Kardiologia Polska 2018; 76, 1: 119–124; DOI: 10.5603/KP.a2017.0165 ISSN 0022–9032

ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

The relationship between exposure to hepatitis B virus and increased atherosclerosis-associated morbidity — a meta-analysis

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Abstract

Background and aim: The relationship between exposure to hepatitis B virus (HBV) and atherosclerosis-associated disease morbidity has not been clearly elucidated. We performed a meta-analysis to explore whether exposure to HBV is a risk factor for atherosclerosis-associated diseases.

Methods: We searched the PubMed, Web of Science, Cochrane Library, Embase, and Scopus databases for related studies. We then chose the eligible studies for meta-analysis and assessed quality assessment and risk of bias.

Results: The meta-analysis of the included studies showed that exposure to HBV tends to increase atherosclerosis-associated disease morbidity, but this increase was not statistically significant.

Conclusions: Hepatitis B virus may not be a risk factor for atherosclerosis-associated diseases, but further studies that employ more sensitive clinical parameters are needed to verify this result.

Key words: hepatitis B virus, atherosclerosis, meta-analysis

Kardiol Pol 2018; 76, 1: 119–124

INTRODUCTION

Atherosclerosis is a common disease with increasing morbidity, which is associated with many cardiovascular and cerebrovascular diseases, including coronary heart disease (CHD) and stroke. The traditional risk factors for atherosclerosis, such as arterial hypertension, diabetes mellitus, and hyperlipidaemia, are well known. However, in clinical practice, certain patients with atherosclerosis do not have the risk factors mentioned above, and this observation highlights the importance of identifying novel risk factors that might contribute to atherosclerosis.

Previous studies have demonstrated that inflammation caused by infection, especially chronic infection, is one of the risk factors for atherosclerosis-associated diseases [1]. A meta-analysis showed that chronic hepatitis C virus (HCV) infection increases atherosclerosis-associated disease mortality [2]. However, in China, in particular South China, the morbidity of hepatitis B virus (HBV) is far higher than that of HCV [3]. Thus, determination of the relationship of exposure to HBV with atherosclerosis-associated diseases merits more attention. Moreover, studies have shown that exposure to HBV could promote oxidative stress [4], increase mean platelet volume (MPV) [5], and affect blood lipid levels [6], all of which can increase atherosclerosis risk.

However, whether exposure to HBV can increase the morbidity of atherosclerosis-associated diseases is controversial [7–13]. In this study, we reviewed relevant studies and performed a meta-analysis to explore whether exposure to HBV is a risk factor for atherosclerosis.

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Received: 18.03.2017 r. **Accepted:** 18.07.2017 r. **Available as AoP:** 21.08.2017 r.

METHODS

Search strategies

We searched for keywords "atherosclerosis or atherosclerotic or arteriosclerosis" and "hepatitis B or hepatitis B virus or HBV" in the "all fields" function of PubMed, Web of Science, Cochrane Library, Embase, and Scopus databases from 1986 to February 13, 2016. No language restrictions were applied to the search strategy. The results were sent to reference management software and duplicates were deleted. Two reviewers (C. L. and S. L.) independently screened the title and abstract of each article and then decided whether the article met the inclusion criteria. Next, the two reviewers read the full text of all selected articles and removed inappropriate articles that met the exclusion criteria. In the event of differences in opinion, the two reviewers discussed their opinions and decided whether to include the article in the final analysis.

Inclusion and exclusion criteria

The inclusion criteria were: (1) exposure to HBV; (2) outcome of atherosclerosis-associated disease, such as CHD, carotid atherosclerosis, and stroke (diagnosed based on standard criteria); and (3) observational study (including cross-sectional study, case-control study, and cohort study). For example, a case-control study was included if it compared the exposure to HBV between individuals with and without CHD.

The exclusion criteria were: (1) concurrent infection with other pathogens; (2) if the relationship between exposure to HBV and atherosclerosis-associated diseases were not studied; and (3) review, workshop summary, animal experiment, and other no observational study.

