Thyroid dysfunction is associated with the loss of hepatitis B surface antigen in patients with chronic hepatitis B undergoing treatment with α-interferon

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Abstract

Objective: To investigate the influence of thyroid dysfunction on the antiviral efficacy of α-interferon in adult patients with chronic hepatitis B (CHB).

Methods: We performed a retrospective study of 342 patients with CHB who underwent interferon treatment for >12 weeks. Patients with thyroid dysfunction before or during treatment were defined as the thyroid dysfunction group (n = 141) and those with normal thyroid function were defined as the normal thyroid function group (n = 201). The prevalences of hepatitis B virus (HBV) DNA undetectability, low hepatitis B surface antigen (HBsAg) titre (<25 IU/mL), HBsAg loss, and hepatitis B envelope antigen loss were compared.

Results: During interferon treatment, 69 of 270 (25.6%) participants with normal thyroid function at baseline developed thyroid dysfunction, whereas 11 of 72 (15.3%) with thyroid dysfunction at baseline regained normal thyroid function. The thyroid dysfunction group had significantly higher prevalences of low HBsAg titre (29.8% *vs.* 18.9%) and HBV DNA undetectability (66.0% *vs.* 40.3%). Multivariate logistic regression analysis showed that thyroid dysfunction was associated with HBsAg loss (odds ratio 4.945, 95% confidence interval 1.325–18.462).

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Conclusions: These results suggest that thyroid dysfunction is not an absolute contraindication, but is associated with HBsAg loss, in patients with CHB undergoing α-interferon treatment.

Introduction

Chronic hepatitis B (CHB) is caused by persistent infection with hepatitis B virus (HBV)[1] and is a leading cause of death worldwide.[2] According to the World Health Organisation Global Hepatitis Report, an estimated 257 million people, or 3.5% of the global population, were chronically infected with HBV in 2015,[3] resulting in 887,000 deaths.[4] In China, nearly 90 million people were chronically infected with HBV, accounting for one-third of the global cases.[5] CHB resulted in prevalences of cirrhosis and hepatocellular carcinoma (HCC) in Chinese patients of 60% and 80%, respectively.[6]

The purpose of antiviral therapy is to delay or ameliorate HBV-related hepatic inflammatory necrosis, liver fibrosis, liver failure, cirrhosis decompensation, HCC and other complications, thereby improving quality of life and prolonging survival.[7] At present, the major clinical guidelines recommend the use of a nucleoside/nucleotide analogue (NA, such as entecavir and tenofovir) and interferon (IFN) as the first-line therapy for CHB.[8–10] IFNs are a family of multifunctional cytokines with antiviral, antiproliferative and immunomodulatory effects[11] and have been demonstrated to reduce the levels of HBV DNA, hepatitis B surface antigen (HBsAg) and HBV covalently closed circular DNA.[11] In addition, it has been shown that IFN is superior to NAs for CHB treatment in terms of HBsAg loss and hepatitis B envelope antigen (HBeAg) seroconversion.[12] However, the current IFN therapy for patients with CHB has variable degrees of adverse effects, including flu-like, dermatologic, hematologic, gastrointestinal, and ophthalmologic symptoms; thyroid dysfunction; and depression.[13]

A phase III clinical trial of α-IFN therapy for CHB showed that the prevalence of thyroid dysfunction during therapy is approximately 4.9%, and this can be either hyperthyroidism or hypothyroidism.[14] The Chinese Expert Consensus on the Management of Adverse Events during IFN Therapy for CHB suggests that patients who have thyroid dysfunction prior to antiviral treatment should have their thyroid dysfunction treated first, and IFN therapy should not be administered until the thyroid dysfunction is controlled.[15] Nevertheless, there is insufficient evidence to suggest that thyroid dysfunction should be an absolute contraindication for IFN therapy. For patients who have normal baseline thyroid function but develop thyroid dysfunction during IFN treatment, the Chinese Expert Consensus recommends that mild side-effects, such as subclinical hypothyroidism or hyperthyroidism, do not need to be treated, but that patients with hypothyroidism or mild Graves' disease can continue IFN therapy alongside thyroxine or anti-thyroid hormone therapy, respectively.[15,16] However, there is no strong evidence to support this

notion. Moreover, with respect to the adverse event of IFN-induced thyroid dysfunction, the impact of thyroid dysfunction on the efficacy of IFN treatment and the final outcome of the thyroid dysfunction are largely unknown. Therefore, to determine the relationship between IFN treatment and thyroid dysfunction, we aimed to investigate the influence of thyroid dysfunction on the therapeutic effect of IFN treatment in adult patients with CHB.

