# INCIDENCE OF THYROID DISORDERS IN MIXED CRYOGLOBULINEMIA: RESULTS FROM A LONGITUDINAL FOLLOW-UP.

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**Abstract**

No study has evaluated the incidence of new cases of thyroid autoimmunity (AT) and dysfunction (TD) in hepatitis C-associated mixed cryoglobulinemia (MC) patients.

We aimed to evaluate the incidence of new cases of AT and TD in a wide group of MC patients, vs. age- and gender-matched controls from the same geographic area.

After exclusion of MC patients with TD at the initial evaluation, the appearance of new cases of TD was evaluated in 112 MC patients and 112 matched controls, with similar iodine intake (median follow-up 67 months in MC vs. 78 in controls).

A high incidence ($P<0.05$) of new cases of hypothyroidism, TD, anti-thyroperoxidase antibody (AbTPO) positivity, appearance of a hypoechoic thyroid pattern, and thyroid autoimmunity in MC patients vs. controls was shown. A logistic regression analysis showed that in MC the appearance of hypothyroidism was related to female gender, a border line high initial thyroid-stimulating hormone (TSH), AbTPO positivity, a hypoechoic and small thyroid.

In conclusion, we show a high incidence of new cases of AT and TD in MC patients. MC patients at high risk (female gender, a border line high initial TSH, AbTPO positivity, a hypoechoic and small thyroid) should have periodically thyroid function follow-up.

***Key terms:*** hepatitis C-associated mixed cryoglobulinemia, autoimmune thyroiditis, thyroid autoimmunity, hypothyroidism, anti-thyroid-peroxidase antibody, TSH.

**Take-home messages:**

- The most important systemic HCV-related extrahepatic disease (HCV-EHD) is HCV-related mixed cryoglobulinemia (MC+HCV) and the most frequent and clinically important endocrine HCV-EHDs are thyroid disorders.
- Increased circulating levels of AbTPO, and increased risk of hypothyroidism in female gender and AbTPO positive subjects characterized the pattern of thyroid disorders observed in MC+HCV patients.
- To the best of our knowledge, no study has evaluated the incidence of thyroid disorders in cryoglobulinemia.
- In this paper we show an elevated incidence of new cases of hypothyroidism, thyroid dysfunction, AbTPO positivity, appearance of a hypoechoic thyroid pattern and thyroid auoimmunity in MC+HCV patients with respect to controls.
- As shown by a logistic regression analysis, in MC+HCV patients the appearance of hypothyroidism was related to female gender, a TSH value at a border line high level (though in the normal range), the presence of AbTPO positivity, and a small thyroid volume, according with what reported by other studies in the general population.
- The clinical profile in MC+HCV patients should involve thyroid function evaluation and ultrasonography, and in the ones at high risk [female gender with a border line high (though in the normal range) TSH, positive AbTPO, hypoechoic and small thyroid] thyroid function follow-up and appropriate treatments should be evaluated periodically (approximately every year).

## 1. Introduction

The most important systemic hepatitis C virus (HCV)-related extrahepatic disease (HCV-EHD) is HCV-related mixed cryoglobulinemia (MC+HCV) and the most frequent and clinically important endocrine HCV-EHDs are thyroid disorders.

Many studies have been addressed to evaluate the prevalence of thyroid autoimmunity (AT) in HCV infected patients, reporting conflicting results.

A large study investigated the prevalence of thyroid disorders in 630 consecutive patients with HCV chronic hepatitis (CHC) with respect to: a control group from an iodine-deficient area (389 subjects); another control group living in an area of iodine sufficiency (268 persons); 86 patients with chronic hepatitis B virus (HBV) infection. Patients with CHC had more frequently hypothyroidism (13%), anti–thyroperoxidase antibodies (AbTPO) (21%), or anti–thyroglobulin antibodies (AbTg) (17%), than the control groups [1, 2]. Also a meta-analysis of the literature reported a significant association between CHC and AT [3-5]. Furthermore, more recently a retrospective cohort study of users of US Veterans Affairs health care facilities, which included 146,394 CHC patients, and 572,293 controls, confirmed the thyroiditis risk was significantly increased in CHC patients [6].

