# Thyroid dysfunction among chronic hepatitis C patients and its relation to Interferon therapy

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**Background**
Thyroid dysfunction (TD) represents an extrahepatic manifestation of chronic hepatitis C (CHC). Moreover, the currently approved treatment of CHC is often associated with TD. However, it remains debatable if TD is mainly virus or treatment related. The aim of this study was to assess the incidence of TD and to identify its predictors in treated and untreated CHC-infected patients.

**Patients and methods**
A total of 1290 patients with CHC were evaluated for TD for 48 weeks: 200 were untreated (control group) and 1090 were treated with pegylated interferon α (PEG-IFN-α) plus ribavirin (treatment group).

**Results**
The incidence of TD was more evident by the end of treatment (week 48); it was found to be 15.5%, mostly in the form of hypothyroidism (8.4%), whereas the least incidence was detected by week 12 (9.1%), mostly in the form of hyperthyroidism (5.2%). Generally, hyperthyroidism was higher than hypothyroidism in multiple folds, but in the end, hypothyroid cases became more dominant. Males were more affected, but the prevalence of hypothyroidism was more in females (10.1%) than males (8.0%). TD was not related to sex, age, BMI, pretreatment viral load, pretreatment laboratory characteristics, post-treatment biochemical tests, treatment duration, severity of hepatic inflammation and fibrosis, type of biopsy used, or virological outcome, but PEG-IFN formulation was related, particularly IFN-α-2a. TD did not lead to dose reduction or therapy withdrawal.

**Conclusion**
Both hepatitis C virus and IFN-α therapy have been found to be inducing thyroid disorders in patients with CHC virus infection. Antiviral therapy of CHC possibly induces de novo or exacerbates pre-existing silent TD especially subclinical hypothyroidism. The role of CHC *per se* in TD remains to be determined.

**Keywords:**
chronic hepatitis C, pegylated interferon alpha, thyroid dysfunction

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## Introduction

Hepatitis C virus (HCV) infection is a major global health problem, being the second most common chronic viral infection in the world with a global prevalence of ~3%. HCV is both a hepatotropic as well as a lymphotropic virus, and chronic infection is known to be responsible for both hepatic and extrahepatic diseases [1–3].

It was found that HCV infection is inclined to a certain degree to some organs, especially thyroid gland, as a high prevalence of thyroid autoimmunity and hypothyroidism [4] as well as of papillary thyroid carcinoma [5] has been reported in patient with chronic hepatitis C (CHC) virus infection.

The current standard treatment for CHC virus is the combination of pegylated interferon α (PEG-IFN-α) and ribavirin (RIB) [6,7] which lead to a sustained virological response (SVR) rates of 54–80% [8,9].

Despite its efficacy, it has a well-known adverse effect profile, including thyroid dysfunction (TD) [10,11].

The aim of this retrospective study was to investigate the association between CHC virus infection whether treated with PEG-IFN or not and TD development.

## Patients and methods

### Patients

This was a case–control study conducted in Assiut University Hospital at EL-Raghy Liver Hospital during the period between 2013 and 2015. Data were collected from the medical records of 1290 patients

with chronic HCV infection and were retrospectively analyzed. Patients were eligible for the study if they had serologically and virologically confirmed chronic HCV infection.

The study population was divided into two groups:

(1) Group 1 (treatment group) included 1090 patients who received combination therapy with PEG-IFN-α-2a (Roche type) or PEG-IFN-α-2b (MSD type) plus RIB, according to the treatment protocol recommended by the National Institutes of Health. The dose of PEG-IFN-α-2a was 180 μg/week and of PEG-IFN-α-2b was 1.5 μg/kg/week. The dose of RIB was 1000 mg/day (body weight ≤75 kg) or 1200 mg/day (body weight ≥75 kg). Duration of treatment was 48 weeks
(2) Group 2 (control group) included 200 patients with documented chronic HCV infection who denied treatment for personal, social, or any other reasons, but they had been followed up in the outpatient clinic. The duration of follow-up for control group was calculated as the time since the initiation of HCV therapy for treatment group until 48 weeks later.