Methods

Patients

We performed a retrospective study of patients with CHB who were treated using IFN at Nanfang Hospital, Southern Medical University, between December 2010 and December 2017. The inclusion criteria were: 1) anti-viral treatment indicated for CHB; 2) age >18 years and 3) IFN treatment for >12 weeks. The exclusion criteria were: 1) co-infection with hepatitis A virus, hepatitis C virus, hepatitis D virus or hepatitis E virus and 2) decompensated cirrhosis, metabolic liver disease or autoimmune hepatitis.

The study was registered with the Chinese Clinical Trial Registry (www.chictr.org.cn; identifier: ChiCTR18000 20428). Ethics approval was given by the Chinese Ethics Committee for the Registration of Clinical Trials (reference number ChiECRCT-20180219) and the requirement for written informed consent was waived by the ChiECRCT due to the retrospective nature of the study.

Data collection

The participants' medical records were retrospectively reviewed to collect baseline demographic (age, sex) and clinical (type of IFN therapy, duration of treatment and laboratory test) data. The laboratory data collected included indices of thyroid function, biochemical parameters, and markers of HBV infection and viral load at various time points before and during treatment (12, 24, 36 and 48 weeks after starting treatment). The thyroid function data collected were thyroid stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4), triiodothyronine (T3), thyroxine (T4), thyroid-stimulating receptor autoantibody (TRAb), anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin antibody (anti-TG). These concentrations were determined using the ADVIA Centaur CP Immunoassay System (Siemens, Erlangen, Germany). Hepatitis B virus marker (HBsAg (lower limit of detection [LLOD] 0.05 IU/mL), HBeAg, and HBeAb) concentrations were determined using chemiluminescent microparticle immunoassays on a Roche Cobas E601 Immunology analyser (Roche, Basel, Switzerland). HBV DNA was determined using a Cobas Taqman 480 analyser (Roche), with a LLOD of 1000 copies/mL.

Thyroid function and participant grouping

Thyroid function was analysed at baseline and during IFN treatment. The types of thyroid dysfunction identified were hyperthyroidism, subclinical hyperthyroidism, hypothyroidism, subclinical hypothyroidism and single indicator abnormality. Hyperthyroidism was defined as a subnormal TSH concentration and high serum concentration of T3, FT3, T4 and/or FT4. Subclinical hyperthyroidism was defined as a low or undetectable serum TSH concentration, with values of T3, FT3, T4 and FT4 within the normal reference ranges. Hypothyroidism was defined as a high TSH concentration and subnormal T3 and FT3 and/or T4 and FT4 concentrations. Subclinical hypothyroidism was defined as a high TSH concentration, with the concentrations of T3, FT3, T4 and FT4 within the

normal reference ranges. Single indicator abnormality was defined as an abnormality in one of the following thyroid function indicators: FT3, FT4, T3, T4, TRAb, anti-TPO and anti-TG.

The participants were placed into groups according to their thyroid function. Participants with normal thyroid function before and during the whole period of IFN treatment were placed into a normal thyroid function group, and those with thyroid dysfunction at baseline and/or during IFN treatment were placed into a thyroid dysfunction group.

IFN treatment and antiviral efficacy

Patients were administered PegIFNα-2a 180 μg once weekly, PegIFNα-2b 80 μg once weekly, IFNα-1b 30 μg every 2 days or IFNα-2b 3,000,000 IU every 2 days. HBV DNA undetectability was defined as HBV DNA <1000 copies/mL and a low concentration of HBsAg was defined as HBsAg <250 IU/mL at the end of the IFN treatment. The cut-off value used to define HBsAg loss was 0.05 IU/mL and that for HBeAg loss was 1.00 signal-to-cut-off (s/co).

Statistical analysis

Categorical data are expressed as counts and percentages and continuous data as mean (standard deviation [SD]) or median (range). Categorical data were analysed using the chi-square test or Fisher's exact test and continuous data were analysed using Student's t-test or the Mann–Whitney U-test. Multivariate logistic regression analysis was used to identify factors that were independently associated with antiviral efficacy. Analyses were performed using SPSS (IBM, Inc., Armonk, NY, USA) and statistical significance was accepted at $p < 0.05$.

