Criteria Grid
Hepatitis C Research Studies, Tools, and Surveillance Systems

Best Practice/Intervention:	Machado MV. et al. (2011) Hepatic steatosis in hepatitis B virus infected patients: meta-analysis of risk factors and comparison with hepatitis C infected patients. *Journal of Gastroenterology & Hepatology*, 26(9):1361-1367
Date of Review:	March 17, 2015
Reviewer(s):	March 17, 2015

Part A

Category:	**Basic Science** ☐ **Clinical Science** ☐ **Public Health/Epidemiology** ☐ **Social Science** ☐ **Programmatic Review** ☒
Best Practice/Intervention:	**Focus:** **Hepatitis C** ☒ **Hepatitis C/HIV** ☐ **Other:** **hepatic steatosis, Hepatitis B** **Level:** **Group** ☒ **Individual** ☐ **Other:** _____ **Target Population:** **patients infected with HBV or HCV** **Setting:** **Health care setting/Clinic** ☒ **Home** ☐ **Other:** _____ **Country of Origin:** **Portugal** **Language:** **English** ☒ **French** ☐ **Other:** _____

Part B

	YES	NO	N/A	COMMENTS
Is the best practice/intervention a meta-analysis or primary research?	☒	☐	☐	Meta-analysis; to determine the prevalence and risk factors for hepatic steatosis in hepatitis B infection and to compare hepatic steatosis prevalence in HBV and HCV infected patients.
Has the data/information been used for decision-making (e.g. program funding developments, policies, treatment guidelines, defining research priorities and funding)?	☐	☒	☐	Results was not used for decision-making
Do the methodology/results described allow the reviewer(s) to assess the generalizability of the results?	☒	☐	☐	

Are the best practices/methodology/results described applicable in developed countries?	☒	☐	☐	
	YES	**NO**	**N/A**	**COMMENTS**
Are the best practices/methodology/results described applicable in developing countries?	☒	☐	☐	Studies in this analysis came from various countries, including ones from Asia, Europe, Middle East and USA
The research study/tool/data dictionary is easily accessed/available electronically	☐	☒	☐	Purchase required for download from http://onlinelibrary.wiley.com/
Is there evidence of cost effective analysis with regard to interventions, diagnosis, treatment, or surveillance methodologies? If so, what does the evidence say? ***Please go to Comments section***	☐	☒	☐	
Are there increased costs (infrastructure, manpower, skills/training, analysis of data) to using the research study/tool/data dictionary?	☐	☒	☐	
How is the research study/tool funded? ***Please got to Comments section***	☐	☒	☐	No funding stated
Is the best practice/intervention dependent on external funds?	☐	☒	☐	
Other relevant criteria: _____	☐	☐	☐	- Prevalence of HS was higher in studies that allowed excessive alcohol consumption - Prevalence of hepatic steatosis in HBV patients varies among studies, ranging from 14% to 70% - Liver biochemistry (except GGT) was not influenced by HS in HBV patients, contradicting results to what happens in HCV patients
WITHIN THE SURVEILLANCE SYSTEM FOR REVIEW				
Are these data regularly collected?	☐	☐	☐	Searched all articles published until 2010
Are these data regularly collected at and/or below a national level?	☐	☐	☐	

Are these data collected manually or electronically?	☐	☐	☐	Electronically: MEDLINE
RESEARCH REPORTS				
Has this research been published in a juried journal?	☐	☐	☐	*Journal of Gastroenterology & Hepatology*
Does the evidence utilize the existing data/surveillance information or has it generated new data and/or information?	☐	☐	☐	Existing data: 17 studies

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META-ANALYSIS AND SYSTEMATIC REVIEWS

Hepatic steatosis in hepatitis B virus infected patients: Meta-analysis of risk factors and comparison with hepatitis C infected patients

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fatty liver, hepatitis B, hepatitis C, prevalence, steatosis.

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We have no conflict of interest to declare.

Abstract

Background and Aims: Although hepatic steatosis (HS) has an association with hepatitis C virus (HCV) infection, an association with hepatitis B virus (HBV) is controversial. We performed a meta-analysis to evaluate HS prevalence and risk factors, in HBV infection.

Methods: Standard guidelines for performance of meta-analyses were followed. Studies with HS assessed by histology were included. Pooled odd ratios (OR) and standardized mean differences (SMD) were obtained with the random-effects model and DerSimonian-Laid method.