#### Exclusion criteria

The following were the exclusion criteria:

(1) Patients with overt thyroid disease
(2) Other causes of chronic liver disease, decompensated liver cirrhosis, previous organ transplantation, coinfection with HBV and/or HIV, and pregnancy
(3) Patients with other treated or untreated pre-existing diseases as well as those with addict substances or alcohol abuse.

#### Ethical considerations

This study was approved by Ethical Committee, Faculty of Medicine, Assiut University. All patients and controls were provided a detailed description of the procedures before being enrolled in this study, and a formal and written consent was obtained from them for participating in the study.

#### Methods

All treated and control patients included were subjected to the following:

(1) Full history taking
(2) Thorough clinical examination
(3) Body height and weight were recorded at the beginning of the study, and the BMI was calculated
(4) Routine biochemical and hematological tests including the following:
    (a) Complete blood count including haemoglobin, white blood cells, and platelets
    (b) Liver function tests including alanine aminotransferase, aspartate aminotransferase, albumin, total bilirubin, and indirect bilirubin
    (c) Kidney function test, including serum creatinine
    (d) Serological markers for viral hepatitis C
    (e) Thyroid-stimulating hormone at baseline and 48 weeks later
    (f) Quantitative viral assay by PCR measuring viral RNA at baseline and after 48 weeks at the end of treatment
    (i) Patients in treatment group were subjected to furthermore investigations to correlate them with TD development.

These investigations were the following:

(1) Blood glucose level
(2) Absolute neutrophil count
(3) Alkaline phosphatase
(4) α-Fetoprotein
(5) Prothrombin concentration
(6) International normalized ratio of prothrombin time
(7) Liver biopsy measuring grades of HCV activity (inflammation) and stages of liver fibrosis that were performed by both types of histopathological scoring systems of the liver biopsy (METAVIR/ISHAK)
(8) Type of IFN-α therapy used in treatment whether Roche type (PEG-IFN-α-2a) or MSD type (PEG-IFN-α-2b)
(9) Quantitative viral assay by PCR measuring viral RNA at weeks 12 and 24 and 6 months after the end of treatment.

#### Data collection

Medical records of all patients were reviewed. The demographic, laboratory, and clinical data were collected.

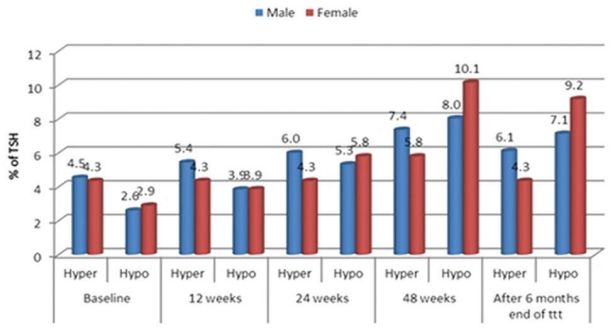
#### Statistical analysis

(1) Statistical analysis was conducted using statistical package for the social sciences version 16.0 for Window software (SPSS Inc., Chicago, Illinois, USA).
(2) Mean and SD were used to express quantitative data.
(3) *P* values of less than 0.05 were considered statistically significant.
(4) *P* values of more than 0.05 were considered statistically insignificant.

## Results

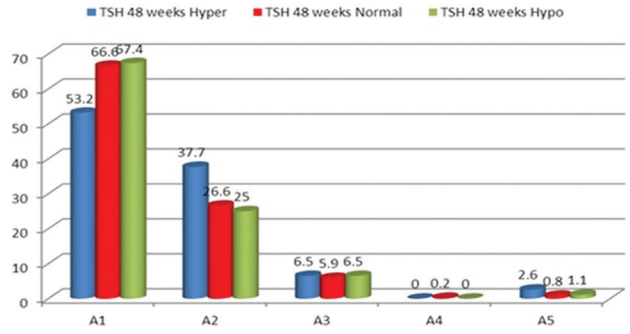
A total of 1290 patients with chronic HCV infection were selected for this study. They were divided into two groups:

**Figure 1**



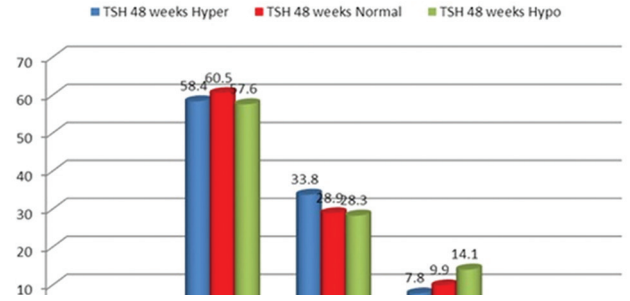

Gender of hypo and hyperthyroid cases along the 48 weeks of therapy.