Results

Demographic and clinical characteristics of the participants

A total of 342 participants with CHB (94 women and 248 men; mean age 28.32 ± 6.25 years) who underwent IFN treatment between December 2010 and December 2017 were included. Before IFN treatment, 270 (78.9%) of the participants had normal thyroid function and 72 (21.1%) had thyroid dysfunction. Thyroid dysfunction at baseline comprised hyperthyroidism (n = 2, 2.78%), subclinical hyperthyroidism (n = 23, 31.94%), hypothyroidism (n = 1, 1.39%), subclinical hypothyroidism (n = 1, 1.39%) and single thyroid indicator abnormality (n = 45, 62.50%).

Development of thyroid dysfunction during IFN treatment

Of the 270 participants with normal thyroid function at baseline, 69 (25.6%) developed thyroid dysfunction during the IFN treatment. Sixteen participants developed hyperthyroidism (5.9%) and five of these discontinued IFN treatment (duration of IFN treatment <48 weeks). Three participants were treated with antithyroid drugs and their thyroid function returned to normal; the other 13 participants were not treated in this way, but their thyroid function returned to normal after stopping the IFN treatment.

Four participants had hypothyroidism (4/270, 1.5%) during IFN treatment, and although none of these were administered anti-hypothyroidism medication, their thyroid function returned to normal after stopping the IFN treatment.

After 12 weeks of IFN treatment, one participant developed Hashimoto's thyroiditis but was not administered drug treatment for hyperthyroidism. However, after 24 weeks, the IFN was discontinued and propylthiouracil was administered for 3 months, until the thyroid function returned

to normal. The thyroid function then remained normal during the follow-up period and the participant showed a good virological response and HBsAg loss.

There were 17 participants with subclinical hyperthyroidism (17/270, 6.3%), six with subclinical hypothyroidism (6/270, 2.2%), and 25 (25/270, 9.3%) with single indicator abnormality. None of these were administered drug treatment for thyroid dysfunction.

Outcomes of baseline thyroid dysfunction after IFN treatment

None of the 72 participants with thyroid dysfunction at baseline experienced serious adverse events during IFN therapy. Thyroid function unexpectedly returned to normal in 11 participants (11/72, 15.3%), but the thyroid dysfunction persisted in the other 61 (61/72, 84.7%). The changes in thyroid function during IFN treatment in the 72 participants who had thyroid dysfunction at baseline are summarized in Figure 1.

In one participant with baseline hypothyroidism, the thyroid function returned to normal during the treatment. The one participant with baseline subclinical hypothyroidism remained subclinically hypothyroid.

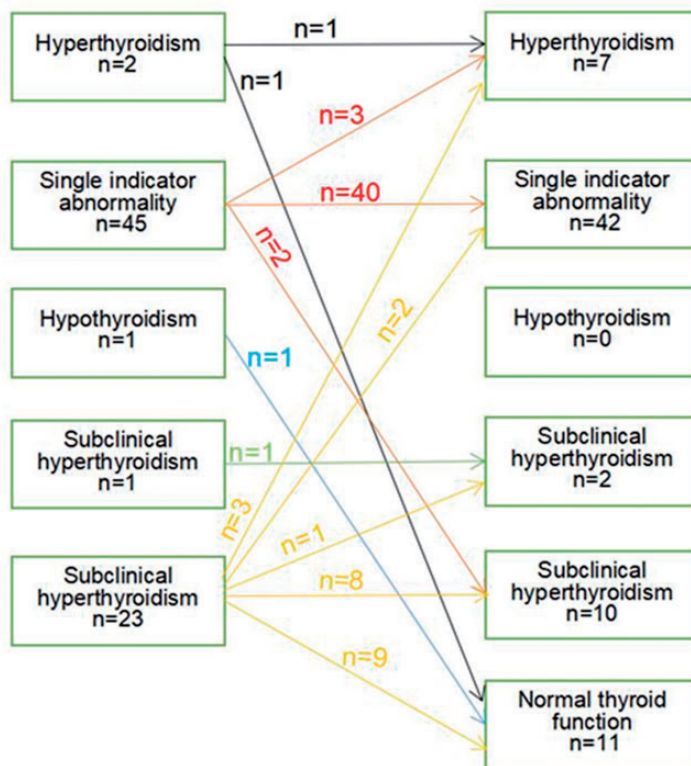Of the two participants with baseline hyperthyroidism, one remained

Figure 1. Changes in thyroid function during interferon treatment in the 72 participants with thyroid dysfunction at baseline.

hyperthyroid, but had no obvious symptoms. IFN therapy was discontinued in this participant after 24 weeks because of a poor virological response. The other participants with baseline hyperthyroidism continued the IFN treatment for 48 weeks and were not administered anti-hyperthyroid drug therapy, but their thyroid function had returned to normal by the 36-week time point.