Quality assessment

Two reviewers (C. L. and S. L.) independently assessed the quality of the studies, according to the Newcastle-Ottawa Scale [14]. The Newcastle-Ottawa Scale assesses the quality of a study based on three aspects: selection, comparability, and exposure. Selection includes four sub-items: adequate case definition, representativeness of the cases, selection of controls, and definition of controls. Comparability pertains to the comparability of case and control when it comes to design and statistical analysis, which includes the important factors and the additional factors. Exposure includes three sub-items: ascertainment of exposure, same method of ascertainment for cases and controls, and non-response rate. If the study fits one sub-item, it is awarded one star; thus, more stars represent higher quality.

Data abstraction

Two reviewers (C. L. and S. L.) decided the item, format, and unit of the data of each eligible study, after discussion. They independently abstracted the necessary data. Finally, the reviewers checked the data and counterchecked the article in case of differences.

Analysis

We performed a meta-analysis of eligible studies using the software Review Manager 5.3, and presented results as odds ratio (OR), 95% confidence interval (95% CI), and p value. The forest plot was drawn by Review Manager 5.3. The risk of publication bias assessment was analysed by funnel plot and Egger test. The funnel plot was drawn by Review Manager 5.3, and the Egger test was performed by Stata 12.0. A p value < 0.05 was considered statistically significant.

RESULTS

Study identification and selection

After searching the PubMed, Web of Science, Cochrane Library, Embase, and Scopus databases, 1071 relevant articles were identified, of which 320 were duplicates and were deleted. The two reviewers screened the titles and abstracts of 751 articles and identified 29 articles that met the inclusion criteria. In the event of differences in opinion, the two reviewers discussed their opinions before deciding whether to include the article in the final analysis. The authors then read the full text of all 29 articles, and excluded studies that were not suitable for this meta-analysis. Eleven articles were excluded because they were the incorrect type of articles, such as reviews and workshop summaries; five articles had the wrong methodology (three included patients who had concurrent infection with other pathogens); one article was a cross-sectional study and did not study the relationship between exposure to HBV and atherosclerosis [15]; one article that considered cerebrovascular disease as an outcome included both ischaemic and haemorrhagic cerebrovascular disease [7]; seven articles had the wrong outcomes (they studied the parameters related to atherosclerosis but did not set a threshold to define atherosclerosis) [4–6, 16–19]; and one article was a cohort study, but there was no other cohort study to perform the meta-analysis [11]. Finally, we included five eligible studies for the meta-analysis [8–10, 12, 13]. This process is shown in Figure 1.

Characteristics of the studies

We collected the year, country, and other characteristics of the five studies (Table 1). The atherosclerosis-associated diseases in these studies included only two types: CHD and carotid atherosclerosis. The diagnosis of atherosclerosis-associated diseases in these five studies fitted the standard diagnostic criteria. The number of patients ranged from 434 to 5044. All studies included both men and women. Only the studies by Amirzadegan et al. [12] and Tong et al. [9] mentioned the storage temperature of serum samples (Table 1).

Risk of bias assessment

The risk of bias assessment is shown in Table 2. The selections of all studies were appropriate. Among four studies that used CHD as their outcome, patients' diagnoses were confirmed by coronary angiography, which documented stenosis > 50% [8, 9, 12, 13]. In one study that used carotid atherosclerosis

