Hepatitis B Virus Infection as a Risk Factor for Developing Diabetes Mellitus: A Meta-Analysis of a Large Observational Studies

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ABSTRACT

Background: *There are a lot of theories about how Hepatitis B Virus (HBV) infection affects many diseases, one of them is Diabetes Mellitus (DM). However, the relation remains controversial between DM and HBV as an infection. This study aims to evaluate HBV infection as a risk factor for developing DM.*

Method: *A systematic review was performed using medical search engines such as Pubmed, ScienceDirect and GoogleScholar. References until February 2021 that met the inclusion criteria were reviewed. The primary outcome was the prevalence of DM. Authors also perform Subgroup analyses based on study type. The extracted data were analyzed using RevMan 5.4 application.*

Results: *A total of 20 studies were analyzed with 245,468,411 subjects included. In which divided into two groups, patients with HBV infected group and non infected HBV group. Authors found that there is a statistically difference between patients with HBV infected groups and non infected HBV groups on the primary outcome which is the prevalence of DM (OR = 1.24; 95% CI, 1.10-1.41; p = 0.0006). Authors also found the same results based on study type both in case-control (OR = 1.76; 95% CI: 1.08-2.85; p = 0.02) and cross-sectional (OR = 1.40; 95% CI: 1.05-1.85; p = 0.02) studies. Meanwhile in Cohort studies the results show no statistically significant difference between the two groups (OR = 1.07; 95% CI: 0.87-1.33; p = 0.52).*

Conclusion: *HBV infected patients have a higher risk of developing DM than patients without HBV infection.*

Keywords: *Diabetes mellitus, Hepatitis B virus, meta-analysis*

ABSTRAK

Latar belakang: *Terdapat berbagai teori tentang pengaruh infeksi Virus Hepatitis B (HBV) terhadap beberapa penyakit, salah satunya adalah Diabetes Mellitus (DM). Namun, hubungan antara DM dan infeksi HBV masih kontroversial. Penelitian ini bertujuan untuk mengevaluasi infeksi HBV sebagai faktor risiko terjadinya DM.*

Metode: *Tinjauan sistematis dilakukan dengan menggunakan mesin pencari medis seperti Pubmed, ScienceDirect, dan GoogleScholar. Referensi yang dipublikasikan hingga Februari 2021 dan memenuhi kriteria inklusi ditinjau. Ekstraksi data utama adalah prevalensi DM. Penulis juga melakukan analisis Subkelompok berdasarkan jenis studi. Data yang telah diekstraksi dianalisis menggunakan aplikasi RevMan 5.4.*

Hasil: *Sebanyak 20 studi dianalisis dengan jumlah subjek 245.468.411 yang terbagi menjadi dua kelompok, yaitu kelompok pasien yang terinfeksi HBV dan kelompok yang tidak terinfeksi HBV. Penulis menemukan bahwa terdapat perbedaan secara statistik antara kelompok terinfeksi HBV dan kelompok tidak terinfeksi HBV pada*

ekstraksi data utama yaitu prevalensi DM (OR = 1,24; 95% CI: 1,10-1,41; p = 0,0006). Penulis juga menemukan hasil yang sama berdasarkan jenis penelitian baik dalam studi case control (OR = 1,76; 95% CI: 1,08-2,85; p = 0,02) maupun cross-sectional (OR = 1,40; 95% CI: 1,05-1,85; p = 0,02). Sedangkan pada studi kohort, menunjukkan hasil yaitu tidak ditemukannya perbedaan yang signifikan secara statistik antara kedua kelompok (OR = 1,07; 95% CI: 0,87-1,33; p = 0,52).

