# Thyroid dysfunction in Egyptian patients with hepatitis C virus: prevalence and possible triggering

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**Background**
The contribution of chronic hepatitis C virus (HCV) infection per se in thyroid autoimmunity and dysfunction remains controversial. We investigate the prevalence of thyroid disorders and the possible association between thyroid dysfunction and different factors in a cohort of HCV-untreated patients.
**Patients and methods**
A total 1050 patients with untreated HCV infection were enrolled in this study. Thyroid function tests, antiperoxidase (TPO-Ab), antithyroglobulin, thyroid ultrasound, real-time PCR to assess HCV RNA viral load, and fibroscan to determine degree of hepatic fibrosis were done.
**Results**
Thyroid dysfunction was found in 17.1% of patients: 11.5% hypothyroidism and 5.6% hyperthyroidism. Subclinical hypothyroidism, overt hypothyroidism, subclinical hyperthyroidism, and overt hyperthyroidism were detected in 8.6, 2.8, 3.3, and 2.3% of patients, respectively. Thyroid ultrasound showed abnormality in 10.2% of patients. TPO-Ab and antithyroglobulin were positive in 5.1 and 6.4% of patients, respectively. TPO-Ab was more frequently positive in hyperthyroid patients compared with euthyroid ($P<0.001$) and hypothyroid ($P<0.001$) patients. Positive TPO-Ab was only significantly associated with thyroid state ($P<0.001$) and duration of HCV infection ($P=0.02$).
**Conclusion**
The prevalence of thyroid dysfunction is 17.1% among patients with HCV infection. Furthermore, thyroid disorder is related mainly to thyroid autoimmunity independent of age, sex, or level of viremia.

**Keywords:**
hepatitis C virus, thyroid antibodies, thyroid

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## Introduction

Hepatitis C virus (HCV) infection is a common health problem worldwide. Approximately 180 million patients are infected with HCV all over the world [1]. In addition, it is a major endemic medical problem in Egypt, with ~14.7% prevalence rate [2]. HCV is associated not only with hepatic complications but also with many extrahepatic diseases like lymphoproliferative, renal, and endocrine disorders [3]. Thyroid dysfunction is one of the common extrahepatic manifestations in patients with chronic HCV infection [4]. It has been reported to have an occurrence of ~15% in HCV-infected patients; however, among different populations, this figure is not constant, and some studies reported very high prevalence, which reached 51% in a recent study [5,6].

Thyroid dysfunction after interferon treatment of HCV-infected patients was reported in many previous studies [7–9], but only few studies have determined their prevalence in non-interferon-treated patients [5]. Moreover, limited number of studies have investigated thyroid disorders in untreated Egyptian patients with HCV [10].

Many factors could affect the relation between HCV infection and the development of thyroid dysfunction, including genetic, demographic, and environmental factors [5]. For example, sex difference has a significant effect on the incidence of thyroid dysfunction in HCV-infected patients, and most research studies have reported higher incidence of thyroid diseases in female [6]; however, others found no significant difference between males and females [5]. Moreover, geographical variations have also been identified as important risk factors for the development

of autoimmune thyroid diseases [11]. The mechanism of HCV effect on thyroid is debatable; it could be related to direct infection of thyroid cells by HCV, stimulation of thyroid autoimmunity, or both [12,13]. Considering these facts we investigated the prevalence of thyroid disorders in nontreated Egyptian patients with HCV infection and the association between possible properties of thyroid dysfunction and the different variables in HCV-infected patients.

## Patients and methods

### Study design and patient population

The study was conducted in a tertiary care hospital between May 2015 and May 2017. Patients who were HCV-PCR positive with no previous treatment for HCV were recruited after approval of the institutional ethical committee. Patients with history of thyroid illness, thyroid surgery, or those who were receiving thyroid therapy were excluded from the study. All patients provided informed consent to participate in this study. The study protocol and procedures conform to the ethical guidelines of the 1975 Declaration of Helsinki.