Results: Seventeen out of 21 studies were included, comprising 4100 HBV infected patients. Overall HS prevalence was 29.6%. Eight studies also included 945 HCV infected patients, showing decreased risk of HS in HBV versus HCV patients (OR 0.55, 95%CI [0.45–0.67], $P < 0.001$). In HBV, HS positively associated with male gender (OR 1.74, 95%CI [1.28–2.38], $P < 0.001$), body mass index (SMD 2.17, 95%CI [1.23, 3.11], $P < 0.001$), obesity (OR 6.59, 95%CI [3.51–12.257], $P = 0.003$), diabetes (OR 2.62, 95%CI [1.37–4.00], $P = 0.004$), glycemia (SMD 0.84, 95%CI [0.00, 1.67], $P = 0.049$), triglycerides (SMD 1.18, 95%CI [0.48, 1.89], $P = 0.001$), cholesterol (SMD 0.88, 95%CI [0.31, 1.45], $P = 0.003$), moderate alcohol consumption (OR 1.54, 95%CI [1.10–2.15], $P = 0.011$) and negatively with HBV DNA (SMD −74.12, 95%CI [−82.93, −65.31], $P < 0.001$). HS had no association with aminotransferases, HBeAg, genotype or hepatic histology, necroinflammation or fibrosis.

Conclusion: HS in HBV seems to be as frequent as in the general population, and lower than in HCV infected patients, relating to metabolic factors but not with hepatic histology severity. A puzzling strong negative association between viral load and HS, may even suggest a protective effect of the virus on HS.

Introduction

Chronic hepatitis B is a major cause of liver disease, with an estimated 350 million hepatitis B virus (HBV) chronically infected patients worldwide.[1] Clearly more frequent in Asian countries, in which epidemiology and virus genotypes ratio are distinct, population migration makes it a global health problem.

In hepatitis C infection, an association with hepatic steatosis (HS) has been well demonstrated.[2] Furthermore, HS has been shown to be a risk factor for liver disease progression[3,4] and to interfere with anti-viral treatment.[5] On the other hand, in HBV infection, an association with HS is not yet clarified, and the true prevalence of HS is unknown, despite several studies addressing this issue, particularly in the last 5 years. Even from a pathogenic perspective, data are discordant regarding a potential steatogenic effect of HBV. Indeed, circumstantial evidence suggested that the presence of HS may contribute to hepatitis B surface antigen (HBsAg) clearance, possibly due to an interference with the cytoplasmic distribution of HBsAg[6] or to a higher susceptibility to apoptosis in HS, decreasing the threshold to HBsAg specific T cell induced apoptosis in infected hepatocytes. Also, the metabolic syndrome, a known strong risk factor for HS, seems less likely to be present in HBsAg positive patients as compared with non-carriers.[7] However, Wong *et al*. suggested an increased risk of liver cirrhosis in hepatitis B infected patients with the metabolic syndrome.[8] Also, recent evidence showed a potential steatogenic effect of HBV protein x (HBx). HBx can lead to lipid accumulation in the hepatocytes through inhibition of apolipoprotein B secretion and induction of peroxisome proliferator-activated receptor γ (PPARγ) and sterol regulatory element binding protein 1c (SREBP-1c)[9] either through direct interaction with liver X receptor α (LXRα)[10,11] or tumor necrosis

Table 1 Main characteristics of the studies

Study	Year	Study location	HBV (*n*)	HCV (*n*)	Steatosis (%) in HBV	Steatosis (%) in HCV	$P^{\dagger}$
Lefkowitch *et al.*[15]	1993	USA	166	161	51	69	0.001
Malhotra *et al.*[16]	2000	India	30	30	67	70	0.009
Rozario and Ramakrishna[17]	2003	India	82	45	40	62	0.018
Gordon *et al.*[18]	2005	Australia	17	74	70	72	0.932
Altiparmak *et al.*[19]	2005	Turkey	164	0	39	NA	NA
Thomopoulos *et al.*[20]	2006	Greece	233	0	18	NA	NA
Papatheodoridis *et al.*[21]	2006	Greece	174	260	57	69	0.011
Cindoruk *et al.*[22]	2007	Turkey	140	0	34	NA	NA
Tsochatzis *et al.*[23]	2007	Greece	213	163	59	72	0.016
Peng *et al.*[24]	2008	China	153	0	27	NA	NA
Shi *et al.*[25]	2008	China	1915	0	14	NA	NA
Minakari *et al.*[26]	2009	Iran	132	0	42	NA	NA
Yun *et al.*[27]	2009	Korea	86	0	51	NA	NA
Tsochatzis *et al.*[28]	2009	Greece	95	176	60	76	0.292
Wong *et al.*[29]	2010	China	266	0	44	NA	NA
Vere *et al.*[30]	2010	Romania	30	36	47	69	0.08
Zheng *et al.*[31]	2010	China	204	0	52	NA	NA