**Figure 2**




Grades of hepatitis C virus activity (A) of different thyroid dysfunction case at week 48. TSH, thyroid-stimulating hormone.

**Figure 3**




Stages of liver fibrosis (F) of different thyroid dysfunction case at week 48. TSH, thyroid-stimulating hormone.

Group 1 (treatment group) included 1090 patients receiving combined therapy (IFN-α+RIB). The group comprised 883 (81.0%) males and 207 (19.0%) females, with mean ± SD age of 38.15 ± 11.18 years and mean BMI of 25.4 ± 3.37.

Group 2 (control group) included 200 patients, comprising 170 (85%) males and 30 (15%) females, with mean ± SD age of 43.09 ± 11.4 and mean BMI of 26.82 ± 3.59.

The two groups were comparable according to pretreatment demographics and laboratory parameters with no significant difference between both groups. The studied groups were compared for pretreatment and after 48 weeks of combined therapy as regards viral load by measuring serum HCV-RNA (quantitative polymerase chain reaction [PCR] assay) with no significant difference between the two groups at the baseline but after treatment for 48 weeks, 1042 (95.6%) patients became negative for HCV but the control group remained all positive for HCV as shown in Table 1. Thyroid stimulating hormone (TSH) was performed for both groups (treatment and control) at baseline and after completion of combined therapy (48 weeks).

**Table 1 Comparison between treatment and control groups regarding quantitative PCR results and thyroid-stimulating hormone levels at baseline and after 48 weeks (end of treatment)**

| | Treatment group (*n*=1090) [*n* (%)] | Control group (*n*=200) [*n* (%)] | *P* |
|---|---|---|---|
| PCR baseline | | | |
| Positive | 1090 (100.0) | 200 (100.0) | – |
| PCR after 48 weeks (end of treatment) | | | |
| Negative | 1042 (95.6) | 0 | <0.001** |
| Positive | 48 (4.4) | 200 (100.0) | |
| Thyroid-stimulating hormone at baseline | | | |
| Hyperthyroidism | **49** (4.5) | **4** (2.0) | 0.257 |
| Normal | 1012 (92.8) | 190 (95.0) | |
| Hypothyroidism | **29** (2.7) | **6** (3.0) | |
| Thyroid-stimulating hormone (mIU/l) 48 weeks (end of treatment) | | | |
| Hyperthyroidism | **77** (7.1) | **8** (4.0) | 0.035* |
| Normal | 921 (84.5) | 183 (91.5) | |
| Hypothyroidism | **92** (8.4) | **9** (4.5) | |

*$P$<0.05, statistically significant difference. **$P$<0.01, statistically significant difference.

At baseline (7.2%) in the treatment group and (5.0%) in the control group had TD. After 48 week of treatment and follow up for the controls, the percentage of patient from treatment group who had TD became (5.5%) (nd that from the control group who had TD became (8.5% s presented in Table 1 with more tendency to develop hypothyroidism than hyperthyroidism. The follow up of the developed TD cases in treatment group along the course of treatment and for 6 monthes after end of the showed increasing incidence of developing hypothyroidism than hyperthyroidism until 48 weeks of treatment with sloppage of this increase after therapy end Table 2. The number of the developed cases of TD in treatment group was more in males (883) than females (207) with more tendency to develop hypothyroidism than hyperthyroidism along the different weeks of the course but this difference did not reach statistical significance. Noticed also that the percent of hypothyroidism was more dominant in females (10.1%) than males (8.0%) by the end of the inspite of the majority of males Fig. 1. Comparison between normal and developed TD cases in treatment group as regard grades of HCV activity (A) and stages