Of the 45 participants with single indicator abnormality, three had become hyperthyroid by 36 or 48 weeks, two became subclinically hyperthyroid, and the other 40 maintained a single indicator abnormality. Of the participants with a single indicator abnormality at baseline (n = 45) or during IFN treatment (n = 25), 47 of 70 (67.1%) achieved HBV DNA undetectability during IFN treatment. In addition, all participants with TRAb abnormality achieved HBV DNA undetectability (n = 6, 100%) and half achieved HBsAg loss (n = 3, 50%). All of the participants with anti-TPO antibodies achieved HBV DNA undetectability (n = 4).

Of the 23 participants with subclinical hyperthyroidism at baseline, eight remained subclinically hyperthyroid, one became subclinically hypothyroid, and two switched to having a single indicator abnormality. In addition, three participants became hyperthyroid, one of whom discontinued their IFN treatment. The thyroid function returned to normal in nine of these participants.

Comparison of the baseline characteristics of the normal thyroid and thyroid dysfunction groups

The 72 participants with thyroid dysfunction at baseline and the 69 with thyroid dysfunction during treatment were placed in the thyroid dysfunction group (n = 141), and the 201 participants with normal thyroid function before and during the entire IFN treatment period were placed in the normal thyroid group (n = 201). Then, the baseline characteristics of the two groups were compared. The mean age of the thyroid dysfunction group was significantly higher than that of the normal thyroid function group (27.71 *vs.* 29.20 years, $P = 0.030$). The HBsAg concentration at the end of treatment was significantly lower in the thyroid dysfunction group than in the normal thyroid function group (2.76 *vs.* 2.43 log10 IU/mL, $P = 0.035$). There were no significant differences in sex, baseline HBsAg, the prevalence of HBeAg positivity, HBV DNA concentration, alanine aminotransferase (ALT) activity, treatment duration or the incidence of an early interruption of IFN treatment (Table 1).

Comparison of the antiviral efficacy of IFN in the two groups

The antiviral efficacy of IFN was evaluated using the prevalences of low HBsAg concentration (<250 IU/mL), HBsAg loss, HBV DNA undetectability and HBeAg loss. In HBeAg-positive participants, the thyroid dysfunction group had significantly higher prevalences of low HBsAg (34/110, 30.9% *vs.* 29/157, 18.5%, $P = 0.018$) and HBV DNA undetectability (75/110, 68.2% *vs.* 72/157, 45.9%, $P < 0.001$) than the normal thyroid function group. However, there were no significant differences in the prevalences of HBsAg loss (8/110, 7.3% *vs.* 4/157, 2.5%, $P = 0.125$) or HBeAg loss (24/110, 21.8% *vs.* 29/157, 18.5%, $P = 0.500$) between the two groups (Table 2). A comparison of the entire group of participants yielded similar results: the thyroid dysfunction group had significantly higher prevalences of low HBsAg (42/141, 29.8% *vs.* 38/201, 18.9%, $P = 0.019$) and HBV DNA undetectability (93/141, 66.0% *vs.* 81/201, 40.3%, $P < 0.001$) than the normal thyroid function group (Table 3).

Table 1. Comparison of the baseline characteristics of the normal thyroid group and the thyroid dysfunction group.

	Normal thyroid function group (n=201)	Thyroid dysfunction group (n=141)	P value
Age (years)	27.71 ± 5.98	29.20 ± 6.53	0.030
Men (n, %)	151 (75.1%)	97 (68.8%)	0.197
Baseline HBsAg (log10 IU/mL)	3.84 (3.26–4.28)	3.85 (3.41–4.28)	0.800
Baseline HBeAg-positive[†] (n, %)	157/178 (88.2%)	110/129 (85.3%)	0.451
Baseline HBV DNA (log10 copies/mL)	7.18 (6.39–7.85)	7.04 (6.11–7.67)	0.090
Baseline ALT activity (U/L)	129.50 (98.00–218.92)	148.00 (100.00–264.00)	0.684
Duration of treatment (weeks)	40.53 ± 10.98	42.00 ± 9.65	0.192
Early interruption of interferon treatment (n, %)	71 (35.3%)	47 (33.3%)	0.703
End-of-treatment HBsAg (log10 IU/mL)	2.76 ± 1.36	2.43 ± 1.49	0.035

