Review Article

Cardiovascular Complications of Gastrointestinal Diseases

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Abstract

It is known that 10% of all deaths in the United States have gastrointestinal disorders as their underlying cause. As many of these patients present with cardiovascular symptoms apparently related to their primary disorder, the relation between the cardiovascular and gastrointestinal systems has been under intensive investigation. Observational studies and case reports have suggested that gastroesophageal reflux disease can lead to atrial fibrillation and this relation is considered to implicate multiple mechanisms as inflammation, autoimmunity and exacerbated autonomic stimulation. Furthermore, current literature understands that atherosclerosis is a result of both traditional (e.g. diabetes mellitus, dyslipidemia) and non-traditional risk factors, such as chronic inflammation due to chronic infections (e.g. *Helicobacter pylori* and Hepatitis C virus infections) and chronic inflammatory diseases (e.g. inflammatory bowel disease). Numerous evidences of systolic and diastolic ventricular dysfunction have been reported in cirrhotic patients, being called cirrhotic cardiomyopathy and characterized by blunted contractile responsiveness to stress, diastolic dysfunction and electrophysiological abnormalities in the absence of underlying cardiac disease. Metabolic liver diseases are also related to cardiovascular injury through iron or copper overload in hemochromatosis and Wilson's disease, respectively. This article intends to review cardiovascular complications due to primary gastrointestinal disorders and their potential physiopathological mechanisms, along with alert physicians of these still neglected gastrointestinal diseases presentations.

Keywords: Gastrointestinal diseases; Atrial fibrillation; Atherosclerosis; Coronary artery disease; Cardiomyopathy

Introduction

It is known that 10% of all deaths in the United States have gastrointestinal disorders as their underlying cause [1]. As many of these patients present with cardiovascular symptoms apparently related to their primary disorder, the relation between the cardiovascular and gastrointestinal systems has been under intensive investigation. This article reviews cardiovascular complications due to primary gastrointestinal disorders and their potential physiopathological mechanisms.

Gastroesophageal Reflux Disease and Atrial Fibrillation

Atrial fibrillation (AF) is the most common clinically significant arrhythmia among the general population, while gastroesophageal reflux disease (GERD) is the most diagnosed gastrointestinal condition in outpatient clinics in the United States [1,2]. When no structural heart disease can be found, this heart condition is called lone AF and several comorbidities can be involved, including GERD.

Small observational studies and case reports have suggested that GERD can lead to AF and this relation is considered to implicate multiple mechanisms: inflammation, autoimmunity and exacerbated autonomic stimulation [3]. Local atrium inflammation, given left atrium's proximity to the oesophagus, and systemic inflammation, also secondary to esophagitis, could be important mechanisms in AF development. Several studies have already considered that high levels of interleukin-6 (IL-6) and C-reactive protein (CRP), inflammatory mediators that may be elevated in GERD, are correlated to the incidence and prognosis of AF through tissue remodelling [4]. Secondly, autoimmune response may also explain AF physiopathology as autoantibodies against myosin heavy chain have been detected in some studies [5]. Furthermore, vagus nerve stimulation is a well-established AF trigger as the cholinergic action slows atrioventricular node conduction and sinus node depolarization rate [6].

Although large randomized trials are still needed to establish the exact relation between GERD and AF, there is some evidence that GERD treatment with proton pump inhibitors (PPI) can lead to conversion to sinus rhythm and ameliorate AF symptoms, being indicated to a selected group of patients that could benefit of it as a less expensive drug with fewer side effects [3,5]. It is still necessary to define what would be this selected group profile.

Primary Gastrointestinal Infections and Cardiovascular Involvement

Atherosclerosis is a multifactorial disease secondary to a chronic inflammatory process. Its progression builds up from endothelial injury in early stages to acute coronary syndrome (ACS) due to plaque instability and thrombus formation as a late event. Current literature understands that its high incidence is presumably a result of both traditional (e.g. diabetes mellitus, dyslipidemia) and non-traditional

risk factors, such as chronic infections leading to chronic inflammation and oxidative stress [7].