$^{\dagger}P$ value regarding the difference in steatosis prevalence between HBV and HCV infected patients, with Fisher's exact test.
HBV, hepatitis B virus infected patients; HCV, hepatitis C virus infected patients; NS, non significant; NA, not applicable.

factor (TNF) receptor 1 leading to NFκB activation and TNF production.[12]

In order to clarify the extensive but discrepant data available, we conducted an in-depth review and meta-analysis of studies on the prevalence and risk factors for HS in HBV infected patients. We also analyzed the data comparing HS prevalence in HBV and HCV chronically infected.

Methods

This analysis was performed with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) criteria.[13] MEDLINE and Current Contents were searched by one investigator to identify relevant articles published until 2010. In the electronic scrutiny, study references and relevant review articles on HBV infection were manually searched; eligible studies were identified through structured keywords: "steatosis," "fatty liver" and "HBV." All analyzed studies had to be published in English and comprised a series of consecutive eligible patients, though allowing for exclusions due to other concomitant liver diseases and not necessarily excluding alcohol consumption. Exclusion criteria were indirect assessment of HS without liver biopsy, studies on pediatric populations and on patients with no evidence of active viral replication.

The abstracts of all papers identified by the initial search were reviewed by another author and both authors reviewed the full text of all eligible studies reporting the prevalence of HS and its risk factors. Data elements sought from each included study were protocol-specified including steatosis prevalence, HCV infection steatosis prevalence comparison data, study location, demographical data, positivity to hepatitis B "e" antigen (HBeAg), alcohol consumption and other risk factors for HS.

Statistical analysis

For calculations, we computed the actual number of subjects from each study and performed a pooled analysis of the data. Pooled estimation of the prevalence of HS in HBV infected patients, odd ratios (OR), standardized mean differences (SMD), and confidence limits were obtained with the random-effects model and the DerSimonian-Laird method.[14] Analysis of the heterogeneity of prevalence across studies was done with λ^2 tests. As all tests showed a great heterogeneity, random effects models were preferred regarding fixed effects models.

Statistical analysis was conducted with the STATA software (Stata Corp., College Station, TX, USA), version 10. Significance was established for $P < 0.05$.

Results

A total of 21 studies were selected,[15–35] of which four were excluded. The reasons for exclusion were data on DNA negative hepatitis B surface antigen (HBsAg) positive patients in one study,[32] data in a pediatric population[33] and statistical analyses in different subsets of patients, namely with HS greater than 30%[34] and with non-alcoholic steatohepatitis features,[35] in the other studies. The 17 studies comprised 4100 HBV infected patients. In eight of these studies,[15–18,21,23,28,30] data regarding HCV infected patients was presented separately, with a total of 945 patients. Three studies had a retrospective recruitment,[20,22,24] two had a mixed retrospective and prospective recruitment[23,28] and the remaining were prospective. Their main characteristics are summarized in Tables 1 and 2.

Inclusion criteria were similar in all studies, which enrolled patients who were HBsAg positive for at least 6 months, with increased alanine aminotransferase (ALT) level in at least two separate determinations in the previous 2 months and liver biopsy

Table 2 Demographic characteristics of the hepatitis B virus (HBV) infected patients