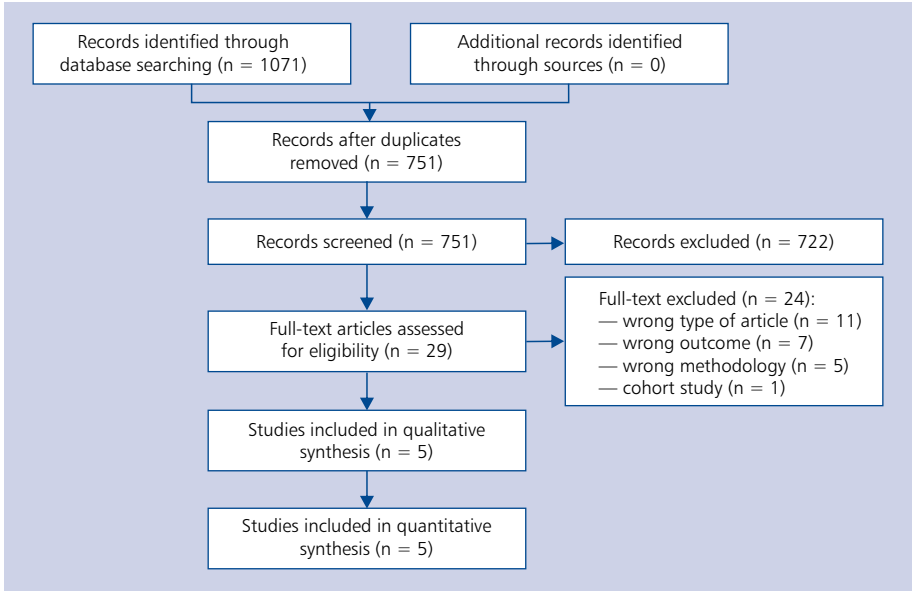

Figure 1. Flowchart. 1071 relevant articles were identified, of which 320 were duplicates and were deleted. Then 29 articles that met the inclusion criteria. But 24 articles were excluded because of wrong type of articles, wrong outcome, wrong methodology, and cohort study. Finally, five articles were included

as the outcome, the diagnoses were confirmed by B-mode ultrasonography, which demonstrated focal thickening of the intima-media layer ≥ 1.3 mm [10]. With the exception of the study by Ishizaka et al. [10], the other four studies all included hospitalised patients as controls. All the five studies considered sex, age, and other confounding factors. With the exception of the study by Amirzadegan et al. [12], which diagnosed HBV exposure by detecting the presence of anti-HBV in patients who had never had HBV infection or received the HBV vaccine, and the study by Tong et al. [9], which diagnosed HBV exposure by detecting the presence of one of the two antigens and three antibodies, all other studies diagnosed HBV infection by the presence of hepatitis B surface antigen (HbsAg) (Table 2).

Exposure to HBV and increased atherosclerosis-associated diseases

The study by Ishizaka et al. [10] used carotid atherosclerosis as the outcome and found that exposure to HBV infection increases the risk of atherosclerosis (OR 1.95, 95% CI 1.04–3.66). The remaining four studies all used CHD as the outcome. The studies by Ghotaslou et al. [8] and Tong et al. [9] found that exposure to HBV increases the risk of atherosclerosis, but this increase was not statistically significant (OR 1.53, 95% CI 0.82–2.84; OR 1.21, 95% CI 0.76–1.92, respectively) [8, 9]. The study by Momiyama et al. [13] found that exposure to HBV results in an insignificant decreased risk of atherosclerosis (OR 0.40, 95% CI 0.07–2.21). The study by Amirzadegan et al. [12] found that exposure to HBV does not increase nor decrease the risk of atherosclerosis (OR 0.99, 95% CI 0.71–1.38). Meta-analysis of these five studies showed that exposure to HBV can increase the risk of atherosclerosis, but this increase is not statistically significant (OR 1.19, 95% CI 0.95–1.49, p = 0.14). The forest plot is shown in Figure 2.

Risk of publication bias assessment

We have drawn the funnel plot and performed the Egger test for the five included studies. The funnel plot shows that the distribution of the eligible studies is similar to a funnel (Fig. 3), and the Egger test shows a p value of 0.915. Thus, there is no publication bias in these five studies.

DISCUSSION

Meta-analysis of five eligible studies showed that exposure to HBV tends to increase the risk of atherosclerosis-associated diseases, but this increase is not statistically significant.

Recently, a similar study reported that HBV infection did not increase the risk of coronary artery diseases [20]. It does not seem that exposure to HBV would increase cardiovascular event morbidity. Nevertheless, exposure to HBV can affect not only the coronary artery, but also cerebrovascular, carotid artery, and other blood vessels. Thus, we chose "atherosclerosis or atherosclerotic or arteriosclerosis" as the key words of our search, and included the studies with the outcomes of CHD, carotid atherosclerosis, and stroke. In our study, the outcome of four studies is CHD, and the outcome of one study is carotid atherosclerosis. However, there is no study report regarding the relationship between exposure to HBV and stroke.

