Thyroid Disturbance in Patients with Chronic Hepatitis C Infection: A Systematic Review and Meta-analysis

Yi Shen1*, Xu-Lin Wang1*, Jin-Ping Xie1, Jian-Guo Shao2, Yi-Hua Lu1, Sheng Zhang1, Gang Qin2

INTRODUCTION

Infection with hepatitis C virus (HCV) may affect not only the liver but also various non-hepatic tissues and organs and may combine with many etiologically unrelated diseases. Therefore, the concept of systemic HCV infection has emerged [1]. Extrahepatic manifestations may result from immunological mechanisms as well as virus invasion and replication in the affected extrahepatic tissues and organs. Meanwhile, treatment with interferon-alpha (IFN-α), a powerful inducer of autoimmunity, may be an additional risk factor for the development of the autoimmune diseases.

In the course of HCV infection, both hypothyroidism and hyperthyroidism may occur. Hashimoto's thyroiditis (HT) is the most common thyroid disorder observed in patients with HCV infection. IFN-α therapy is associated with development of thyroid dysfunction in chronic hepatitis C (CHC) patients, usually exposing preexisting subclinical thyroid abnormalities [2]. The prevalence of anti-thyroid antibodies (anti-thyroid peroxidase antibody, TPOAb; anti-thyroglobulin antibody, TGAb; anti-thyroid microsomal antibody, ATMA) varied markedly, from 2% to 48% in IFN-α treated CHC patients [3-5]. However, some studies suggested that the prevalence of thyroid disease was also increased in CHC patients after exclusion of...
those being treated with IFN-α compared with normal subjects [6, 7]. Besides, anti-thyroid antibodies had been found in sera of HCV infected subjects before IFN-α therapy [8, 9].

The association between HCV infection and autoimmune thyroid diseases remains controversial. The aim of our study was to assess the prevalence of anti-thyroid antibodies and thyroid dysfunction in IFN-α naïve HCV-infected subjects compared with non-HCV infected controls through a meta-analysis.

METHODS

This systematic review and meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [10].

Data sources

We searched MEDLINE, EMBASE, OVID, and Cochrane Library Database (from January 1990 to August 2015) using the following terms: (“autoimmune thyroid disease” or “thyroid autoimmunity” or “thyroid disorders” or “AITDs” or “hypothyroidism” or “hyperthyroidism” or “Graves’ disease” or “Hashimoto thyroiditis”) and (“chronic hepatitis C” or “hepatitis C virus” or “hepatitis type C” or “HCV”). We also hand-searched the reference lists in the relevant articles to find out more articles of interest.

Study selection

Full texts of those citations were assessed according to the following inclusion criteria: (i) HCV-infected subjects naïve for IFN-α treatment (HCV group) and non-HCV controls (non-HCV group) were compared; (ii) the subjects were aged 18 years or older; (iii) data was available for thyroid disturbance, i.e. thyroid dysfunctions (hyperthyroidism or hypothyroidism), or thyroid antibodies (TPOAb, TGAb, or ATMA); (iv) published in English.

Study eligibility was assessed by two authors (X.L.W. or J.P.X.) independently. Discrepancy was resolved by discussion and consultation with a third author (Y.S. or G.Q.).

Data extraction

The following characteristics were collected in each study: (i) the first author, year of publication, country of origin; (ii) study design; (iii) demographic characteristics of study participants (total number, age, sex); (iv) definition and measurement of HCV infection, anti-thyroid antibodies and thyroid function.

An adapted Newcastle-Ottawa quality assessment scale (NOS) was used to evaluate the methodological quality of the studies according to the selection of participants, comparability of groups and exposure/outcome ascertainment [11].

The data from the included articles were extracted independently by two co-authors (X.L.W and J.G.S.). Disagreements were resolved through discussion or consultation with a third author (G.Q.).

Statistical analysis

The odds ratios (ORs) with 95% confidence intervals (95% CIs) were calculated for dichotomous outcomes [12]. Heterogeneity across studies was assessed with the Cochrane Q statistics the I² test. An I² value greater than 50% was considered substantial heterogeneity and the random-effect model was conducted; otherwise, the fixed-effect model was used [13]. Publication bias was assessed visually by funnel plots, and statistically by a rank correlation test (Begg’s test) and a regression asymmetry test (Egger’s test). Moreover, sensitivity analysis was performed using a 1-study-removed method.

In the studies which had no events in both groups, the Peto one-step OR method was applied [14]. Statistical significance level was set at P < 0.05 and 95% CI with quoted throughout.