### Procedure

All patients were subjected to thorough medical evaluation including demographic and anthropometric measures and biochemical tests including complete blood count, alanine transaminase, prothrombin time, bilirubin, serum albumin, and serum creatinine. Viral load was measured using Cobas Ampli Prep/Cobas TaqMan HCV-RNA assay (Roche Diagnostics, Pleasanton, California, USA).

Thyroid assessment was done by measuring serum free triiodothyronine, free thyroxine (FT4), and thyroid-stimulating hormone (TSH) by enzyme-linked immunosorbent assay. Thyroid antibodies including antiperoxidase (TPO-Ab) and antithyroglobulin were measured by a microplate enzyme immunoassay (DRG International, Springfield, New Jersey, USA). Normal ranges in our laboratory were FT4 (0.8–1.8 ng/dl), free triiodothyronine (1.3–5.4 pg/ml), and TSH (0.25–5.0 mIU/ml). Thyroid dysfunction was categorized according to TSH and FT4 as follow: overt hypothyroidism if TSH more than 5 mIU/l and FT4 less than 0.8 ng/dl, subclinical hypothyroidism if TSH more than 5 mIU/l and FT4 at least 0.8 ng/dl, hyperthyroidism if serum TSH was up to 0.1 mIU/l and FT4 more than 1.8 ng/dl, and subclinical hyperthyroidism if serum TSH was up to 0.1 mIU/l and FT4 at least 1.8 ng/dl.

Assessment of degree of liver fibrosis was done using FibroScan (FibroScan 502; EchoSense, Paris, France). Thyroid examination of all patients was done using a frequency linear array transducer (7.5 MHz) (ATL HDI 5000; Philips, Guangzhou , Guangdong , China) ultrasound aiming to detect any thyroid nodules and to evaluate the size and echogenicity of the gland.

### Statistical analysis

Pre-coded data were entered and analyzed through the statistical package of the social sciences software program, version 23 (IBM SPSS statistics for Windows, version 23.0; IBM Corp., Armonk, New York, USA). Data were presented using mean, SD, median, and interquartile range for quantitative variables and frequency and percentage for qualitative ones. Comparison between groups was performed using Kruskal–Wallis and Mann–Whitney tests for quantitative variables and $\chi^2$ and Fisher's exact test for qualitative ones. Spearman correlation coefficients were calculated to explore the association between different quantitative and/or ordinal variables. *P* values less than 0.05 were considered statistically significant.

## Results

The study involved 1050 cases with untreated HCV infection. The age range showed a minimum of 26 years and a maximum of 62 years, with a mean age of 39.1±7.9 years. The study included 516 (49.1%) females and 534 (50.9%) males. Fibroscan of our patients revealed that higher percentage of them (76.4%) had fibrosis stage less than 3, whereas the rest had severe fibrosis or cirrhosis (stage≥3; Table 1).

Assessment of thyroid function in HCV-infected patients revealed that 82.9% of patients were euthyroid. Among the rest of the patients, 11.5% had hypothyroidism and 5.6% had hyperthyroidism. Furthermore, subgroup analysis of hypothyroid patients showed that 8.6% had subclinical hypothyroidism and 2.8% had overt hypothyroidism. However, 3.3% of them had subclinical hyperthyroidism and 2.3% had overt hyperthyroidism (Table 2).

Thyroid ultrasound was abnormal in 10.2% of HCV-infected patients. The most revealing abnormality was heterogeneous echogenicity of the thyroid gland reported in 6.6% of patients. Diffuse thyroid gland enlargement and multinodular goiter were reported in 3 and 0.6% of the patients, respectively.