Simpulan: *Pasien yang terinfeksi HBV memiliki risiko lebih tinggi untuk berkembang menjadi DM dibandingkan pasien tanpa infeksi HBV.*

Kata kunci: *Diabetes melitus, Hepatitis B Virus, meta analisis*

INTRODUCTION

Hepatitis B Virus (HBV) is a serious and prevalent health problem. Worldwide, approximately 2 billion people have been infected, and more than 240 million are chronic carriers with risk of developing progressive liver diseases, such as cirrhosis, liver failure, and hepatocellular carcinoma (HCC).[1] The HBV infection accounts for more than 780,000 deaths each year, with HCC currently being the fifth most frequent cancer and the second most common cause of cancer mortality.[2] Although HBV infection is prevalent all over the world, its prevalence is much higher and differs among different areas of the Asia-Pacific region and 74% of global deaths from liver cancer occur in Asia.[1,3] Meanwhile, as a country with more than 270 million people, it is estimated that 7.1% of 40,791 people are positive for the hepatitis B surface antigen (HBsAg) in Indonesia.[4] Hepatitis B Virus (HBV) infection is a major risk factor that can result in chronic liver malfunction, liver cirrhosis, and hepatocellular carcinoma.[5]

Diabetes mellitus (DM) and pre-diabetes mellitus (pre-DM) are two common glucose metabolism disorders. DM is defined as a group of metabolic disorders characterized by high blood glucose levels.[6] DM in the world has reached 415 million in 2015, and is projected to be up to 642 million by 2040.[7] In Indonesia, the prevalence of DM has reached up to 10,681,400 cases among adult population and has been a major health problem.[8] As we know, DM can cause many complications such as increases the risk of cancers, including liver, pancreatic, and colorectal cancer and many others. Thus, prevention and management of DM are especially important to prevent complications and curb the prevalence rate of DM in Indonesia.[9]

Insulin resistance and β-cell dysfunction are important mechanisms of DM. Glycometabolism disorder is the key point of the development of DM. Since liver is one of the primary organs involved in glucose homeostasis such as glucose storage in the form of glycogen, the conversion of this glycogen to glucose and the production of glucose from non-carbohydrate sources, hepatic dysfunction caused by HBV infection may lead to glycometabolism disorder and even DM.[10] The association between HBV infection and DM remains controversial. The aim of our study is to evaluate HBV infection as a risk factor for developing DM.

METHOD

The Pubmed, Science Direct, Google Scholar and Research Gate, were used to search for relevant articles published until February 2021. The search was restricted to human studies and publications in English or Bahasa. The keywords listed below were used: ‘Hepatitis B Virus’, ‘HBV’, ‘hepatitis B’, ‘diabetes’, ‘diabetes mellitus’, ‘DM’, ‘diabetes mellitus type 2’, ‘insulin resistance’, ‘risk factor’, and ‘glucose intolerance’.

Authors restricted our review to studies that met the following criteria: (1) observational studies (cohort, case control, and cross sectional), (2) involve people with HBV infection and DM, then compared to the control group, (3) studies with accessible full texts, (4) DM confirmed based on a) self-reported DM (i.e., diagnosed by a physician), b) fasting plasma glucose levels >7.0 mmol/L on two separate occasions or c) impaired fasting glycemia of 6.1-7.0 mmol/L without insulin medication. To validate HBV infection, hepatitis B surface antigen (HBsAg) and/or antibody against hepatitis B core antigen (anti-HBc) and/or HBV DNA were detected. The following were the exclusion conditions for this study: (1) Gestational DM; (2) observational studies without control groups; (3) a subset of a published article containing the same details and written by the same authors; (4) studies involving patients with chronic liver disease caused by autoimmune hepatitis, steatohepatitis, cirrhosis, primary biliary cirrhosis, hepatocellular carcinoma, and primary cholangitis.

Figure 1 show the flowchart of the selection process of the studies. We excluded the majority of articles after evaluating them individually at the level of title, abstract and full text and 21 articles were included. Nine were studies cross-sectional studies, 5 were case-control studies and 5 were cohort studies.