**Table 2 Incidence of new cases of thyroid dysfunction in different weeks of treatment course (treatment group)**

| Thyroid dysfunction | TSH at baseline [*n* (%)] | TSH at week (12) of treatment [*n* (%)] | TSH at week (24) of treatment [*n* (%)] | TSH at week (48) end of treatment [*n* (%)] | TSH (6) months after end of treatment [*n* (%)] |
|---|---|---|---|---|---|
| Hyperthyroidism | **49** (4.5) | **57** (5.2) | **62** (5.7) | **77** (7.1) | **63** (5.8) |
| Normal | 1012 (92.8) | 991 (90.9) | 969 (88.9) | 921 (84.5) | 945 (86.7) |
| Hypothyroidism | **29** (2.7) | **42** (3.9) | **59** (5.4) | **92** (8.4) | **82** (7.5) |

TSH, thyroid-stimulating hormone.

**Table 3 Comparison between thyroid dysfunction cases in treatment group regarding type of histopathological scoring system of the liver biopsy (METAVIR/ISHAK) and type of interferon-α therapy used in treatment group**

| | TSH 48 weeks of treatment [*n* (%)] | | | *P* |
|---|---|---|---|---|
| | Hyperthyroidism (*n*=77) | Normal (*n*=921) | Hypothyroidism (*n*=92) | |
| Biopsy type (METAVIR/ISHAK) | | | | |
| ISHAK | 0 | 2 (0.2) | 0 | 0.832 |
| METAVIR | 77 (100.0) | 919 (99.8) | 92 (100.0) | |
| IFN type | | | | |
| MSD (PEG-IFN-α-2b) | **25** (32.5) | 158 (17.2) | **24** (26.1) | 0.001** |
| Roche (PEG-IFN-α-2a) | **52** (67.5) | 763 (82.8) | **68** (73.9) | |

PEG-IFN, pegylated interferon; TSH, thyroid-stimulating hormone. NS, *P*>0.05, no statistically significant difference. **P*<0.05, statistically significant difference. **Statistically significant difference (*P*<0.01) and as this what was found in the Table 3 (*P* value= 0.001) so, we can exchange (**) by( *) in Table 3.

**Table 4 Comparison between treatment responses at different weeks of treatment course and thyroid dysfunction cases in treatment group**

| Type of treatment response | Treatment group (*n*=1090) [*n* (%)] | | | *P* |
|---|---|---|---|---|
| | Hyperthyroidism | Normal | Hypothyroidism | |
| Early virological response week 12 | 57 cases | | 42 cases | |
| Yes | 48 (4.9) | 897 (91.2) | 39 (4.0) | 0.250 (NS) |
| No | 9 (8.5) | 94 (88.7) | 3 (2.8) | |
| Response at week 24 | 62 cases | | 59 cases | |
| Yes | 56 (5.5) | 909 (89.0) | 56 (5.5) | 0.507 (NS) |
| No | 6 (8.7) | 60 (87.0) | 3 (4.3) | |
| End of treatment response week 48 | 77 cases | | 92 cases | |
| Yes | 72 (7.0) | 877 (84.7) | 86 (8.3) | 0.640 (NS) |
| No | 5 (9.1) | 44 (80.0) | 6 (10.9) | |
| Sustained virological response 6 months after end of treatment | 63 cases | | 82 cases | |
| Yes | 59 (5.7) | 906 (86.9) | 77 (7.4) | 0.523 (NS) |
| No | 4 (8.3) | 39 (81.3) | 5 (10.4) | |

NS, *P*>0.05, no statistically significant difference.

of liver fibrosis (F) both measured by liver biopsy was done. Grade A1 was more dominant in both hypothyroid and hyperthyroid cases followed by grade A2, while grade A4 didn't be found in any patient's biopsy [Figs. 1 and 2]. Stage F1 was more dominant in patient's biopsies followed by stage F2, while both stages F0 and F4 couldn't be detected in the biopsies [Figs. 2 and 3].

Type of histopathological scoring system of the liver biopsy (METAVIR/ISHAK) and type of interferon-alpha therapy used in treatment group were evaluated in treatment group patients and found that most of them were assessed by using METAVIR type of biopsies except for 2 patients of normal TSH level who were assessed by ISHAK type [Table 3].

