Large biologics registries have also proved a useful source of information. In 2013, the British Society for Rheumatology's Biologics Registry was used to review the ischemic stroke risk in rheumatoid arthritis patients. This study of more than 14,000 patients demonstrated no increased risk of stroke in TNF antagonist treated, compared to DMARD-treated patients.[27] More recently, a large study of patients with spondyloarthropathy also demonstrated a rise in cardiovascular events in these patients, which was counteracted by the use of TNF antagonist medicines as treatment.[28]

Patients with heart failure have been observed to have elevated levels of plasma TNF-α. The clinical significance of this finding is not fully elucidated but TNF-α is understood to affect the function of beta-adrenergic receptors and produce a negative inotropic effect on myocardiocyte activity.[29] In contrast to the positive effect of TNF antagonists on blood pressure discussed above, these medicines have been shown to worsen heart failure. The 2003 ATTACH trial investigated infliximab as a treatment for moderate-to-severe heart failure; no clinical benefit was

derived, but it was associated with a deterioration in heart failure, particularly at higher doses.[30] Reassuringly, treatment of IBD with infliximab in clinical trials was not associated with the development of new heart failure or cardiovascular complications,[31] but initiation in patients with moderate-to-severe heart failure in contraindicated in clinical practice.

Conclusion

In summary, the current evidence indicates that there is an overlap in some of the physiological mechanisms involved in the development of acute and chronic inflammatory diseases such as IBD and cardiovascular disease. Although the evidence based is limited, increased rates of cardiovascular disease and poorer cardiovascular outcomes are observed in individuals with IBD. Commonly prescribed TNF antagonists may mitigate this increased cardiovascular risk. It is unclear if this is a direct effect of TNF antagonism or reflects better control of inflammation. With an aging and increasingly comorbid IBD population, future research should focus on an improved understanding of the cardiovascular impact of IBD-related inflammation, the risk of adverse outcomes, and the potential effects of IBD treatment on cardiovascular risk profiles. This knowledge should allow better risk stratification when selecting treatment options, contributing to our goal of personalising the approach to IBD treatment.

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How to cite this article: Shields S, Seenan JP, Macdonald J. Inflammatory Bowel Disease and Cardiovascular Disease (Review). Hypertens 2021;7(3): 112-115.

Source of support: Nil, **Conflicts of interest:** None