Study	HBV (*n*)	Men (%)	Age (years)	BMI (kg/m^2)	HBeAg + (%)
Lefkowitch *et al.*[15]	166	NR	NR	NR	NR
Malhotra *et al.*[16]	30	NR	NR	NR	NR
Rozario and Ramakrishna[17]	82	NR	32 ± NR	NR	82
Gordon *et al.*[18]	17	65	33 ± 13	25 ± 5	76
Altiparmak *et al.*[19]	164	69	35 ± 11	NR	NR
Thomopoulos *et al.*[20]	233	70	45 ± 16	26 ± 4	16
Papatheodoridis *et al.*[21]	174	75	NR	NR	0
Cindoruk *et al.*[22]	140	63	43 ± 11	25 ± 5	30
Tsochatzis *et al.*[23]	213	75	50 ± 14	26 ± 3	0
Peng *et al.*[24]	153	76	32 ± 10	23 ± 4	79
Shi *et al.*[25]	1915	78	31 ± 10	NR	71
Minakari *et al.*[26]	132	58	37 ± 12	NR	26
Yun *et al.*[27]	86	100	21 ± 2	23 ± NR	79
Tsochatzis *et al.*[28]	95	55	42 ± 13	26 ± 3	0
Wong *et al.*[29]	266	76	45 ± 11	24 ± 4	43
Vere *et al.*[30]	30	73	44 ± 12	NR	NR
Zheng *et al.*[31]	204	82	NR	NR	0

BMI, body mass index; HBeAg +, hepatitis B "e" antigen positive virus infected patients; NR, not reported.

performed to evaluate liver damage in anti-viral therapy candidates. All studies evaluated treatment naïve patients only, with the exception of one study that allowed previous anti-viral therapy, in 9% of the patients.[22]

Exclusion criteria were similar but not alike across studies. All of them systematically excluded other causes of liver disease except alcohol intake. In fact, alcohol intake was not an exclusion criterion in five studies.[16–18,21,23,28] The remaining excluded excessive alcohol intake, specified as higher than 20–40 g per day in man and higher than 20 g per day in women in eight studies.[20,24–27,29,31]

Other exclusion criteria were malignant disease in three studies,[21,25,29] immunosuppressive therapy or human immunodeficiency virus (HIV) infection in eight studies.[15,20,21,23,25,26,28,29] Liver biopsies with less than 10 mm length were considered as an exclusion criterion in just five studies[17,21,23,28,31] and less than 15 mm in another.[25] One study also excluded patients under oral antidiabetic drugs or insulin.[29] Decompensated liver cirrhosis was a transversal exclusion criterion.

Definitions and grading of HS were not homogeneous in all studies, although the majority[17,18,21,22,25–27,29,31] used Brunt's criteria or similar.[36] Four studies[15,19,20,23,24,28] considered any degree of steatosis, one considered at least 3% of hepatocytes affected[20] and the remaining at least 5%. Necroinflammation and fibrosis were graded or staged by METAVIR[18,19,24–27] or Ishak classifications.[37]

Steatosis prevalence

In HBV infected patients the overall prevalence of HS was 29.6%, ranging from 14% to 70%. If the five studies allowing inclusion of patients with excessive alcohol consumption[16–18,21,23,28] were not taken into consideration, the prevalence of HS would be slightly lower, 25.6%. In the eight studies[15–18,21,23,28,30] that also evaluated HCV infection, the overall prevalence of HS in HCV infected patients was 69%, ranging from 62% to 76%.

Evaluating all data together, HS was less frequent in HBV infected patients as compared to HCV, pooled OR 0.55, 95% CI [0.45–0.67], $P < 0.001$ (Fig. 1).

Shi *et al*.[25] found a significant progressive increase in HS prevalence from 2005 to 2007 (11%, 14% and 18% respectively, $P < 0.001$). However, when we compared the prevalence in the studies prior and subsequent to 2008, we found a decreased risk of HS in the most recent ones (24% *vs* 42%, OR 0.45, 95% CI [0.39–0.52], $P < 0.001$).

Regarding the grade of steatosis, the pooled analysis of 10 studies showed that the majority, 78%, had mild (less than 33% of hepatocytes), 15% moderate (33–66% of hepatocytes) and only 7% severe steatosis (more than 66% of hepatocytes).[18,20–27,29]

Demographic associations

Male gender, assessed in eight studies,[18,19,22–26,31] was associated with an increased risk for HS, pooled OR 1.74, 95% CI [1.28–2.38], $P < 0.001$, although individually half of the studies failed to demonstrate that association[18,22,24,31] (Table 3).

Age presented a variable association with HS among the eight studies that evaluated it[19,20,22–27,31] and the pooled data did not confirmed it as a risk factor, SMD 0.06, 95% CI [–0.17, 0.29], $P = 0.614$.