**Table 1 Clinical, laboratory, and radiological data of patients with hepatitis C virus**

| Variables | Mean±SD |
|---|---|
| Age (years) | 39.1±7.9 |
| Sex [*n* (%)] | |
| Male | 534 (50.9) |
| Female | 516 (49.1) |
| Smoking [*n* (%)] | 347 (33.0) |
| BMI (kg/m$^2$) | 23.0±3.0 |
| Duration of HCV (months) | 32.2±20.9 |
| ALT (IU/l) | 35.4±20.6 |
| Prothrombin time (s) | 13.1±1.2 |
| Albumin (g/dl) | 3.7±0.3 |
| Bilirubin total (mg/dl) | 0.9±0.1 |
| HCV PCR level [*n* (%)] | |
| Low viremia | 146 (13.9) |
| Moderate viremia | 656 (62.5) |
| High viremia | 248 (23.6) |
| Fibroscan score [*n* (%)] | |
| F1 | 146 (13.9) |
| F2–F3 | 656 (62.5) |
| F3–F4 | 155 (14.8) |
| F4 | 93 (8.9) |

ALT, alanine transaminase; HCV, hepatitis C virus.

**Table 2 Thyroid function, thyroid antibodies, and ultrasonographic data of patients with hepatitis C virus infection**

| Variables | *N* (%) |
|---|---|
| Thyroid function state | |
| Euthyroid | 873 (83.2) |
| Hypothyroidism | 126 (12) |
| Subclinical hypothyroidism | 93 (8.85) |
| Overt hypothyroidism | 33 (3.14) |
| Hyperthyroidism | 51 (4.8) |
| Subclinical hyperthyroidism | 26 (2.47) |
| Overt hyperthyroidism | 25 (2.38) |
| Thyroid antibody positivity | |
| Antithyroglobulin antibodies | 67 (6.4) |
| Antiperoxidase antibodies | 54 (5.1) |
| Thyroid ultrasound | |
| Normal | 943 (89.8) |
| Thyroid enlargement with normal echogenicity | 32 (3.0) |
| Thyroid enlargement with heterogeneous echogenicity | 69 (6.6) |
| Multinodular goiter | 6 (0.6) |

Comparison between males and females revealed no significant difference of TSH level (3.32±6.95 vs. 3.13 ±7.07 mIU/ml; *P*=0.7), TPO-Ab level (28.26±21.56 vs. 25.04±15.11 IU/ml; *P*=0.25) or antithyroglobulin level (41.77±42.2 vs. 37.47±34.97 IU/ml; *P*=0.43).

Comparison between HCV-infected patients with euthyroidism, hypothyroidism, and hyperthyroidism is shown in Table 3. TPO-Ab was more frequently positive in hyperthyroid patients compared with euthyroid (55.9 vs. 2.2%; *P*<0.001) and hypothyroid (55.9 vs. 1.7; *P*<0.001) patients. There was no significant difference among the three groups regarding age (*P*=0.12), sex (*P*=0.05), HCV infection duration (*P*=0.11), level of HCV viremia (*P*=0.83), or fibrosis stage (*P*=0.77).

The incidence of TPO-Ab positivity among HCV-infected patients with thyroid disorders was 57.6%, which is significantly higher as compared with HCV-infected patients with normal thyroid function (2.2%). To clarify the association of different variables with TPO-Ab positivity, a comparison of TPO-Ab-positive and TPO-Ab-negative HCV-infected patients is shown in Table 4. TPO-Ab-positive patients had significantly higher FT4 level, lower TSH level, and longer duration of HCV infection compared with TPO-Ab-negative patients. TPO-Ab positivity was independent of patient age, sex, level of HCV viremia, or degree of liver fibrosis.

## Discussion

This study showed that thyroid disorders were found in 17.1% of the HCV-infected patients. This number is in agreement with other studies from different populations, which revealed thyroid dysfunction in 7–15% of untreated HCV-infected patients [4,14,15]. Moreover, this figure is higher than the commonly reported prevalence of thyroid disease, which is ~5–8% in the general population [16,17]. Local studies recently reported higher incidence of thyroid dysfunction that reached 21 and 51% of HCV-infected patients; however, in these studies, patients previously treated with interferon have not been excluded [6,10].