Some studies evaluated autoimmune thyroid disorders (AITD) in MC+HCV patients. Codes et al. [7] studied 127 CHC patients. In CHC patients infected by genotype 3 ($P = 0.05$) thyroid dysfunction (TD) occurred in 23.3% and cryoglobulinemia in 38%. Zarebska-Michaluk et al. [8] studied 340 untreated CHC consecutive patients. Two hundred ten patients with CHC (61.7%) presented at least 1 HCV-EHDs, including MC (37.1%), and AT (16.2%). Furthermore, anecdotal studies reported TD in MC+HCV patients [9, 10].

More recently, a case-control prospective study has been conducted in 93 MC+HCV patients, matched by gender and age (+/- 2 years) to 93 CHC patients without MC and 93 HCV-negative controls. Thyroid autoimmune manifestations [AbTPO (28% vs. 9%), serum AbTPO and/or AbTg (31% vs. 12%), AT (35% vs. 16%)], and subclinical hypothyroidism (11% vs. 2%), were more frequent in MC+HCV patients than in HCV-negative controls, or in CHC patients (AbTPO, 28% vs. 14%) [11]. Increased circulating levels of AbTPO, and increased risk of hypothyroidism in female gender and AbTPO positive subjects characterized the pattern of thyroid disorders observed in MC+HCV patients [2, 4].

To the best of our knowledge, no study has evaluated the incidence of thyroid disorders in cryoglobulinemia.

The aim of our study was to evaluate the incidence of new cases of clinical and subclinical TD in a wide group of MC+HCV patients.

## 2. Patients and Methods

One hundred and fifty-one MC+HCV patients consecutively referred to the Internal Medicine or Rheumatology Units of the University of Pisa and Modena (from 1992 to 2011) underwent a thyroid evaluation.

The diagnosis of MC was based on the presence of serum mixed (IgG-IgM) cryoglobulins and the classical clinical triad (purpura, weakness, arthralgias), and the exclusion of other well-known systemic disorders, such as immuno-rheumatic, neoplastic, and infectious diseases [12, 13].

HCV infection was systematically evaluated in all patients, who were excluded if they were HCV-negative.

MC+HCV patients were excluded from the study, if they had been previously treated with external radiotherapy in the region of the neck or mediastinum, or if they had had IFNalpha treatments.

Among the MC+HCV patients, those with subclinical or clinical hypothyroidism, subclinical hyperthyroidism or Graves' disesase, were excluded too. One hundred twelve MC+HCV patients without TD were eligible for the longitudinal study. They were studied again, at least 1 year after the initial evaluation, one or more times. The median follow-up period from the initial evaluation was 67 months (range 12-191 months).

Each of the 112 MC+HCV patients eligible for the study was gender- and age-matched, one-to-one with a control group, without TD, of the background population from the same geographic area (North-West Tuscany) with a similar iodine intake (that is an important environmental risk factor for the appearance of thyroid autoimmune disorders) [14].

This control group was extracted from a larger sample of > 2000 subjects in a population-based survey of thyroid disorders, who were initially studied in 1994 and subsequently reevaluated (by thyroid function, autoantibodies and ultrasonography) in 2002-2003 (see above). The median follow-up period from the initial evaluation was 97 months (range 87-112 months).

All 112 MC+HCV patients and controls were reevaluated, by: a- physical examination; b- thyroid ultrasonography, as previously reported [15]; c- circulating free triiodothyronine (FT3) and free thyroxine (FT4) (AMERLEX-MAB FT3/FT4 Kit; Amersham, UK), thyroid-stimulating hormone (TSH) (reference range 0.3-3.6 μU/mL) (DiaSorin, USA), AbTPO and AbTg antibodies (ICN Pharmaceuticals, USA; positivity > 100 IU/mL).

If TD appeared during the follow-up, 112 MC+HCV patients were appropriately treated and excluded from a further evaluation.

The study was approved by the institutional ethic committee, and all subjects gave their informed written consent to participate.

Mean group values were compared using one-way ANOVA for normally distributed variables, otherwise by the Mann-Whitney U test. The $\chi^2$ test was used to compare categorical variables. A logistic regression analysis was performed in MC+HCV patients including gender, age, smoking, TSH, AbTPO positivity, AbTg positivity, thyroid hypoechogenicity (presence/absence), thyroid volume (all at the start of evaluation) as independent variables, and hypothyroidism at last evaluation as dependent variable.