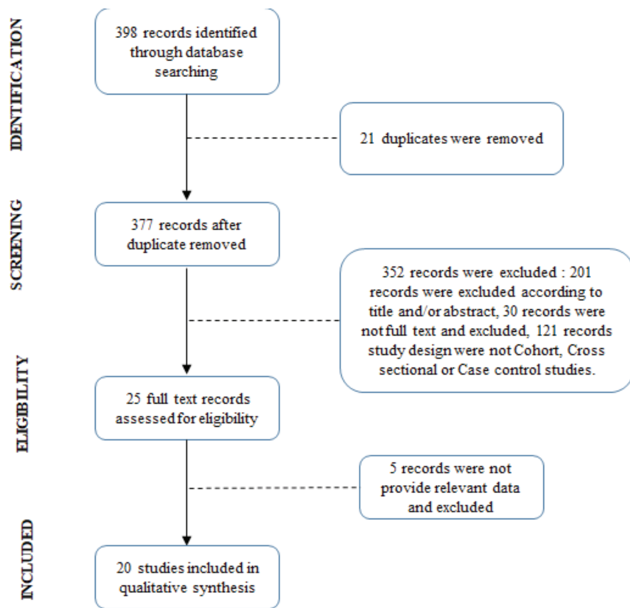

Figure 1. QUOROM (quality of reporting of meta-analyses) flow-chart of the study selection process

The primary outcome was the prevalence of DM. Subgroup analyses were performed based on study types. The methodological index for non-Randomized Studies (MINORS) was used to measure the probability of bias in the included researches.[11] Each study examines seven domains related to the risk of bias: (1) aim (i.e., clearly stated aim); (2) rate (i.e., inclusion of consecutive patients and response rate); (3) data (i.e., prospective collection of data or data collected using a high-quality population-based data set); (4) bias (i.e., unbiased assessment of study endpoints); (5) time (i.e., follow-up time appropriate); (6) loss (i.e., loss to follow- up); (7) size (i.e., calculation of the study size). The decisions of the study authors were graded as 'low risk,' 'high risk,' or 'unclear risk of bias' and disagreements were settled by discussion. The authors only included low risk graded studies to avoid unreliable results caused by invalid data from high risk bias studies.

The extracted data were analyzed using RevMan software version 5.4. A two-tailed $p < 0.05$ was found statistically important. A systematic review was performed in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

RESULTS

Figure 2 outlines the characteristics of included studies. A total of 20 (12, 13, 14, 15, 16, 17, 18, 19, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32) studies were analyzed with 245,468,411 subjects were enrolled this

	AIM	RATE	DATA	BIAS	SIZE	LOSS	TIME
Choi 2017	+	+	+	+	−	−	−
Hong 2017	+	+	+	+	+	+	−
Huang 2010	+	+	+	−	+	+	−
Imazeki 2008	+	+	+	−	+	+	−
Jan 2006	+	+	+	+	+	−	−
Keywani 2013	+	+	+	−	+	+	+
Khursid 2019	+	+	+	+	+	−	−
Knobler 2000	+	+	+	−	+	+	+
Li-Ng 2007	+	+	+	+	+	+	−
Masood 2017	+	+	+	+	−	−	−
Million 2019	−	+	+	+	+	+	+
Qureshi 2002	+	+	+	−	+	+	−
Reilly 2012	+	+	+	+	+	−	−
Schillie 2012	+	+	+	−	+	+	−
Shaoyuan 2020	+	+	+	+	+	+	−
Spradling 2013	+	+	+	−	+	+	−
Wang 2010	+	+	+	+	+	+	−
Yang 2002	+	+	+	−	+	+	+
Yang 2003	+	+	+	−	+	+	+
Zhao 2006	+	+	+	+	+	+	−

Figure 3. Assessment of risk of bias. (A) Summary of risk of bias for each trial; Plus sign: low risk of bias; minus sign: high risk of bias; question mark: unclear risk of bias. (B) Risk of bias graph about each risk of bias item presented as percentages across all included studies.

study which were published between 2003 to 2020. In which divided into two subgroups, 12,982,158 patients with HBV infected group and 232,486,253 patients in non infected HBV groups. Sixteen studies showed a significantly higher prevalence of DM in HBV-infected patients than in the control.