Different forms of thyroid hormone disturbance are reported in association with chronic HCV infection [18]. The most common thyroid dysfunction reported in patients with HCV infection is hypothyroidism [15]. Moreover, a recent meta-analysis demonstrated that hypothyroidism is three times more common in HCV-infected patients than healthy participants [19]. This is in concordance with our results which showed higher incidence of hypothyroidism compared with hyperthyroidism in HCV-infected patients.

Although interferon therapy of chronic HCV infection was the major cause of thyroiditis which could be immune or nonimmune, HCV itself induces the development of various autoimmune diseases [20]. Chronic HCV infection has been shown to be

**Table 3 Comparison between hepatitis C virus-infected patients with euthyroid, hypothyroid, and hyperthyroid state**

| Variables | Thyroid function [*n* (%)] | | | *P* value | Pairwise comparisons | | |
|---|---|---|---|---|---|---|---|
| | Euthyroid (*n*=870) | Hypothyroid (*n*=121) | Hyperthyroid (*n*=59) | | 1*2 | 1*3 | 2*3 |
| Sex | | | | | | | |
| Male | 430 (49.4) | 66 (54.5) | 38 (64.4) | 0.058 | 0.291 | 0.078 | 0.209 |
| Female | 440 (50.6) | 55 (45.5) | 21 (35.6) | | | | |
| Age (years) | 38 (33–45) | 39 (34–47) | 38 (33–47) | 0.126 | 0.144 | 0.497 | 0.583 |
| Smoking | 290 (33.3) | 35 (28.9) | 22 (37.3) | 0.487 | 0.333 | 0.834 | 0.258 |
| DM | 181 (20.8) | 29 (24) | 10 (16.9) | 0.536 | 0.425 | 0.478 | 0.283 |
| BMI (kg/m$^2$) | 23 (21.2–25) | 23.5 (21.8–25) | 23 (19–25) | 0.202 | 0.213 | 0.251 | 0.070 |
| Duration of HCV (months) | 27 (16–42) | 30 (18–56) | 26 (15–38) | 0.113 | 0.057 | 0.487 | 0.082 |
| HCV PCR | | | | | | | |
| Low viremia | 120 (13.8) | 19 (15.7) | 7 (11.9) | 0.839 | 0.561 | 0.906 | 0.608 |
| Moderate viremia | 541 (62.2) | 78 (64.5) | 37 (62.7) | | | | |
| High viremia | 209 (24) | 24 (19.8) | 15 (25.4) | | | | |
| Fibrosis score | | | | | | | |
| F1 | 120 (13.8) | 19 (15.7) | 7 (11.9) | 0.774 | 0.761 | 0.572 | 0.571 |
| F2–F3 | 541 (62.2) | 78 (64.5) | 37 (62.7) | | | | |
| F3–F4 | 133 (15.3) | 15 (12.4) | 7 (11.9) | | | | |
| F4 | 76 (8.7) | 9 (7.4) | 8 (13.6) | | | | |
| Positive Tg-Ab | 23 (2.6) | 3 (2.5) | 41 (69.5) | **<0.001** | 0.916 | **<0.001** | **<0.001** |
| Positive TPO-Ab | 19 (2.2) | 2 (1.7) | 33 (55.9) | **<0.001** | 0.704 | **<0.001** | **<0.001** |
| Normal thyroid ultrasound | 832 (95.6) | 102 (84.3) | 9 (15.3) | **<0.001** | **<0.001** | **<0.001** | **<0.001** |
| Abnormal thyroid ultrasound | – | 19 (15.7) | 50 (84.7) | **<0.001** | **<0.001** | **<0.001** | **<0.001** |

DM, diabetes mellitus; HCV, hepatitis C virus; Tg-Ab, thyroglobulin antibody; TPO-Ab, antiperoxidase antibody. *1: Euthyroid; 2: Hypothyroid; 3; Hyperthyroid. Bold means statistically significant P value.