RESULTS

Literature search

Supplementary Fig. S1 presents the flowchart of the study selection process. Briefly, we first identified 837 potentially relevant studies through online search and manual search. Then, by reviewing the titles and abstracts, we excluded 748 and 55 studies respectively. After retrieving the full-texts of the 34 remaining studies, we excluded 22 studies because of duplicate publication, data missing, non-English language, or lack of relevant subpopulations. Finally, 12 studies were included in the present meta-analysis.

Characteristics of the included studies

Among the 12 studies, hypothyroidism was reported in 11 [7, 15-24], while hyperthyroidism in 5 studies [16, 20, 21, 23, 24]. TGAb was covered in 8 studies [7, 15, 17, 18, 20-23], TPOAb in 6 studies [16, 17, 20-23] and ATMA in 5 studies [6, 7, 15, 19, 22].

Countries of origin of these studies were France, Spain, Italy, China, Japan, and Brazil. Study characteristics are shown in Table I. The design of these studies was cross-sectional [17, 22], case-control [7, 16, 19-21, 23] or cohort (prospective control) [6, 18, 24, 25]. A total of 1,735 HCV-infected and 1,868 non-HCV infected subjects were involved. Except for one study [17], the overall percentage of females was comparable in the two groups (59.4% vs. 57.5% in HCV and non-HCV group, respectively).

The detection methods and normal reference value of anti-thyroid antibodies and thyroid hormones are shown in Table II.

Association of HCV infection with the prevalence of anti-thyroid antibodies

TGAb was determined in 8 studies [7, 17, 18, 20-23, 25]. The pooled OR was 2.40 (95% CI 1.85-3.13), suggesting that TGAb was more prevalent in HCV group. In 6 studies [16, 17, 20-23], the mean OR for TPOAb was 1.96 (95% CI 1.19-3.23), suggesting that the HCV group had a two-fold higher prevalence of TPOAb. ATMA was tested in only 5 studies [6, 7, 19, 22, 25]. The positive rate of ATMA in the HCV group was higher than that in the control group, with the pooled OR of 1.86 (95% CI 1.17-2.96) (Fig. 1).

The results of sensitivity analysis showed that no individual study significantly affected the pooled values of OR (data not shown).
Association of HCV infection with the prevalence of thyroid dysfunction

Eleven studies reported the prevalence of hypothyroidism, which involved 1,605 patients in HCV group and 1,626 in the non-HCV group [7, 15-24]. The prevalence of hypothyroidism was significantly higher in the HCV group than in the non-HCV group (OR, 3.10; 95% CI 2.19-4.40 [I2 =0.0%]) (Fig. 2).

Five studies involving 1,117 HCV infected subjects and 1,092 non-HCV infected subjects reported the prevalence of hyperthyroidism for each group [16, 20, 21, 23, 24]. The HCV group and non-HCV group comprised 67 (6.0%) and 64 (5.86%) patients with hyperthyroidism, respectively. The pooled OR of 1.10 with a 95% CI of 0.77-1.57 (I2 = 0%) indicated that HCV infection might not be significantly associated with the presence of hyperthyroidism (Fig. 3). The sensitivity analysis results showed that no study affected the pooled values of the clinical events both in patients with hypothyroidism and with hyperthyroidism (data not shown).

Table I. Characteristics of the studies included in the meta-analysis

<table>
<thead>
<tr>
<th>Source</th>
<th>Country</th>
<th>Enrollment time</th>
<th>Sex, n (male/female)</th>
<th>Age, years ± SD</th>
<th>Study design</th>
<th>NOS score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Custo 1997 [18]</td>
<td>Italy</td>
<td>NA</td>
<td>104 (74/30)</td>
<td>47.3±10.1</td>
<td>cohort 7</td>
<td>7</td>
</tr>
<tr>
<td>Huang 1999 [6]</td>
<td>Taiwan, China</td>
<td>NA</td>
<td>103 (62/68)</td>
<td>50 (20-75)</td>
<td>cohort 7</td>
<td>7</td>
</tr>
<tr>
<td>Peo’ch 2001 [19]</td>
<td>France</td>
<td>NA</td>
<td>99 (55/44)</td>
<td>42.5±17.8</td>
<td>case control</td>
<td>8</td>
</tr>
<tr>
<td>Antonelli 2004 [20]</td>
<td>Italy</td>
<td>1999-2001</td>
<td>93 (17/76)</td>
<td>63.2±6.4</td>
<td>case control</td>
<td>7</td>
</tr>
<tr>
<td>Floreni 2006 [22]</td>
<td>Italy</td>
<td>2001</td>
<td>71 (23/48)</td>
<td>65.4±12.8</td>
<td>case control</td>
<td>8</td>
</tr>
<tr>
<td>Yang 2011 [23]</td>
<td>China</td>
<td>NA</td>
<td>195 (85/110)</td>
<td>42±5</td>
<td>case control</td>
<td>8</td>
</tr>
<tr>
<td>Danilovic 2013 [24]</td>
<td>Brazil</td>
<td>2007-2009</td>
<td>103 (40/63)</td>
<td>35±10.3</td>
<td>cohort 8</td>
<td>8</td>
</tr>
</tbody>
</table>