Three studies[20,24,25] evaluated the effect of moderate alcohol consumption (less than 30 g per day in men and 20 g per day in women) in the risk of HS. Although individually two studies[20,24] could not find an effect, pooled data of 2301 patients showed an increased risk, OR 1.54, 95% CI [1.10–2.15], $P = 0.011$ (Table 3). Only Tsochatzis *et al*.[23] studied the effect of greater alcohol consumption and found no association (16% *vs* 7%, $P = 0.177$).

Metabolic factors

There was a strong association between body mass index (BMI) and the prevalence of HS, in individual studies and in the pooled data, pooled SMD 2.17, 95% CI [1.23, 3.11], $P < 0.001$, in nine

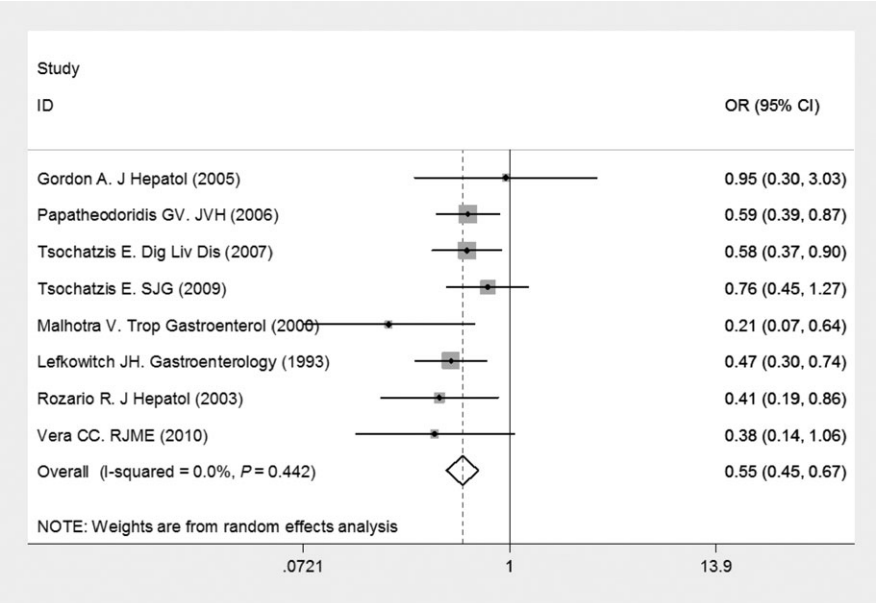

Figure 1 Meta-analysis of the prevalence of hepatic steatosis in hepatitis B virus (HBV) *versus* hepatitis C virus (HCV) infected patients.

Table 3 Factors associated with hepatic steatosis in hepatitis B virus (HBV) patients

Variable	Number of studies	Number of patients	OR or SMD, (95% CI)	*P*
Male sex	8	2938	OR 1.74 (1.18, 2.38)	< 0.001
BMI (kg/m^2)	9	3273	SMD 2.17 (1.23, 3.11)	< 0.001
Obesity	2	2181	OR 6.59 (3.51, 12.26)	< 0.001
Moderate alcohol consumption	3	2301	OR 1.54 (1.10, 2.15)	0.011
Diabetes mellitus	4	2442	OR 2.68 (1.37, 5.00)	0.004
Glycemia	6	2723	SMD 0.84 (0, 1.67)	0.049
Serum triglycerides	9	3240	SMD 1.18 (0.48, 1.89)	0.001
Serum total cholesterol	8	3087	SMD 0.88 (0.31, 1.45)	0.003
HBV viral load	7	3067	SMD –74.12 (–82.93, –65.31)	< 0.001
γ-GT	8	3087	SMD 0.64 (0, 1.22)	0.043

BMI, body mass index; γ-GT, gama glutamyl transpeptidase; OR, odds ratio; SMD, standardized mean differences.

studies[19,22–27,29,31] (Table 3). Likewise, obesity strongly associated with HS in the pooled data of two studies,[25,29] OR 6.59, 95% CI [3.51–12.257], $P = 0.003$ (Table 3).