**Table 4 Comparison between hepatitis C virus-infected patients with positive antithyroid peroxidase antibody and patients with negative antibodies**

| Variables | Antiperoxidase antibody | | *P* value |
|---|---|---|---|
| | Positive (*n*=54) | Negative (*n*=996) | |
| Sex | | | |
| Male | 38 (70.4) | 496 (49.8) | **0.003** |
| Female | 16 (29.6) | 500 (50.2) | |
| Age (years) | 38 (33–47) | 38 (33–45) | 0.272 |
| BMI (kg/m$^2$) | 23.5 (21.5–25) | 23 (21.2–25) | 0.935 |
| Duration of HCV (months) | 20.5 (14–33) | 28 (17–48) | **0.021** |
| Smoking | 22 (40.7) | 325 (32.6) | 0.217 |
| Diabetes | 8 (14.8) | 212 (21.3) | 0.255 |
| HCV PCR | | | |
| Low viremia | 5 (9.3) | 141 (14.2) | 0.532 |
| Moderate viremia | 37 (68.5) | 619 (62.1) | |
| High viremia | 12 (22.2) | 236 (23.7) | |
| Fibrosis score | | | |
| F1 | 5 (9.3) | 141 (14.2) | 0.717 |
| F2–F3 | 37 (68.5) | 619 (62.1) | |
| F3–F4 | 7 (13) | 148 (14.9) | |
| F4 | 5 (9.3) | 88 (8.8) | |
| Thyroid condition | | | |
| Euthyroid | 19 (35.2) | 851 (85.4) | **<0.001** |
| Hypothyroid | 2 (3.7) | 119 (11.9) | |
| Hyperthyroid | 33 (61.1) | 26 (2.6) | |
| Abnormal thyroid ultrasound | 53 (98.1) | 54 (5.4) | **<0.001** |
| TSH | 0.1 (0.1–0.5) | 1.6 (0.9–3) | **<0.001** |
| FT4 | 1.5 (1.2–2.3) | 1.2 (1.1–1.4) | **<0.001** |
| FT3 | 3.4 (2.5–6) | 2.8 (2.4–3.3) | **<0.001** |

FT3, free triiodothyronine; FT4, free thyroxine; HCV, hepatitis C virus; TSH, thyroid-stimulating hormone.

associated with increased incidence of clinical and subclinical autoimmune thyroiditis with the prevalence of antithyroid antibody ranging between 2 and 48% in this population [21,22]. In this study, thyroid antibody positivity was the only variable related to the thyroid state. A novel observation in the current study is that structural thyroid gland abnormality was detected by ultrasound in 97% of HCV-infected patients with positive thyroid antibody but only in 2% of thyroid antibody-negative patients. This finding could indicate that thyroid autoimmunity is the main mechanism through which HCV affects the thyroid gland.Many previous studies have reported higher incidence of thyroid disorders in female patients compared with male patients because of high incidence of thyroid autoimmunity in female patients [9,23]. However, our results showed no significant difference between males and females regarding thyroid function which could be related to the nonsignificant difference of thyroid antibody positivity in male patients compared with female patients. The same results were obtained in two previous studies [5,24].

In this study, no significant difference was found between HCV-infected patients with thyroid disorders and those with normal thyroid function regarding level of HCV viremia or liver fibrosis stage. This result suggests that the pathogenesis of thyroid disorder is not likely to be related to the level of viremia but most possibly associated with autoimmunity.

## Conclusion

In this study, the prevalence of thyroid dysfunction is 17.1% of patients with HCV infection. Hypothyroidism is the most commonly encountered thyroid dysfunction in HCV-untreated patients. Thyroid disorders may develop secondary to an autoimmune mechanism triggered by HCV infection.

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### Conflicts of interest

There are no conflicts of interest.

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