Acute Coronary Syndromes and Inflammatory Bowel Disease

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Inflammatory bowel disease (IBD) induces a process of systemic inflammation, sharing common ground with acute coronary syndromes (ACS). Growing evidence points towards a possible association between IBD and an increased risk of ACS.

Keywords: acute coronary syndromes (ACS) ; inflammatory bowel disease (IBD) ; Crohn's disease ; ulcerative colitis ; myocardial infarction

1. Introduction

Inflammatory bowel disease (IBD), comprising Crohn's disease (CD) and Ulcerative colitis (UC), outlines the incurable chronic inflammation of the gastrointestinal tract affecting approximately 2.2 million people in Europe [1] and 7.7 million Americans [2], whilst in Asia the incidence is 1.4 per 100,000 [3]. Nevertheless, the discrepancies in healthcare infrastructure and epidemiological reporting should be considered.

The number of patients with IBD is growing exponentially and is expected to significantly increase in the western world. Previously, IBD was thought to be limited to Caucasians in western countries but not anymore, as IBD was found to be rather related to environmental factors than ethnicity or heredity since most people do not present a family history and twin studies have not proven any concordance [4]. In addition, the incidence of IBD differs between regions in which the genetic background is similar. An increase in IBD incidence and prevalence in newly industrialized countries is being explained by the populations' shift towards urbanism, lifestyle changes such as smoking and diet, and increased exposure to pollution and sedentarism [5].

CD and UC mostly affect young adults and adolescents between 20–30 and 30–40 years, respectively, although they have been reported to show a second peak at 60–70, showing a bi-modal distribution with the incidence of UC twice that of CD [5]. Smoking and appendectomy are risk factors demonstrated to affect the IBD risk [6]. Taking into consideration the demographics most affected by this condition and the relapsing course of this disease, chronic management is necessary. Although not yet fully understood, IBD pathogenesis involves a series of pathologic immune-mediated processes in individuals with a genetic predisposition [7].

Inflammation, being a key process in IBD, is also involved at all levels of coronary atherosclerosis and acute coronary syndromes (ACS), from the initial plaque formation to the thrombus rupture. It is worth noting the well-established association between IBD and the increased risk of venous thromboembolism due to the pro-atherogenic nature of the disease, especially during active flares [1].

ACS is the clinical manifestation of acute myocardial ischemia or infarction. ACS encompasses non-ST elevation ACS (NSTE-ACS), non-ST elevation myocardial infarction (NSTEMI), unstable angina (UA), and ST-elevation ACS (STE-ACS) [8].

2. Current Insights

The issue of whether IBD increases the risk of ACS has been addressed in several studies with conflicting results. Our work addresses this issue, as it includes twenty articles with a total study population of approximately 132 million individuals, out of which, fifteen studies reported an increased risk of ACS in IBD patients. All but two of these fifteen studies were rated with a score of >7 stars on quality assessment using NOS, while the remaining two received 5–6 stars on the quality assessment [9][10]. All five studies reporting no significant increase in ACS risk in IBD patients received >7 stars. Furthermore, the studies that reported a significant association between ACS and IBD nine of them were cohort

studies, three cross-sectional and one case–control. On the other hand, among the studies that reported no significant association four were cohort studies and one case–control.

In our work, several findings need to be elaborated. Several studies associated an increased risk of MI and morality in ambulatory IBD patients, coupled with other studies that claim a lower percentage of ACS in hospitalized IBD patients. In addition, the study by Tsai et al. reported that patients who needed two or more hospitalizations on average were 20-fold more likely to have ACS than those who required one hospitalization per year. Similarly, Barnes et al. found that IBD patients had 0.51-fold odds of having an acute MI as opposed to non-IBD patients. Furthermore, comorbidities and complications were reported to be independent predictors linked with increased risk and mortality from ACS in acute flares and fulminant stages with IBD. On the other hand, the risk of MI and cardiovascular events did not increase during the remission stages of the disease [1][11][12][13].

Studies that reported an increased percentage of ACS in young IBD patients had a younger study population in contrast to studies that reported no increased risk of ACS in IBD patients. The study conducted by Ha et al. showed that a high percentage of women that used oral contraceptive pills (OCP) had an elevated risk of MI. It is possible that there is a compounding of the risk brought by contraceptives, especially estrogen containing oral contraceptives [14], with the pro-inflammatory state of IBD. This could possibly explain the increased risk of ACS in young women with IBD.