[†]HBeAg-positivity was defined as ≥1.00 s/co. Continuous data were analysed using Student's t-test and categorical data were analysed using the chi-square test. P-values < 0.05 are shown in bold and italics.
HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B envelope antigen; HBV, hepatitis B virus; ALT, alanine aminotransferase.

Table 2. Comparison of the antiviral efficacy of interferon treatment in HBeAg-positive participants in each group.

	Normal thyroid function group (n = 157)	Thyroid dysfunction group (n = 110)	P-value
Low HBsAg concentration (<250 IU/mL)	29 (18.5%)	34 (30.9%)	0.018
HBsAg loss	4 (2.5%)	8 (7.3%)	0.125
HBV DNA undetectability	72 (45.9%)	75 (68.2%)	<0.001
HBeAg loss	29 (18.5%)	24 (21.8%)	0.500

Data are presented as n (%). The groups were compared using the χ^2 test. P-values < 0.05 are shown in bold and italics.
HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HBeAg, hepatitis B envelope antigen.

Table 3. Comparison of the antiviral efficacy of interferon in each group.

	Normal thyroid function group (n = 201)	Thyroid dysfunction group (n = 141)	P-value
Low HBsAg concentration (<250 IU/mL)	38 (18.9%)	42 (29.8%)	0.019
HBsAg loss	7 (3.5%)	8 (5.7%)	0.33
HBV DNA undetectability	81 (40.3%)	93 (66.0%)	<0.001

Data are presented as n (%). The groups were compared using the χ^2 test. P-values < 0.05 are shown in bold and italics.
HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

Factors independently associated with antiviral efficacy

To identify factors that were independently associated with the antiviral efficacy of IFN, univariate and multivariate logistic regression analyses were performed. The univariate regression analysis showed that high baseline ALT activity was associated with HBV DNA undetectability (odds ratio

[OR]=1.004, 95% confidence interval [CI]=.002 to 1.007, $P < 0.001$). Thyroid dysfunction was associated with HBsAg loss (OR=5.407, 95% CI=1.354 to 21.596, $P = 0.017$). In addition, female sex (OR=2.411, 95% CI=1.083 to 5.365, $P = 0.031$) and younger age (OR=0.944, 95% CI=0.895 to 0.995, $P = 0.032$) were significantly associated with HBeAg loss in HBeAg-positive participants (Table 4).

In the multivariate analysis, among the HBeAg-positive participants, female sex was found to be independently associated with HBeAg loss (OR=2.389, 95% CI=1.062 to 5.372, $P = 0.035$). In the entire sample, ALT activity was associated with HBV DNA undetectability (OR=1.003, 95% CI=1.001 to 1.006, $P = 0.005$). In addition, thyroid dysfunction was independently associated with HBsAg loss (OR=4.945, 95% CI=1.325 to 18.462, $P = 0.017$). However, the differences between the groups with respect to HBV DNA undetectability, low HBsAg, and HBeAg loss were not significantly different (Table 5).

Discussion

In the present study, we investigated the relationship between thyroid dysfunction and the therapeutic efficacy of IFN treatment in adult patients with CHB. During the IFN treatment, 69 out of 270 (25.6%) participants with normal thyroid function at baseline developed thyroid dysfunction, whereas the thyroid function returned to normal in 11 of 72 participants (15.3%) who had thyroid dysfunction at baseline. The thyroid dysfunction group had significantly higher prevalences of low HBsAg concentration and HBV DNA undetectability than the normal thyroid function group. Furthermore, multivariate logistic regression analysis demonstrated that thyroid dysfunction was associated with HBsAg loss. Taken together, these results suggest

that thyroid dysfunction is not an absolute contraindication for IFN therapy, and may in fact improve the therapeutic efficacy of IFN for CHB. To the best of our knowledge, this is the first study to report an association between thyroid dysfunction and the treatment of CHB with IFN.