Helicobacter pylori is a gram-negative bacteria estimated to infect half of the world's population and it is one of the main causes of chronic gastritis and low grade chronic inflammatory response [8]. Epidemiological studies have suggested a correlation between atherosclerosis and *H. pylori* infection, reinforced by the detection of *H. pylori* specific DNA in atherosclerotic plaques [9] and the improvement in inflammatory markers and lipid profile after *H. pylori's* eradication [10], although no causal role could be established. It is also suggested that *H. pylori* Cag-A positive strains would be more involved in coronary artery diseases (CAD), still studies have shown controversial results [11]. It is proposed that multiple mechanisms would be involved in *H. pylori* related atherosclerosis, such as chronic inflammation, endothelial dysfunction, increase in platelet aggregation, hyper-homocysteinaemia and dyslipidemia, though multicentre randomised trials are still needed as the evidence supporting such correlation is ambiguous [10].

Atherosclerosis has also been associated with chronic Hepatitis C Virus (HCV) infection, probably related to its chronic inflammatory process rather than the patient's cholesterol profile [12]. Furthermore, patients infected with HCV are more likely to develop hepatic steatosis and subsequent metabolic syndrome, exacerbating their cardiovascular risk. Still, it is supported that HCV infection should considered an independent risk for CVD regardless hepatic steatosis as much as the severity of liver fibrosis [13]. Although some studies could not reproduce such correlation, previous studies have shown HCV RNA sequences with atheromatous plaque and most of the literature seems to support the impact of HCV chronic infection on the risk of early atherogenesis, increased carotid intima-media-thickness and CVD. Further studies are required to better evaluate this association and the impact of HCV infection treatment on cardiovascular risk [14]. Additionally, HCV infection is also linked to myocarditis, dilated cardiomyopathy and hypertrophic cardiomyopathy [12].

Inflammatory Bowel Disease and Coronary Artery Disease

As previously mentioned, chronic inflammation has an important role in atherosclerotic process and plaque stability, as much as in thrombosis predisposition. Inflammatory bowel disease (IBD) refers to two entities, Crohn's disease (CD) and ulcerative colitis (UC), which are both associated to chronic inflammatory process involving mainly the gastrointestinal tract. Some extra-intestinal manifestations are well documented, however coronary artery disease (CAD) has yet a debatable association with IBD.

Observational studies have suggested the correlation between IBD and CAD through multiple aspects. IBD classically presents with elevated homocysteine and CRP, inflammatory markers that correlate with enhanced oxidation of intimal lipid particles, promoting the attachment of inflammatory cells to the endothelium and consequent plaque formation and destabilization [15]. Furthermore, IBD patients present with increased carotid intimal thickness and carotid arterial stiffness, which are predictors of cardiovascular events [16].

It is well accepted that IBD flares are associated with venous thromboembolic events and most recent studies demonstrate some increase in risk of coronary artery disease, notably in females [17]. Apart from hypertension, traditional CAD risk factors as smoking, diabetes and obesity have not been clearly established as risk factor in

this population [18]. Although further prospective longitudinal studies are needed, physicians should be aware of this correlation in order to better manage traditional risk factors as well as inflammatory response in IBD patients.

Cirrhosis and Cardiomyopathy

Cardiac dysfunction in the presence of cirrhosis was assumed to be due to alcoholic cardiomyopathy until the last 20 years, when studies documented cardiac function impairment in non-alcoholic cirrhotic patients. Since then, numerous evidences of systolic and diastolic ventricular dysfunction have been reported in cirrhotic patients disregarding cirrhosis aetiology [19]. The term cirrhotic cardiomyopathy (CCM) was then introduced and it is characterized by blunted contractile responsiveness to stress, diastolic dysfunction and electrophysiological abnormalities in the absence of underlying cardiac disease [20].

Most of cirrhotic patients will have normal LVEF at rest and subnormal LVEF will only be found under physical, pharmacological or pathological stress. On the other hand, diastolic dysfunction is reported in about 50% of cirrhotic patients and it is characterized by echocardiographic findings as change in the transmitral blood flow with increased atrial contribution to the late ventricular filling. Conductance abnormalities, especially prolonged QT interval, are also reported in the majority of cirrhotic patients [21].

Multiple physiopathological mechanisms seem to contribute to CCM, such as defects in beta-adrenergic receptors, membrane biophysical alterations and increased circulation of endogenous substances responsible for hyperdynamic circulation and negative inotropism (e.g. nitric oxide, endocannabinoids, carbonic monoxide) [22]. Furthermore, cardiac dysfunction seems to contribute to the development of hepatorenal syndrome, which is a well-established indicator of poor prognosis.