Table 1. Study characteristics

Author	Year	Country	Study design	Outcomes	Diagnosis of exposure to HBV	Storage of serum samples	No. of subjects	Mean age [years]	Male [%]	Hyper-tension [%]	Diabetes [%]	Mean cholesterol [mmol/L]	Mean triglyceride [mmol/L]	Mean BMI	Smokers [%]
Ghotaslou et al. [11]	2008	Iran	Case--control	CAD	HBsAg	NR	HBV+ 159	NR	NR	NR	NR	NR	NR	NR	NR
							HBV– 4845	NR	NR	NR	NR	NR	NR	NR	NR
Amirzadegan et al. [15]	2007	Iran	Case--control	CAD	Anti-HBS	–80°C	HBV+ 239	57.18	71.1	35.6	18.8	5.3	2.1	27.61	29.7
							HBV– 591	56.93	61.8	40.9	27.1	5.3	2.1	26.67	26.2
Tong et al. [12]	2005	China	Case--control	CAD	HBsAg, HBeAg, anti-HBs, anti-HBc, anti-HBe	–70°C	HBV+ 329	62.12	70.2	62.3	14.6	NR	NR	NR	32.8
							HBV– 105	62.49	73.3	64.8	15.2	NR	NR	NR	40.9
Momiyama et al. [16]	2005	Japan	Case--control	CAD	HBsAg	NR	HBV+ 6	NR	NR	NR	NR	NR	NR	NR	NR
							HBV– 624	NR	NR	NR	NR	NR	NR	NR	NR
Ishizaka et al. [13]	2002	Japan	Case--control	CA	HBsAg	NR	HBV+ 40	58	65	NR	NR	5.1	1.1	23.1	18
							HBV– 4646	57	67	NR	NR	5.4	1.5	23.2	27
							HBV– 18542	NR	48.9	6.1	2.5	NR	NR	NR	24.7
							HBV– 478747	41.5	100	17.3	4	4.93	NR	23.4	59.3

BMI — body mass index; CA — carotid atherosclerosis; CAD — coronary artery disease; HBV — hepatitis C virus; NR — not reported

Table 2. Newcastle-Ottawa Scale

Authors, year	Selection				Comparability			Exposure		Score
	Is the case definition adequate	Representa-tiveness of the cases	Selection of controls	Definition of controls	Important factors	Additional factors	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non--response rate	
Ghotaslou et al., 2008 [11]	★	★	–	★	1,2,3,4,5,6	8	★	★	★	★★★★★★★
Amirzadegan et al., 2007 [15]	★	★	–	★	1,2,3,4,5,6,7	8,10	★	★	★	★★★★★★★★
Tong et al., 2005 [12]	★	★	–	★	1,2,3,4,5,6	8,10,11	★	★	★	★★★★★★★★
Momiyama et al., 2005 [16]	★	★	–	★	1,2,3,4,5,6	13	★	★	★	★★★★★★★
Ishizaka et al., 2002 [13]	★	★	★	★	1,2,3,4,6	8,13	★	★	★	★★★★★★★★

Important factors: 1 — age; 2 — sex; 3 — hyperglycaemia; 4 — hypertension; 5 — diabetes; 6 — smoking; 7 — body mass index. Five items or more get one star.
Additional factors: 8 — C-reactive protein; 9 — alanine transaminase; 10 — history of cardio-cerebrovascular diseases; 11 — family history; 12 — other infectious diseases; 13 — others. Two items or more get one star.

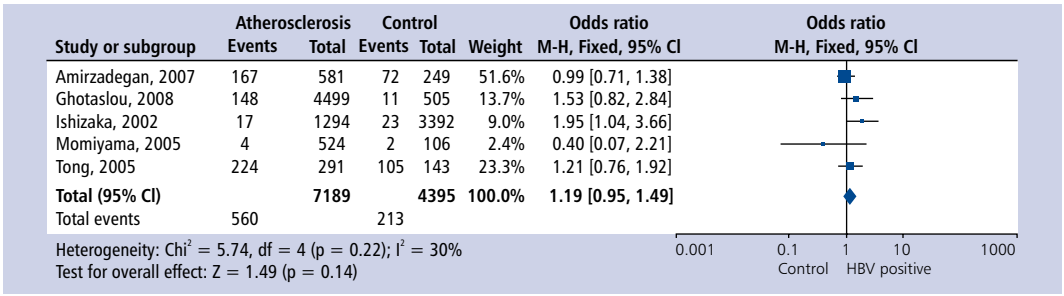

Figure 2. Forest plot. The figure shows that exposure to hepatitis B virus (HBV) can increase the risk of atherosclerosis, but this increase is not statistically significant (OR 1.19, 95% confidence interval [CI] 0.95–1.49, p = 0.14)