Most of TD cases have received Roche type (PEG- IFN alpha 2a) (hyperthyroidism=52 case, hypothyroidism=68 case), while least TD cases received MSD type (PEG- IFN alpha 2b) (hyperthyroidism=25 case, hypothyroidism=24 case) [Table 3].

Correlation between virological responses in the different weeks and developed TD cases whether hypo or hyperthyroidism in the same corresponding weeks was done and positive correlation between them was found but with no statistically significant difference between the different weeks [Table 4].

## Discussion

HCV is an emergent national health problem in Egypt. The combination of PEG-IFN with RIB was considered the established therapy for CHC, and it was associated with several adverse effects, including TD [12–14]. The immunostimulatory effects of IFN-α have been well described, with thyroid being the most common endocrine organ affected [15,16]. The role of RIB in

the development of TD is also under discussion [17]. Moreover, it is generally speculated that HCV infection itself may perpetuate the immune cascade, which leads to the appearance of autoimmune thyroid disorders, especially in genetically predisposed patients [18,19].

We found that both age and BMI of the patients have no relation to TD in both groups. There was no correlation between pretreatment laboratory and biochemical tests and TD. Moreover, viral load of HCV at baseline showed no significant difference, and so, it had no relation to the presence of subclinical TD in both groups.

In this study, 7.2% of the treated patients were found to have subclinical TD at the baseline, which became 15.5% during treatment (48 weeks), whereas 5% of the control group had subclinical TD at baseline and became 8.5% during the same follow-up period [20,21]. These data suggest that IFN-α therapy, which is known to induce, reveal, or exacerbate various autoimmune disorders, probably causes TD in chronic HCV-infected patients. Additionally, TD development in our study population was linked to HCV infection itself, as shown in baseline existing subclinical TD before treatment as well as those who developed TD in the control group. It can be concluded that interferon therapy and HCV infection may have synergistic effect in the causation of thyroid disease. In disagreement with the current results, two previous population-based studies by Huang *et al.* [22] and Loviselli *et al.* [23] excluded a specific role of HCV infection in determining the development of thyroid disease. Similarly, in the studies of Marazuela *et al.* [24], Floreani *et al.* [25] and Barrett *et al.* [26], no correlation was found. Another important observation is the relatively same incidence (15.5%) of TD in the treatment group of this study compared with the corresponding rates reported previously from similar studies using standard IFN monotherapy (3–18%) by Ward and Bing-You [12], studies using standard IFN and RIB (10.7–12.5%) by Kee *et al.* [10], as well as that using PEG-IFN-α plus RIB therapy (12–12.8%) by Freidrich-Rust *et al.* [20]. Other studies like that of Preziati *et al.* [27] and Imagawa *et al.* [28] found that the prevalence of TD varied markedly ranging from 3.4 to 31.4%.

This study demonstrated the high tendency of hypothyroid state in chronic HCV-infected patients whether treated with combined therapy or those who had been followed up. This result agreed with a previous study by Nadeem *et al.* [29].

The incidence of new cases of TD among the patients of treatment group was more by the end of treatment (week 48) to be 15.5%, mostly in the form of hypothyroidism (8.4%) and hyperthyroidism (7.1%), whereas the least incidence was detected by week 12 in the form of hyperthyroidism (5.2%) and hypothyroidism (3.9%). Generally, hyperthyroidism was higher than hypothyroidism in multiple folds, but in the end, hypothyroid cases became more evident.

Moreover, we found that TD in this study was more common in males than females at baseline and after 48 weeks of treatment, unlike previous studies by Fernandez-Soto *et al.* [21] and Deutsch *et al.* [30]. Such a factor as a relatively small number of female patients in our study (only 237 female from total 1290 patients) could play a role in the observed lack of association between female sex and TD. The percentage of TD (hypothyroidism) cases at the end of treatment was more in females (10.1%) than males (8.0%) in spite of their small number. This was against the study of Yuming Wang *et al.* [31], where sex was an independent factor in predicting the occurrence of TD as well as those of Fernandez-Soto *et al.* [21] and Jamil *et al.* [32]. However, some studies by Amir *et al.* [33] did not find this correlation of sex with TD, as well as Muratori *et al.* [34], and Stefanova-Petrova *et al.* [35], who approved that females were not more prone to TD. Moreover, Mumtaz Ali Chutto *et al.* [36] found that female sex was not a risk factor for developing TD in HCV-infected patients. This is similar to the result of a study by Lisker-Melman *et al.* [37], which agrees also with our results [Fig. 1].