HCV: hepatitis C virus; NOS: Newcastle-Ottawa quality assessment scale; NA: not available

Table II. The detection method and normal value of anti-thyroid antibodies and thyroid hormones in the studies included in the meta-analysis

<table>
<thead>
<tr>
<th>Source</th>
<th>Anti-thyroid antibodies</th>
<th>Thyroid hormone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TGAb</td>
<td>TPOAb</td>
</tr>
<tr>
<td>Boadas 1995 [16]</td>
<td>NA</td>
<td>RIA, &lt;100 U/mL</td>
</tr>
<tr>
<td>Matsuda 1995 [17]</td>
<td>RIA</td>
<td>RIA, &lt;0.4 U/mL</td>
</tr>
<tr>
<td>Custo 1997 [18]</td>
<td>&lt;10 IU/mL</td>
<td>&lt;2.0 IU/mL</td>
</tr>
<tr>
<td>Huang 1999 [6]</td>
<td>Haemagglutination, &lt;1:100</td>
<td>Haemagglutination, &lt;1:100</td>
</tr>
<tr>
<td>Ganne-Carrie 2000 [7]</td>
<td>Haemagglutination, &lt;1:640</td>
<td>RIA, &lt;1:100</td>
</tr>
<tr>
<td>Peo’ch K2001 [19]</td>
<td>ELISA, &lt;200 IU/L</td>
<td>ELISA, &lt;50 IU/L</td>
</tr>
<tr>
<td>Antonelli 2004 [20]</td>
<td>IRMA, 0–150 UI/mL</td>
<td>IRMA, 0–150 UI/mL</td>
</tr>
<tr>
<td>Antonelli 2004 [21]</td>
<td>IRMA, 0–150 UI/mL</td>
<td>IRMA, 0–150 UI/mL</td>
</tr>
<tr>
<td>Floreni 2006 [22]</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Yang 2011 [23]</td>
<td>&lt;40 U/mL</td>
<td>&lt;50 U/mL</td>
</tr>
<tr>
<td>Danilovic 2013 [24]</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

TGAb: anti-thyroglobulin antibody; TPOAb: anti-thyroid peroxidase antibody; ATMA: auto-thyroid microsomal antibody; TSH: thyroid stimulating hormone; FT4: free thyroxine; FT3: free triiodothyronine; NA: not available; IF: immunofluorescence; RIA: radioimmunoassay; ELISA: enzyme-linked immunosorbent assay; IRMA: immunoradiometric assay
Publication bias
We assessed publication bias for all pooled ORs with CIs using Egger and Begg tests. The publication bias was $P < 0.05$ in Egger and Begg test, respectively (data not shown). The funnel plots are shown in Fig. 4.

DISCUSSION
The liver is important in the metabolism of the thyroid hormone, such as synthesis of thyroid hormone binding proteins and peripheral metabolism of thyroxine (T4) and triiodothyronine (T3). Conversely, thyroid hormones play crucial roles for the normal hepatic function and bilirubin metabolism. Liver changes may be secondary to thyroid dysfunction. On the other hand, changes in thyroid hormone metabolism may occur secondary to liver diseases. In the present study, we have demonstrated that chronic HCV infection confers a nearly 2-fold higher prevalence for anti-thyroid antibodies and 3-fold higher prevalence of hypothyroidism in IFN-α naïve subjects as compared with non-HCV controls.

Autoimmune thyroid diseases (AITDs) are the most frequent autoimmune disorders, the commonest pathological conditions of the thyroid gland, and are characterized by the presence of circulating anti-thyroid antibodies and thyroid dysfunction. The AITDs result from the immune attack on the
thyroid and are T cell-mediated organ-specific autoimmune disorders. The prevalence of AITDs is estimated to be 2-5% [13, 26, 27], while the prevalence of antithyroid antibodies such as TPOAb, TGAAb and ATMA may be even higher [28]. The AITDs comprise two main clinical presentations: Graves’ disease (GD) and HT, with clinical hallmarks of thyrotoxicosis and hypothyroidism, respectively. The development of AITDs may be affected by differences in geographic distribution, the genetic background of populations, and environmental cofactors such as iodine intake or infectious agents [21].