Glycemia presented an association with HS. In fact, although four[20,25–27] of six studies[20,24–27,31] individually could not show a significant association, pooled data did so: SMD 0.84, 95% CI [0.00, 1.67], $P = 0.049$, $P = 0.197$. Homeostasis model assessment (HOMA), an indirect assessment of insulin resistance, was higher in patients with steatosis only in the study by Zheng *et al*.[31] Pooled data analysis of three studies[23,27,31] failed to demonstrate a difference: SMD 1.06, 95% CI [–0.68, 2.81], $P = 0.231$. Regarding the presence of diabetes mellitus (DM), four studies[21–23,25] analyzed a possible association with increased risk for HS and once again a strong association individually and in the pooled data was found, OR 2.62, 95% CI [1.37–4.00], $P = 0.004$ (Table 3).

Globally, in nine studies,[19,20,22–27,31] triglycerides levels were higher in patients with HS, pooled SMD 1.18, 95% CI [0.48, 1.89], $P = 0.001$ (Table 3). However, individually, four studies[20,23,24,27] failed to find that difference. Total cholesterol showed a similar difference, being the pooled data of eight studies:[19,20,22,23,25–27,31] SMD 0.88, 95% CI [0.31, 1.45], $P = 0.003$, $P = 0.014$ (Table 3). Individually, two studies failed to reach statistical significance.[20,23]

HBV factors associations

Regarding HBV infection, pooled data did not corroborate a positive association with possible risk factors for HS. In fact, two studies[24,29] evaluated the influence of genotype B or C on the risk of HS and found no association: pooled data: OR 0.96, 95% CI [0.58–1.59], $P = 0.876$ and OR 1.13, 95% CI [0.70–1.84], $P = 0.617$, respectively. Also, regarding HBeAg *status*, eight studies[19,20,22,24–27,29] showed no association, either individually or as pooled data: OR 0.89, 95% CI [0.73–1.79], $P = 0.227$.

Although individually, studies showed different associations between viral load and steatosis, four presented a significant nega-

tive association[19,24,25,31] and one a positive association,[29] pooled data of seven studies[19,20,24–26,29,31] found a strong negative effect of viral load on HS-pooled SMD −74.12, 95% CI [−82.93, −65.31], $P < 0.001$ (Table 3).

Biochemical abnormalities

Five[20,23,24,26,27] out of nine studies[19,20,22–27] did not find different levels of ALT regarding the presence of HS, two studies found lower levels[19,25] and two studies[22,31] found higher levels in patients with HS. That association was also not demonstrated in the pooled data: SMD −0.37, 95% CI [−0.99, 0.24], $P = 0.236$.

The same studies also evaluated aspartate aminotransferase (AST) levels, with similar findings: pooled SMD −0.35, 95% CI [−0.88, 0.18], $P = 0.199$.

Regarding γ-glutamyltranspeptidase (GGT), once again, only three[22,26,31] out of six studies[19,20,22,23,25–27,31] showed a positive association with HS. However, pooled data analysis showed a weak association: SMD 0.62, 95% CI [0.02, 1.22], $P = 0.043$ (Table 3).

Of the seven studies[19,22–24,26,27,31] that evaluated alkaline phosphatase (ALP), only one[31] showed an association with HS and pooled data was not significant: SMD 0.74, 95% CI [−0.21, 1.69], $P = 0.125$.

Finally, bilirubin was evaluated in two studies[20,25] with conflicting results. Pooled data showed no association with HS: SMD 0.16, 95% CI [−0.52, 0.84], $P = 0.652$.

Histological correlations

A possible correlation between HS and severe necroinflammatory activity was assessed in six studies,[19,20,24–26,29,31] most of them finding no relation and only two[25,31] suggesting a negative association. A meta-analysis of those six studies failed to confirm that association: pooled OR 0.69, 95% CI [0.35–1.39], $P = 0.305$. The grade of inflammation using Knodell classification, did not differ according to the presence of HS, in a meta-analysis of two studies[22,23] or in the individual studies: pooled SMD 9.04, 95% CI [−0.29, 0.37], $P = 0.823$.

Also, fibrosis was not predicted by HS, either considering meta-analyses of fibrosis higher than 3 – pooled OR 0.63, 95% CI [0.21–1.85], $P = 0.401$[19,20,23,24,31] or higher than 2 – pooled OR 0.46, 95% CI [0.18–1.19], $P = 0.111$,[19,25,27,31] according to the METAVIR classification. Finally, fibrosis staging was not different in patients with or without HS, in a meta-analysis of five studies,[19,22,23,26,31] pooled SMD 0.22, 95% CI [−0.84, 0.41], $P = 0.495$, although, individually, studies were not concordant.