We analyzed the primary outcome based on study type to investigate the factors that could impact the overall results. The results of the study type-based subgroup analysis indicated that the prevalence of DM in the HBV group was significantly higher than that in the control group, both in case-control (OR = 1.76; 95% CI: 1.08-2.85; p = 0.02) and cross-sectional (OR = 1.40; 95% CI: 1.05-1.85; p = 0.02) studies. Meanwhile in Cohort studies the results show no

Table 1. Study design and baseline characteristics of the included studies

Study	Year	Design, Period	Country	HBV Infection Cases	Confirmation of HBV	Detection	DM Cases	Confirmation of DMDM
Spradling	2013	Cohort	USA	6,525	HBsAg	-	49,664	Clinically diagnosed
Wang	2010	Cohort	Chinese Taipei	417	HBsAg	ELISA	2,842	Criteria ADA
Reilly	2012	Case control	USA	802	HBsAg	-	91,644	Patient reported
Zhao	2006	Case control	China	305	HBV DNA	PCR	615	WHO
Yang	2003	Case control	China	227	HBsAg	ELISA	33538	Criteria ADA
Qureshi	2002	Case control	Pakistan	98	HBsAg	ELISA	508	Clinically diagnosed
Knobler	2000	Case control	Israel	88	HBsAg and anti-HBc	ELISA	178	Criteria ADA
Keyvani	2013	Cross sectional	Iran	103	Anti-HBc	ELISA	334	Patient reported
Schillie	2012	Cross sectional	USA	12952525	Anti-HBc	ELISA/CLIA	231559812	Patient reported
Huang	2010	Cross sectional	Chinese Taipei	142	HBsAg	-	1,229	FPG or 2-hPPG
Imazeki	2008	Cross sectional	Japan	286	HBsAg	ELISA	408	FPG or 2-hPPG
Li-Ng	2007	Cross sectional	USA (Asian Americans)	16	HBsAg	-	229	Random blood glucose
Li-Ng	2007	Cross sectional	USA (Pacific Islanders)	40	HBsAg	-	178	Random blood glucose
Jan	2006	Cross sectional	Chinese Taipei	5,994	HBsAg	RIA	47,693	FPG
Yang	2002	Cross sectional	China	122	HBsAg	ELISA	2,525	WHO
Hong	2017	Cohort	South Korea	8,694	HBsAg	-	219,448	Patient reported
Khursid	2019	Case control	Pakistan	120	HBsAg	-	240	Random blood glucose
Shaoyuan	2020	Cohort	China (Hubei)	18,6	HbsAg, anti-Hbc, Anti Hbs	ELISA	56,15	FBG level≥7.0 mmo/any use of anti-diabetic agents, or a selfreported physician's diagnosis
Masood	2017	Cross sectional	Iran (Tabas)	156	HBsAg	ELISA	1,245	HbA1c >6.5, blood sugar > 200mg/dL
Choi	2017	Cohort	South Korea	7,189	HBsAg	-	428,659	FPG
Million	2019	Cross sectional	Ethiopia	65	HBsAg	ELISA	610	FPG > 126mg/dL, 2 hPP>200mg/dL

statistically significant difference between patients with HBV infection and those who were not infected with HBV (OR = 1.07; 95% CI: 0.87-1.33; p = 0.52). The results of the present meta-analysis demonstrated that the HBV-infected patients had a higher risk of developing DM when compared with the uninfected patients (OR = 1.24; 95% CI: 1.10-1.41; p = 0.0006).