There is no specific treatment for CCM and its management should follow the recommendation for patients with heart failure [23], being liver transplantation the single proven treatment with specific beneficial effect on this population [21]. Patients with worsening hemodynamic status should be assessed and early recognition of systolic or diastolic dysfunction may help prevent cardiac dysfunction due to TIPS or liver transplant.

Metabolic Liver Diseases and Cardiovascular Injury

Hereditary hemochromatosis is a genetic disorder involving proteins responsible for iron metabolism that results in iron overload through increased intestinal absorption. There are four types of hemochromatosis and phenotypic expression is unsafely foreseeable, although its classic clinical trial is cirrhosis, bronzed skin and diabetes mellitus in the fourth or fifth decade of life [24]. It is know that the level of cardiac iron overload is directly associated with cardiac dysfunction and death [25]. Initially, iron deposition leads to a restrictive cardiac dysfunction and, if not treated properly, it precipitates left ventricle (LV) remodelling and subsequent dilated cardiomyopathy with decreased left ventricle ejection fraction (LVEF) [26]. A minority of patients will not degenerate to dilated cardiomyopathy, but diastolic dysfunction will lead to pulmonary hypertension and right ventricular dilation without LF remodelling [24]. Although iron deposition occurs mainly in the myocardium, it can also affect the conduction system leading to arrhythmias. It is rational to estate that iron overload cardiomyopathy is a result of direct

cardiac injury and indirect effects of other dysfunctional organs (e.g. hepatic cirrhosis as discussed above, which appears as an earlier clinical manifestation). Thus, therapeutic phlebotomy should be used to prevent iron-induced organ damage in all four types of hemochromatosis as it may be able to reverse cardiac injury before systolic dysfunction [26].

Wilson's disease is an autosomal recessive disorder that leads to copper accumulation in multiple tissues due to function impairment of hepatic enzyme ATP7B. It usually presents with hepatic and neuropsychiatry symptoms, although concentric left ventricular remodelling can also be expected [12] as much as dilated cardiomyopathy and supraventricular arrhythmias [27]. Nevertheless, the few histopathological examination studies conducted were not able to correlate copper content to the degree of myocardial involvement at autopsy or clinical manifestations severity [28,29].

Hepatic inflammation on liver biopsy, which may or may not be present in nonalcoholic fatty liver disease (NAFLD), is called non-alcoholic steatohepatitis (NASH) and it has metabolic syndrome and insulin resistance as its main etiological factor. NAFLD affects 20 to 30% of the world population and steatohepatitis is now the leading cause of chronic disease in the United States and a leading cause of hepatocellular carcinoma worldwide. The association between NAFLD and cardiovascular risk comes from their similar risk factors and it is discussed if cardiovascular disease is caused by metabolic syndrome solely or if cardiovascular disease would lead to NAFLD. It is not easy trying to discriminate these factors as lifestyle, diet and socioeconomic factors lead to both cardiovascular disease and NASH [30]. It seems that the presence of NAFLD leads to increased risk of cardiovascular disease in diabetics and transplanted and studies with risk markers such as carotid intima-media thickness and coronary calcium score by computed tomography attested increased cardiovascular risk in NASH patients. There are also reports that patients with NASH have elevated markers of endothelial injury, such as sICAM-1, sVCAM-1 and E-selectin [31]. Nevertheless, more recent studies have shown that liver histology does not define cardiovascular risk [32]. An American Cardiology Association study selected patients with metabolic syndrome and NAFLD with elevated liver enzymes to treatment with lifestyle changes (diet and exercise) and treatment of metabolic syndrome (atorvastatin in dyslipidemia, metformin for glucose intolerance and antihypertensives drugs and orlistat for obesity). At the end of 42 months of follow-up, there was a significant reduction in cardiovascular events. Although it there is much more to be enlightened, assessing cardiovascular risk in the NAFLD patients population with or without NASH is highly recommended.

Conclusion

Cardiovascular complications of gastrointestinal diseases are more prevalent than thought before and should be investigated in specific groups of patients. Even though more studies are still needed to determined their physiopathological mechanisms and guide their management, non-cardiology physicians should be especially aware of their clinical presentation.

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