In fact, the increased risk of ACS and mortality in active disease is consistent due to the role of systemic inflammation in increasing atherosclerosis being consistent with the high lipidic profile in IBD patients. Patients with IBD have an increased production of reactive oxygen species (ROS), increased expression of inflammatory cytokines (TNF-α and IL-6) and antibodies that lead to vascular smooth muscle cell proliferation (VSMC), endothelial dysfunction, and the development of CVD [15]. This was illustrated in a recent study conducted by Hernández-Camba et al. that reported a higher frequency of IBD patients being reclassified into a very-high cardiovascular risk via ultrasound assessment of carotid plaques [16]. Interestingly, IBD patients see lower frequencies of acute MI when compared to other chronic inflammatory diseases such as rheumatoid arthritis and systemic lupus erythematosus, which might perhaps highlight a different pathophysiological mechanism where platelet dysfunction is more involved [17].

Two studies cited steroid therapy in IBD as an explanation for the increased relative risk of ACS [18][19]. However, steroids are used in the management of acute flares of IBD, and as stated earlier, several studies have demonstrated an increased risk of ACS in acute flares and the fulminant and active stages of IBD. It is possible that steroid use is not associated with the increased odds of ACS, but the severity of the disease in which they happen to be used more in, which is acute flares and severe IBD. Although the association of corticosteroid usage in IBD patients and ACS is controversial, it is hypothesized that steroids usage increases CVD risk through several pathways including the sympathetic stimulation of the renin–aldosterone–angiotensin axis [15]. All things considered, further studies should evaluate the benefit of immunosuppressive therapy and further investigate the association between corticosteroids and ACS in IBD patients and more aggressive anti-inflammatory therapies should be explored to reduce atherosclerosis, cardiovascular comorbidities, and mortality.

Furthermore, we noticed that two studies reached opposite findings. While Tsai et al.'s findings point towards an increased risk of ACS upon hospitalization, Card et al. claim that there is no significant increase. This discrepancy may have several explanations, one of which is that Card et al. excluded patients previously diagnosed with vascular disease while Tsai et al. only excluded patients hospitalized with a previous diagnosis of ACS. Another explanation could be the lack of data in Tsai et al.'s study that could represent a significant confounder such as the smoking history, family history of CAD, alcohol consumption, etc. Furthermore, Card et al. states that a possible explanation for the ~25% decreased risk of MI in IBD patients (attributed to hospitalization) in comparison to the controls might be since for many IBD patients hospitalization will be due to IBD and hence the admission related to vascular factors will represent a smaller proportion. In addition, Tsai et al. uses hospitalization as a surrogate marker for IBD severity, which could have created a bias towards sicker patients. Meanwhile, Card et al. uses corticosteroid prescription as a surrogate marker for IBD severity [20][13]. It is worth noting that six papers of the 20 included in this study discussed ACS mortality in IBD [1][21][18][22][23][24], but none assessed IBD severity using the CDAI for Crohn's disease and DAI score for ulcerative colitis.

3. Conclusions

In conclusion, the risk of ACS increases significantly with hospitalization and acute active flares, in addition to prolonged periods of active disease. On the other hand, IBD patients in remission present with a lower risk for ACS. The general increased risk of ACS in young IBD patients, possibly due to corticosteroid use, in addition to the effects of estrogen containing OCPs in young IBD female patients, should be further investigated. The interplay between several risk factors

including chronic inflammation, thrombosis, corticosteroid use, lipid and endothelial dysfunction, and gut dysbiosis are likely to play a crucial role in the association between IBD and increased ACS risk. A better understanding of these mechanisms may possibly lead to developing novel therapeutic targets in patients with IBD.

Managing IBD patients with ACS risk should be performed through a multidisciplinary team-based approach, while aiming to induce disease remission. Screening and management of cardiovascular risk factors are required, especially in IBD patients with increased risk. Future research is required to better elucidate the pathophysiological mechanisms behind the increased ACS risk in IBD patients. Moreover, further studies assessing the severity of IBD, aside from hospitalizations or corticosteroid prescriptions as surrogate markers for severity, in addition to the effect of biological agents in hospitalized IBD patients, on the risk of ACS remain necessary.

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