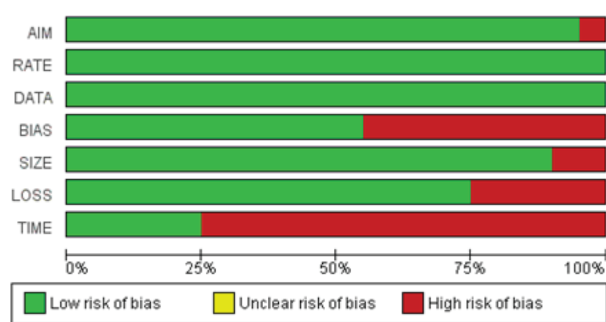

Figure 3. Study type-based subgroup analysis on the prevalence of diabetes mellitus in the HBV infection group compared with the control group. HBV, hepatitis B virus; OR, odds ratio; CI, confidence intervals

DISCUSSION

This meta analysis demonstrated that HBV infected patients have a higher risk for developing DM than patients without HBV infection. Authors conducted subanalysis based on study type, due to authors found the opposite result in several cohort studies.[19] It found that there was no detected association between DM and HBV infection.[20] This finding was unclear because some factors could affect this analysis such as older age and higher proportion of metabolic syndrome in the control group than those with HBV infection. However, authors did not include two variables in this analysis: genetic backgrounds and dietary patterns of the participants. These things could have big role in the statistic results.

Genetic factors had an important role in diabetes mellitus. some genes such as TCF7L2, KCNQ1, and KCNJ1 active in beta cells. Also, involve in insulin secretion, specifically insulin sensitivity.[33] Diabetes is a complex disorder between environment and genetics.[34] Therefore, a history of diabetes mellitus in both parents is an important risk factor. Apart from genetic factors, there is also a diet. Diet is an important factor in the occurrence of diabetes mellitus in the future. In fact, one study conducted by Beigrezaei et al showed that diet as a risk factor has an OR value of 16.65, 95% CI: 2.99–92.84.[35] Also supported by other studies.[36]

Another possibility affecting the results was undefined HBV infection status as highlighted by Zhang et al. After infection, the patients may either developed immunity and clear the disease in the short term (acute infection) or become chronic virus carriers.[37] The association between glucose metabolism disorder and hepatotropic virus infection may only occur for chronic hepatotropic infection and only long term HBV infection in extrahepatic organs can trigger

extrahepatic autoimmune diseases such as glucose metabolism disorders.[20] In the cohort studies included in this meta-analysis, the status of HBV infection was mostly determined by HBsAg. The authors compared the general population, which could be HBV-infected, to the uninfected population.

In accordance with the previous meta-analysis conducted by Cai, et al,[38] patients with hepatitis B infection are at risk for developing diabetes mellitus in the future. Both with cross sectional study design (OR = 1.41; 95% CI: 1.04–1.90; p =0.027) and case control design (OR = 1.89; 95% CI: 1.08–3.30; p = 0.025). Correlation between HBV and diabetes is still a controversial. Be required for clinical trials to assess the correlation.[39] In addition, the duration of cohort studies' follow-up is not "long enough" to cause extrahepatic autoimmune disease as the authors have cited above may also influence the results of the cohort study subanalysis. Further studies are needed to verify the relationship between chronic HBV infection and DM.

Some experts argue, HBV infection makes insulin resistance worse.[40] This is thought to be the basis for HBV infection as a risk factor for future diabetes. It is advisable,to take the hepatitis B vaccination. Because, in people who have already been vaccinated against hepatitis B, the risk of developing diabetes is reduced by 50%.[40,41] The CDC and Advisory Committee on Immunization Practices (ACIP) guidelines call for hepatitis B vaccination for all unvaccinated adults with diabetes who are under age 60.[40,41]

Our study's strength was that it used a large study to analyze the association between different HBV infection statuses and DM, which helped us better understand the mechanism between HBV infection and DM. We also conducted a research type-based subgroup analysis to consider the impact on the final results. However, there are several limitations to this study. First, because the majority of the studies in this study were from Asia, the data did not represent the general population. Second, we did not collect the information on hepatitis B vaccination. In several studies, fasting glucose and blood sugar level were still being used to diagnose DM.

CONCLUSION

In conclusion, this study found that patients with HBV infection is associated with DM. Patients with HBV infection have a higher risk of developing DM compared with patients without HBV infection. Therefore, due to our limitation in this meta-analysis further studies are needed to verify the association between chronic HBV infection and DM.

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