Letter to the Editor

Non-alcoholic fatty liver disease in patients with inflammatory bowel disease might boost cardiovascular disease burden

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Submitted: 22 August 2019
Accepted: 5 November 2019

Arch Med Sci Atheroscler Dis 2019; 4: e250–e251
DOI: https://doi.org/10.5114/amsad.2019.90147

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Recent data suggest that the presence of inflammatory bowel disease (IBD) increases the odds for non-alcoholic fatty liver disease (NAFLD) almost by 4.5 times [1], with the latter representing the most common hepatobiliary manifestation among IBD patients [2]. Independent risk factors of hepatic steatosis in IBD patients include disease relapse rate, surgery for disease and its complications and extent of intestinal involvement [3]. However, this association also encompasses several cardio-metabolic risk factors, such as type 2 diabetes, hypertension, insulin resistance, metabolic syndrome and obesity [4, 5].

Patients with IBD face the risk of premature cardiovascular disease (CVD), with cardiovascular risk being greater for young rather than older adults [6]; a previous meta-analysis confirmed that IBD patients exhibit significantly higher carotid-femoral pulse wave velocity (cfPWV), a validated marker of aortic stiffness, compared to controls, documenting the early vascular ageing occurring during the disease course [7]. In clinical practice, it has been established that patients with IBD feature greater odds for ischemic heart disease and cerebrovascular disease, compared to controls, while younger patients are more susceptible to cerebrovascular accidents [8]. Interplay between chronic inflammation and conventional risk factors accounts for the development of CVD in this population [8]. On the other hand, it has also been established that NAFLD itself is closely related to fatal and non-fatal cardiovascular events; however, pathophysiologic causality has yet to be determined [9].

Interestingly, even underweight patients with IBD have greater liver fat content, corresponding to mild/moderate liver steatosis, compared to healthy controls [10]. Lean NAFLD patients exhibit the entire spectrum of metabolic syndrome, sharing a common metabolic profile with obese NAFLD patients [11]. Based on the fact that subclinical CVD is usually present even in lean NAFLD patients [12], it seems that IBD and NAFLD concomitance might enhance the overall cardiovascular risk.

Unfortunately, current evidence is not adequate to shed light on the underlying pathophysiologic mechanisms accounting for this close relationship between NAFLD and IBD. According to a recently published experimental study, mice fed a high-fat diet in order to develop a NAFLD phenotype exhibited significantly higher serum high mobility group box 1 (HMGB1) levels, which triggered a significant increase in the levels of monocyte chemoattractant protein-1 (MCP-1), transforming growth factor β (TGF-β), interleukin-1β (IL-1β) and interferon-γ (IFN-γ) in mouse intesti-

nal tissue via a NOX-2 dependent manner, finally resulting in intestinal inflammation [13]. Additionally, it was demonstrated that HMGB1-induced NADPH oxidase 2 (NOX2) activation increased expression of toll-like receptor 4 (TLR4)-pathway cytokines IL-1β and interleukin-6 (IL-6), crucial for the promotion of intestinal inflammation [13]. The latter cytokines have been established as cardiovascular risk markers for the last two decades [14, 15]. However, and despite the fact that circulating HMGB1 might function as a diagnostic and prognostic biomarker of CVD [16], one could only speculate that HMGB1-induced signaling pathway is partially responsible for systemic inflammation and subsequently for the development of CVD among patients with NAFLD-IBD concomitance.

It should be highlighted that, despite the established knowledge that NAFLD is associated with increased risk for the development of CVD, two recently published large cohort studies provide contradictory results on the monitoring of these patients: one suggests that NAFLD patients should be closely monitored for CVD disease prevention [17], while the other proposes that cardiovascular risk stratification in NAFLD patients should be made in the same way as in the general population [18]. We also know that cardiovascular evaluation is rather conservative for asymptomatic NAFLD patients, based on current recommendations, unless they feature intermediate or high risk or have progressed to NASH cirrhosis [19]. However, no data exist concerning cardiovascular assessment in patients with NAFLD-IBD concomitance. As the latter might boost overall CVD risk, physicians should also consider, besides utilization of risk prediction scores and thorough laboratory investigation, performance of echocardiography, along with measurement of arterial stiffness and carotid intima media thickness, if available.

In conclusion, these patients require close monitoring and a multilevel diagnostic and therapeutic approach irrespective of body mass index, early after the onset of the disease. Further prospective studies are needed, in order to establish the interconnection between this triad at a pathophysiologic level and assess the safety and efficacy of potential, multitargeted treatment options.

Conflict of interest

The author declares no conflict of interest.

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