Hepatitis C virus is mainly a hepatotropic virus, which also induces the development of various autoimmune diseases. Considerable studies have focused on the thyroid complications in HCV patients receiving IFN-α treatment. It is easy to understand the association of the IFN-α regime with thyroid disorders, because increased levels of IFN-α have numerous immunomodulatory functions, including activating both innate and adaptive immune responses. The underlying molecular mechanisms may include polymorphisms in the IFN-α signaling pathways, a feed-forward loop of IFN-α production, and a mutually positive regulatory feedback loop between IFN-α and estrogen receptor-α [29].

In fact, thyroid disorders have also been observed in a significant proportion of CHC patients before IFN-α treatment [30]. Recently, it has been shown that HCV could directly infect the human thyroid cell line (ML1) \textit{in vitro}. This finding suggests that HCV infection of thymocytes may play a role in the association between CHC and thyroid diseases [31]. More studies suggested that dysthyroidism was mediated by immunological mechanisms, rather than directly by HCV infection. It may involve the breaking of tolerance to self-antigens and the consequent triggering of auto-reactivity. Some hypotheses have emphasized the important role played by the sustained stimulation of the immune system by HCV, infection of the lymphatic cells, viral proteins, chromosomal aberrations, cytokines, or microRNA molecules [32]. It has been hypothesized recently that HCV envelope proteins can induce thyroidal inflammation directly, thereby triggering thyroiditis via a so-called “bystander activation” mechanism. HCV envelope glycoprotein E2 was shown to bind to CD81
receptors expressed on thyroid cells and induce a cascade of signals [33].

To date, there is another published review concerning the association of HCV infection with thyroid autoimmune disorders and hypothyroidism [34]. Our findings are consistent with this previous review. With the accumulated evidence and enlarged sample size, our statistical power has been enhanced to provide more precise and reliable risk estimates. Admittedly, our study has some limitations. First, such a meta-analysis of observational studies should be interpreted with caution. Randomized controlled trials have studied the thyroid dysfunction of HCV-infected subjects during IFN-α treatment [35, 36]. To the best of our knowledge, the data from the observational studies available here for IFN-α naïve patients could provide useful information as well. Second, the fact that we only included studies published in English-language means some relevant studies might have been missed in particular ethnic groups if they were published in non-English language. However, only a small minority of studies was excluded specifically because they were not in English. Another limitation of our study is that diagnosis of particularAITD has not been covered, although the association of HT with anti-thyroid antibodies and hypothyroidism has been well-established [37].

CONCLUSION

Our study for the first time has confirmed the association of thyroid disturbance with chronic HCV infection in IFN-α naïve patients through a thorough meta-analysis. It is advisable for the clinicians to monitor thyroid antibodies and function in the course of chronic HCV infection, independent of administration of IFN-α therapy.

Fig. 4. Funnel-plot of studies investigating the prevalence of anti-thyroglobulin antibody (A), anti-thyroid peroxidase antibody (B), auto-thyroid microsomal antibody (C), hypothyroidism (D), and hyperthyroidism (E).

Supplementary material: To access the supplementary material visit the online version of the J Gastrointestin Liver Dis at http://www.jgld.ro/wp/archive/

Conflicts of interest: The authors have no disclosures to report.

Authors’ contributions: Y.S.: study concept and design, drafting of the manuscript; X.L.W.: study concept and design, analysis and interpretation of data; J.P.X.: analysis and interpretation of data; J.G.S. and Y.H.L.: valuable discussion and support; G.Q.: overall study concept and design, critical revision and final drafting of the manuscript.

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REFERENCES


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N=1405 records identified through database searching: (MEDLINE=320, EMBASE=260, OVID MEDCINE=478, COCHRANE=347)

N=28 additional records identified through other sources

Excluded due to: N=596 repeated articles

N=837 Potentially relevant citations identified and screened

Titles and key words were reviewed: N=7 reviews, meta-analysis N=25 animals studies N=680 obviously irrelevant studies N=36 special population studies

N=89 Abstract retrieved for further evaluation

Excluded due to: N=26 lack of non-HCV control N=17 case report N=12 data not reported

N=34 Full text retrieved for detail evaluation

Excluded due to: N=12 lack of events of interest N=10 control group were only HBV

N=12 Controlled studies included in the meta-analysis

N=12 Anti-thyroid antibodies

- N=8 TGAb
- N=6 TPOAb
- N=5 ATMA
- N=3 TGAb or TPOAb

N=11 Thyroid dysfunction

- N=11 Hypothyroidism
- N=5 Hyperthyroidism

Supplementary Fig. 1. Study flowchart