Discussion

Hepatic steatosis prevalence in HBV-infected patients showed great discrepancy among studies, ranging from 14% to 70%. Differences in the populations evaluated, such as ethnic background, may partially explain that finding. In fact, several studies came from Asia, others from Europe, Middle East and one from USA. In addition, although inclusion criteria were very similar among studies, exclusion criteria were slightly different, such as the amount of alcohol intake allowed. Accordingly, the prevalence of HS was higher in the studies that allowed excessive alcohol consumption: OR 3.77, 95% CI [3.15–4.51]. It was not possible to analyze separately the patients without significant alcohol consumption; however, the prevalence of hepatic steatosis in the studies that excluded patients who drank was 25.6%, which seems to be a more accurate prevalence of nonalcoholic steatohepatitis, in this population. Finally, HS was assessed by liver biopsy, which is known to be associated with sampling errors[38] due to the fact that fat deposition is not homogenous throughout the liver. Another potential bias is the fact that only six[17,21,23,25,28,31] studies predefined liver specimens' length. Furthermore, HS definition was not transversal among studies, with five studies[15,19,20,23,24,28] considering less than the classically accepted cut-off for steatosis of at least 5% of hepatocytes affected.[39] However, patients not fulfilling those criteria are certainly a small minority.

Overall, HS occurred in almost one third of the HBV-infected patients, which is not so different from that estimated in the general population[40] in Western countries. However, since in this meta-analysis, there is a high representation of Asian countries, with two thirds of the patients included, which are allegedly low risk populations for HS,[41] the worldwide risk for HS in HBV infected patients may be underestimated. Compared to HCV, HBV infected patients have an almost twofold lower risk of HS (OR 0.55). Additionally, the prevalence of HS on HBV infection does not seem to be increasing. On the contrary, studies subsequent to 2008 had a more than twofold decrease in the prevalence of HS when compared to previous studies (OR 0.45).

Predictably, in HBV infected patients male gender was a strong risk factor for HS (OR 1.74), which mimics the general population.[42] However, unexpectedly, age had no influence. That can only be explained by the consistent age homogeneity with low range intervals among studies, with most of the patients being in the late thirties.

Alcohol consumption seems to have a pathological role, since even mild consumption was associated with an increased risk of HS (OR 1.54). Higher consumption was assessed in only one study not powered for a definitive conclusion.

Metabolic factors were indeed the most important associations to HS. Obesity and DM conferred a more than 6-fold and a 2.5-fold increased risk of HS, respectively. Furthermore, increased BMI, dyslipidemia, hypertriglyceridemia and hypercholesterolemia showed a clear positive association with the presence of HS. Once again, these data resemble the risk factors in the general population, in which metabolic factors are so important that nonalcoholic fatty liver disease has been considered as a consequence of the metabolic syndrome.[43]

The type of HBV infection, regarding either genotype or HBeAg *status*, did not seem to have any influence on hepatocyte fat accumulation. On the other hand, strongly expressive results showed a negative association with viral load. That noteworthy evidence raises the question whether HS enhances viral clearance thus associating with lower viral loads, as proposed elsewhere,[6] or whether the virus has itself anti-steatogenic effects that supersede the already described steatogenic effects of HBx.[9]

In the present study, liver biochemistry, with the exception of GGT, was not influenced by the presence of HS, which is in agreement with our findings of a lack of association between the presence of HS and the severity of either necroinflammation or fibrosis. This is in contradiction to what happens in hepatitis C, and the reasons for this apparent paradox are not clear. We may speculate that in HCV, it is the virus that is steatogenic and

common mechanisms simultaneously inducing necroinflammation and steatosis may be present,[44] opposite to HBV where the presence of steatosis seems to depend mostly on the host factors. Furthermore, it is also possible that liver injury induced by the virus itself overcomes the potential deleterious effects of fat accumulation. Interestingly, in HBsAg positive patients, with non-detectable viral load, hepatic steatosis is the main cause of elevated aminotransferases.[32]

In conclusion, HS occurs in almost one third of HBV infected patients, being twice less frequent than in HCV. In HBV infected patients, HS relates mainly with metabolic factors, namely obesity, DM, dyslipidemia and probably alcohol consumption. HS does not seem to play a role in liver disease severity. Moreover, a strong negative association with HBV viral load suggests an effect of HBV in preventing ectopic fat accumulation in the liver.

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