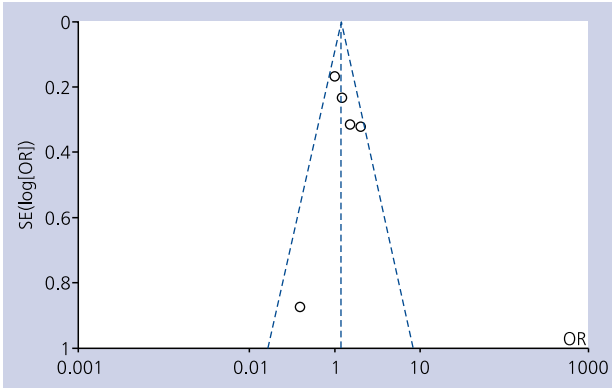

Figure 3. Funnel plot. The figure showed no publication bias in these five studies

This finding is similar to that obtained by Sung et al. [11] in a cohort study that was excluded in this analysis. Among four studies that used CHD as the main outcome, and which confirmed patients' diagnosis by coronary angiogram showing stenosis > 50%, there was no statistically significant effect of HBV on atherosclerosis risk. Thus, we consider that diagnosing CHD using a coronary angiogram may be more accurate, but less sensitive in diagnosing atherosclerosis compared with carotid atherosclerosis. So, in our opinion there might be some pathologic changes when exposing to HBV, although exposure to HBV does not increase cardiovascular event morbidity. Furthermore, a study found that exposure to HBV increases the intima-media thickness [19]. Increased oxidative stress [4] and MPV [5] caused by exposure to HBV mainly affect the early pathological changes seen in atherosclerosis. Meanwhile, studies that showed a positive relationship between HCV infection and increased atherosclerosis-associated disease morbidity mainly used carotid atherosclerosis as the outcome of interest [21]. Thus, it is necessary to explore the relationship between exposure to HBV and atherosclerosis-associated diseases using a more sensitive parameter.

Furthermore, another study considered that exposure to HBV can decrease the risk of atherosclerosis, which was related to hepatic dysfunction caused by exposure to HBV, and the authors confirmed this hypothesis in a subgroup analysis [11]. This finding may be attributed to the pivotal role of the liver in coagulation factor synthesis and lipid metabolism. In addition, the secondary hypersplenism caused by liver cirrhosis can lead to thrombocytopaenia. All the factors mentioned above can play important roles in atherosclerosis.

Limitations of the study

Our study has some limitations. First, the number of included articles was small, which may be attributed to the lack of studies on the relationship between exposure to HBV and atherosclerosis and the possibility that studies with negative findings were scarce. Second, the included studies were mainly from Asian countries, which may be attributed to the high HBV morbidity in Asian countries compared with other countries. However, given that differences in race exist in the reaction of vascular endothelial cells to infection [22], further research is warranted to investigate the relevance of race in HBV-related atherosclerosis risk.

CONCLUSIONS

Thus, we think that the influence of exposure to HBV to atherosclerosis depends on the function of the liver. When the function of the liver is normal, exposure to HBV can increase the risk of atherosclerosis, especially during the early stage of pathological atherosclerotic lesions. Conversely, when exposure to HBV leads to hepatic dysfunction, it can decrease the risk of atherosclerosis. However, this hypothesis requires further investigation in order to be confirmed or refuted.

Funding: *This work was supported by the project of the National Natural Science Foundation of China (No. 81371276) and the Natural Science Foundation of Guangdong Province, China (No. 2014A030313065) to J.Y. It was also supported by the Medical Scientific Research Foundation of Guangdong Province, China (No. A2015480) to S.L.*

Conflict of interest: *none declared*

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Cite this article as: Li C, Liao S, Que J, et al. The relationship between exposure to hepatitis B virus and increased atherosclerosis--associated morbidity — a meta-analysis. Kardiol Pol. 2018; 76(1): 119–124; doi: 10.5603/KP.a2017.0165.