There was no correlation between post-treatment laboratory biochemical and hematological tests and different categories of the developed TD cases in treatment group.

Furthermore, TD was related to early grades of liver activity to HCV (A) (grades A1 and A2) and stages of liver fibrosis (F) (stages F1 and F2) than others in the liver biopsy, which means that TD cannot be predicted from the degree of hepatic disease as most of TD cases had a small degree of fibrosis and inflammation. Unlike our study, Rodriguez-Torres *et al.* [38] demonstrated that patients with HCV and severe fibrosis are more prone to develop TD during treatment with IFN-α as compared with those with mild fibrosis, whereas Morisco *et al.* [39] showed no significant differences between patients with TD and liver inflammation or fibrosis [Figs. 2 and 3].

Type of histopathological scoring system of the liver biopsy (METAVIR/ISHAK type) and the type of IFN-α therapy used in treatment group whether type 2a or 2b were assessed to evaluate which type is more likely to be associated with TD, and we found that all biopsies of TD cases were done using METAVIR classification, whereas for IFN-α type used, PEG-IFNα-2a therapy

was significantly associated with TD compared with PEG-IFNα-2b therapy. These results are in contrast with the study of Hwang *et al.* [40], which found that PEG-IFNα-2b therapy was significantly associated with TD compared to PEG-IFNα-2a therapy. Studies of Dalgard *et al.* [14] and Kee *et al.* [10] had found no association between thyroid disease and PEG-IFN formulations.

A positive correlation was observed between the developed TD cases whether hyper or hypothyroidism and virological responses in the different weeks of therapy, but with no significant difference. Few published reports have assessed the development of TD in relation to SVR. Our results are in agreement with Vezali *et al.* [17], who reported no relationship between TD and SVR in patients with CHC receiving PEG-IFN/RBV therapy. Other studies by Tran *et al.* [41] demonstrated a positive association between thyroid disease and viral clearance. Moncoucy *et al.* [42] found that TD was not associated with SVR of CHC to IFN-α therapy, as also demonstrated by Hsieh *et al.* [43], but they are in contrast to previous reports by Lisker-Melman *et al.* [37] and Reid *et al.* [44].

Limitations of this study were its retrospective and observational nature, small number of female patients included, the absence of data concerning thyroid-specific autoantibodies and the genotype of the hepatitis C virus at baseline. Therefore, the relations between TD development and these factors cannot be determined, so further studies are needed to discuss this.

Our large short-term retrospective observational study demonstrates that TD occurs in approximately one-sixth of chronic HCV-infected patients treated with the currently proposed combination treatment and ~9% of untreated chronic HCV patients. Transient subclinical hypothyroidism which frequently needs hormone replacement therapy represents the most common thyroid disorder in these patients. TD probably cannot be predicted by any pretreatment human or virological parameter (sex, age, BMI, pretreatment laboratory tests, and viral load), as well as it seems not to be associated with the total dose of PEG-IFN-α and RIB, or the duration of therapy, nor to be linked to the viral kinetics or virological outcome in treated patients. The actual relevance of the TD to chronic HCV infection *per se* remains to be fully clarified in large prospective, controlled studies.

## Conclusion

In this study, we found that both HCV itself and IFN-α therapy have been found to be inducing thyroid disorders in patients with chronic HCV infection. Patients who are treated with IFN-α and RIB therapy should be informed about the risks of developing TD, and therefore screening of thyroid function should be done regularly during and after the treatment course.

### Recommendation

(1) We recommend to study and follow-up chronic HCV-infected patients treated with combined therapy with measurement of thyroid function tests during and after withdrawal of therapy for early and accurate diagnosis of TD development and proper management
(2) For further studies, it is advisable to detect thyroid-specific autoantibodies and the genotype of HCV before treatment in large prospective controlled studies later on
(3) Use of thyroid function tests as a routine assessment and follow-up of chronic HCV-infected patients who are liable to receive the combination therapy should be done.

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### Conflicts of interest

There are no conflicts of interest.

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