IFN therapy may induce thyroid dysfunction. In the present study, 69 patients with normal thyroid function developed thyroid dysfunction during treatment. However, in most of these patients, thyroid function returned to normal after discontinuation of the IFN therapy. If thyroid dysfunction occurs during IFN therapy, drug treatment may be considered, and the determination of whether to continue IFN therapy should be based on the response to treatment. In the present study, only three participants with hyperthyroidism and one with Hashimoto's thyroiditis were administered drug treatment for thyroid dysfunction. The mechanism underlying IFN-induced thyroid dysfunction is still not fully understood. The results of some studies have suggested that IFN may induce thyroid dysfunction *via* its immuno-modulatory effects[17,18] or through direct toxic effects on the thyroid.[19,20] IFN has diverse effects on the immune response and may induce thyroid autoimmunity, which leads to thyroid dysfunction.[17] In the present study, participants with an abnormality in a single indicator were placed in the thyroid dysfunction group. However, in clinical practice, a single abnormality may not be of clinical significance or require medication, but rather just regular follow up to monitor thyroid function. Nevertheless, a single abnormality in patients with CHB who are undergoing IFN therapy, and particularly in those with abnormal TRAb or anti-TPO concentrations, might be associated with a better outcome of IFN treatment.

In the present study, of the 72 participants with thyroid dysfunction at baseline,

Table 4. Results of univariate logistic regression analysis to identify factors that are independently associated with antiviral efficacy.

Parameter	HBV DNA undetectability			Low HBsAg concentration			HBsAg loss			HBeAg loss		
	Odds ratio	95% CI	P-value	Odds ratio	95% CI	P-value	Odds ratio	95% CI	P-value	Odds ratio	95% CI	P-value
Age	0.965	0.923–1.008	0.112	0.980	0.933–1.028	0.406	0.983	0.900–1.075	0.712	0.944	0.895–0.995	**0.032**
Sex (Female)	0.577	0.281–1.103	0.093	0.872	0.453–1.680	0.683	0.777	0.209–2.886	0.706	2.411	1.083–5.365	**0.031**
Baseline HBsAg concentration (log10IU/mL)	0.467	0.193–1.126	0.090	1.000	1.000–1.000	0.861	1.000	1.000–1.000	0.156	1.000	1.000–1.000	0.470
Baseline HBeAg (positive vs. negative)	0.932	0.409–2.123	0.866	0.757	0.322–1.783	0.525	0.954	0.210–4.331	0.951			
Baseline HBV DNA concentration (log10 copies/mL)	1.000	0.998–1.001	0.644	1.000	1.000–1.000	0.385	1.000	1.000–1.000	0.837	1.000	1.000–1.000	0.899
IFN regimen (short-acting vs. long-acting)	1.384	0.737–2.597	0.312	0.964	0.496–1.874	0.914	0.809	0.214–3.053	0.754	1.205	0.596–2.435	0.604
Thyroid function (abnormal)	0.781–2.618	0.860–3.936	0.247	1.124	0.608–2.077	0.709	5.407	1.354–21.596	**0.017**	1.075	0.550–2.102	0.832
Duration of treatment (weeks)	1.022	0.952–1.097	0.543	1.055	0.979–1.136	0.160	1.156	0.955–1.399	0.138	0.997	0.922–1.077	0.932
Patients with an early interruption of IFN treatment (n, %)	1.059	0.245–4.577	0.939	2.222	0.499–9.908	0.295	9.365	0.371–236.295	0.174	0.621	0.121–3.176	0.567
End-of-treatment HBsAg (log10IU/mL)	1.291	0.860–1.938	0.218	1.508	0.971–2.341	0.067	1.190	0.465–3.050	0.717	1.204	0.776–1.868	0.408
Baseline ALT activity (U/L)	1.004	1.002–1.007	**<0.001**	1.001	0.999–1.003	0.426	1.000	0.997–1.004	0.785	1.001	0.999–1.003	0.556

P-values < 0.05 are shown in bold and italics.

HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B envelope antigen; HBV, hepatitis B virus; IFN, interferon; ALT, alanine aminotransferase; CI, confidence interval.

Table 5. Results of multivariate logistic regression analysis to identify factors independently associated with antiviral efficacy.

