ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

World Journal of *Gastroenterology*

World J Gastroenterol 2022 January 28; 28(4): 402-501

Published by Baishideng Publishing Group Inc

World Journal of Gastroenterology

Contents

Weekly Volume 28 Number 4 January 28, 2022

World Journal of Gastroenterology

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NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

EDITORS-IN-CHIEF
Andrzej S Tarnawski

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PUBLICATION DATE
January 28, 2022

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World J Gastroenterol 2022 January 28; 28(4): 497-499

DOI: 10.3748/wjg.v28.i4.497

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LETTER TO THE EDITOR

Interplay between chronic hepatitis B and atherosclerosis: Innovative perspectives and theories

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Author contributions: Ranković I and Bezmarević M designed the research and analyzed the data; Ranković I and Milivojević V performed the research; Ranković I drafted the letter; Pavlović Marković A revised the letter.

Conflict-of-interest statement: The authors have no conflicts of interest to declare.

Country/Territory of origin: Serbia

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

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Abstract

Elaboration of carotid atherosclerosis in the setting of hepatitis B virus (HBV) infection should emphasize the significance of extrahepatic manifestations of the infection pathogenesis. Diverse processes comprise the pathoevolution of HBV infection, rendering it a multi-systemic disease in its essence. Our work not only exemplified atherosclerosis as an often-underestimated contributor to the severity of HBV infection but has also highlighted the bidirectional relationship between the two. Therefore, it is suggested that HBV-induced inflammation is one of the root causes of atherosclerosis, which in turn has a consequent effect on the severity of the chronic infection disease state, creating a vicious cycle. Additionally, we coupled prior data with the current concepts of HBV infection to postulate intriguing perspectives and theories.

Key Words: Hepatitis B virus infection; Carotid atherosclerosis; Hepatitis B e antigen; Arterial inflammation; Perspectives and trends

Core Tip: Hepatitis B virus (HBV) infection is a multifaceted disease, with significant cardiovascular morbidity. Our innovative approach to this pathophysiologic

Received: September 20, 2021
Peer-review started: September 20, 2021
First decision: November 7, 2021
Revised: November 17, 2021
Accepted: January 14, 2022
Article in press: January 14, 2022
Published online: January 28, 2022

P-Reviewer: Cao X, Ghoneim S
S-Editor: Fan JR
L-Editor: A
P-Editor: Fan JR

relationship harbors several key ideas. First, HBV infection may carry a specific atherosclerosis distribution pattern, with predilection for carotid arteries. Second, we propose wider use of more sensitive inflammatory markers, such as high-sensitivity C-reactive protein and homocysteine. Third, macrophage phenotype function should be investigated, utilizing its potential role as an atherosclerosis biomarker in HBV infection and therapeutic target. Last but not least, we reason that statins should be exploited more in current practice, due to their favorable pleotropic effects.

Citation: Ranković I, Milivojević V, Pavlović Marković A, Bezmarević M. Interplay between chronic hepatitis B and atherosclerosis: Innovative perspectives and theories. *World J Gastroenterol* 2022; 28(4): 497-499
URL: https://www.wjgnet.com/1007-9327/full/v28/i4/497.htm
DOI: https://dx.doi.org/10.3748/wjg.v28.i4.497

TO THE EDITOR

We read with interest the study of Riveiro-Barciela *et al*[1] which elucidates the possible interplay between hepatitis B virus (HBV) infection and carotid atherosclerosis. It has high-yield trial properties due to its large sample size and prospective method. Although its inclusion and exclusion criteria were precise and broad, as with any case-control study, there remains the possibility of bias as a consequence of inferring causation from statistically significant correlations which can be complicated by difficulty in determining the chronological order of exposure to HBV (*i.e.* the starting time of infection and latency).

The authors concluded that the presence of subclinical atherosclerosis and carotid plaques were more frequent in patients with HBV infection than in controls and that liver damage was an independent factor associated with subclinical atherosclerosis and carotid plaques, regardless of the presence of classical cardiovascular factors.

In general, we agree with the authors, since many of our patients render a similar atherosclerotic disease profile which cannot be attributed solely, *sui generis*, to the cardiovascular substrate. Therefore, their study's findings have the capacity not only to raise the index of suspicion of a practicing clinician but to optimize the established diagnostic framework of HBV patients in order to prevent atherosclerosis occurrence and complications.

Furthermore, the study implicates chronic HBV infection (*i.e.* the specific point of the naïve hepatitis B e antigen (HBeAg)-negative phase) as being an important atherosclerotic contributor. Conversely, a prior study by Tong *et al*[2] has concluded that HBV infection not only negatively correlates with C-reactive protein (CRP) levels but seems to not be associated with coronary atherosclerosis. Additionally, Kiechl *et al*[3] found no significant association between chronic hepatitis and the development of new carotid atherosclerotic plaques; although, they did not specify the type of hepatitis virus. Of course, these conflicting results have to be considered cautiously, as they originate from patients in different phases of the HBV infection and divergent research materials and methods. With all this said, it may be that the window of opportunity for early atherosclerosis detection and preemptive therapeutic intervention in HBV could represent the subpopulation of naïve and HBeAg-negative patients.

However, the general discrepancies in the conclusions of the aforementioned trials made us postulate some intriguing perspective theories. First, it may be that HBV infection harbors specific propensity towards anatomically different vascular structures, thereby affecting carotid arteries more often than coronary arteries. This notion is in concordance with the previously published data inferring that viruses have different sites of endothelial predilection[4]. Second, we may utilize other, more sophisticated inflammatory markers, namely high-sensitivity (hs-)CRP with or without homocysteine for optimal HBV patient stratification regarding atherosclerosis risk[5]. Third, the potential role of macrophage phenotype variation during HBV infection may be one of the crossroads between the processes of atherosclerosis and HBV infection[6]. Current cardiology investigations have revealed the significant role of macrophages, encompassing their local, endothelial, as well as systemic effects *via* T-helper lymphocytes and cytokine release modulation[7]. Having stated that, we

postulate that HBV infection may trigger macrophage phenotype alteration, rendering it to be a contributive precipitant of atherosclerotic disease as well as the crosslink point between the two diseases. Last but not least, the study of Riveiro-Barciela *et al*[1] may open the door for broader statin use, addressing two end goals concomitantly: Lowering the risk of cirrhosis and hepatocellular carcinoma in viral hepatitis patients [8], and engaging in the prevention and treatment of atherosclerosis and its complications.

We believe that prospects in this field should be diversified in the manner that one-size does not fit all. Upcoming trials and future viewpoints should render better comprehension of the delicate HBV pathodynamics from which implementation of optimized and specific therapy would be more feasible.

Our group envisions many possible pathways between HBV infection and atherosclerosis, *i.e*. cardiovascular diseases which may be potential targets for clinical management, and thus encourages future research work in this field.

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