Parameter	HBV DNA undetectability			Low HBsAg concentration			HBsAg loss			HBeAg loss		
	Odds ratio	95% CI	P-value	Odds ratio	95% CI	P-value	Odds ratio	95% CI	P-value	Odds ratio	95% CI	P-value
Age	0.969	0.927–1.012	0.196							0.954	0.907–1.004	0.069
Sex (Female)	1.802	0.979–3.319	0.089							2.389	1.062–5.372	*0.035*
Baseline HBsAg concentration (log10 IU/mL)	1.000	1.000–1.000	0.203									
Thyroid function (abnormal)							4.945	1.325–18.462	*0.017*			
End-of-treatment HBsAg (log10 IU/mL)				1.175	0.954–1.446	0.130						
Baseline ALT activity (U/L))	1.003	1.001–1.006	*0.005*									

P-values <0.05 are shown in bold and italics.

HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B envelope antigen; HBV, hepatitis B virus; IFN, interferon; ALT, alanine aminotransferase; CI, confidence interval.

thyroid function returned to normal in 11 during IFN therapy. Only one participant with hyperthyroidism showed persistent hyperthyroidism during IFN treatment and had to discontinue IFN and undergo treatment with propylthiouracil. During the follow-up period, this participant's thyroid function returned to normal. None of the other participants had severe thyroid dysfunction or related clinical symptoms. This suggests that thyroid dysfunction is not an absolute contraindication for IFN therapy. Conversely, thyroid function may return to normal in some patients during IFN therapy. In future studies, it would be worth investigating whether antiviral treatment ameliorates the harmful effects of HBV on the thyroid gland, thereby improving thyroid function.

For some participants in the present study, the HBsAg concentration was determined using an HBsAg detection kit that had an upper detection limit of 250 IU/mL. In addition, it has been shown that among patients with HBV DNA <2,000 IU/mL, the incidence of liver cancer is lower in those with HBsAg <1000 IU/mL than in those with HBsAg >1000 IU/mL,[21] which suggests that patients with CHB who have a low HBsAg concentration have a better prognosis. Therefore, the cut-off for HBsAg was set at 250 IU/mL for the evaluation of efficacy. In univariate analysis, we found that the prevalences of participants with low HBsAg (<250 IU/mL) and HBV DNA undetectability were significantly higher in the thyroid dysfunction group than in the normal thyroid function group. In addition, the multivariate logistic regression analysis demonstrated that participants with thyroid dysfunction, either at baseline or during IFN therapy, had a 4.945-times higher prevalence of HBsAg loss than those with normal thyroid function. These results suggest that patients with CHB and thyroid dysfunction may respond better to IFN

treatment than those with normal thyroid function. One possible explanation for this is that some patients with thyroid dysfunction may have more active autoimmunity, which may contribute to better antiviral efficacy of IFN. However, further studies are needed to investigate the underlying mechanism. Univariate analysis showed that HBV DNA undetectability in the thyroid dysfunction group was achieved more often than in the normal thyroid function group. However, multivariate logistic regression analysis did not identify thyroid dysfunction as an independent predictor of HBV DNA undetectability. One possible explanation for this is that a high ALT activity or other factors mask the effect of thyroid dysfunction on HBV DNA undetectability. In addition, multivariate logistic regression analysis reduces the impact of confounding factors, such as baseline HBsAg concentration and age, and demonstrated that thyroid dysfunction is associated with HBsAg loss. The multivariate logistic regression analysis also demonstrated that female sex is an independent predictor of HBeAg loss and high ALT activity is an independent predictor of HBV DNA undetectability, which are consistent with the results of previous studies.[22–25]

There were some limitations to the present study. First, it was a single-centre retrospective study. In addition, the HBsAg concentration of some of the participants was determined using an HBsAg detection kit that had an upper detection limit of 250 IU/mL, which may have affected the findings. However, this study provides real-world evidence and was relatively large. In the future, prospective clinical trials or multi-centre studies should be conducted to validate the findings of the present study. Moreover, the mechanism underlying the beneficial effect of thyroid dysfunction on the efficacy of IFN treatment should be elucidated.

In conclusion, we have shown that thyroid dysfunction before and/or during α-IFN administration improves its efficacy for the treatment of CHB. Furthermore, thyroid dysfunction is associated with HBsAg loss. The results imply that thyroid dysfunction is not an absolute contraindication for IFN therapy.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Author contributions

WL, SW, HC, YW and JP conceived, designed and wrote the manuscript. WL and SW conducted the data collection and analysis and edited the manuscript. JP reviewed and gave final approval to the manuscript. All the authors read and approved the final version of the manuscript.

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