## 3. Results

The clinical features of the 112 eligible MC+HCV patients are reported in **Table 1.**

The thyroid status of MC+HCV patients entering the longitudinal study and matched controls is reported in **Table 2**. The prevalence of subjects with positive AbTPO, thyroid hypoechoic pattern, and thyroid volume < 6 mL were higher in the MC+HCV group than in controls (**Table 2**), and TSH was slightly but significantly higher in MC+HCV patients. On the whole, indices of thyroid autoimmunity (AbTg, or AbTPO, or ultrasonographic diagnosis of thyroiditis) were more frequent in MC+HCV than in controls.

At the last evaluation (after a median of 67 and 97 months, respectively in MC+HCV patients and controls: $P < 0.01$, ANOVA) TSH levels and AbTPO titers were significantly higher in MC+HCV patients than in controls (**Table 2**). Subclinical hypothyroidism was more common in MC+HCV patients than in controls. The

prevalence of subclinical hyperthyroidism was higher in MC+HCV patients than in controls. On the whole the prevalence of TD (subclinical or clinical hypo- and hyper-thyroidism) was significantly more frequent in MC+HCV patients (**Table 2**). The prevalence of subjects with positive AbTPO, thyroid hypoechoic pattern, and thyroid volume < 6 mL was significantly higher in the MC+HCV group than in controls.

The prevalence and the incidence of new cases of thyroid disorders is reported in **Table 3**. Thyroid dysfunctions, subclinical hypothyroidism, hypothyroidism, AbTPO positivity, a thyroid hypoechoic pattern, and thyroid autoimmunity were significantly more frequent in MC+HCV than in controls.

The possible association of thyroid disorders with clinical and serological parameters of MC+HCV patients was investigated in the patients with TD, however no statistical significant difference was observed with respect to MC+HCV patients without TD.

In MC+HCV patients at the end of the follow-up, hypothyroidism was significantly associated with presence of AbTPO-positivity ($P < 0.001$), a small thyroid volume (< 6 mL) ($P < 0.01$), and a hypoechoic pattern ($P < 0.01$) (all by $\chi^2$); no relationship was found with the other thyroid parameters. Moreover, no significant association was observed among the clinical and serological parameters of MC+HCV patients and thyroid autoantibodies, or others of the studied parameters.

In MC+HCV patients, the logistic regression analysis [in a model including, age, gender, TSH value, AbTPO positivity, AbTg positivity, thyroid hypoechogenicity (presence/absence), thyroid volume (all at the start of evaluation) as independent variables, and hypothyroidism at last evaluation as dependent variable] shows that the appearance of hypothyroidism was related to, female gender [coefficient, 0.872; Exp(coef), 2.378; 95% lower, 1.231; 95% upper, 5.67; $P = 0.001$], a border line high initial TSH [coefficient, 0.931; Exp(coef), 2.104; 95% lower, 1.014; 95% upper,

4.51; $P = 0.045$], AbTPO positivity [coefficient, 0.801; Exp(coef), 1.973; 95% lower, 1.101; 95% upper, 3.562; $P = 0.0178$], and a small thyroid volume [coefficient, -0.211; Exp(coef), 0.821; 95% lower, 0.794; 95% upper, 0.923; $P < 0.01$].

## 4. Discussion

In this paper we show an elevated incidence of new cases of hypothyroidism, TD, AbTPO positivity, appearance of a hypoechoic thyroid pattern, and thyroid autoimmunity in MC+HCV patients with respect to controls. It is noteworthy that the incidence of new cases of hypothyroidism and AbTPO in control subjects was similar to the one reported by other epidemiological studies [16-18], indicating that the control group is not biased, vs. a low AT [19].

Mean TSH value, thyroid hypoechoic pattern and small thyroid volume, and the percentage of antithyroid antibodies were significantly higher in MC+HCV patients than in the control group, according with other studies, and our previous transversal study [20].

As shown by the logistic regression analysis, in MC+HCV patients the appearance of hypothyroidism was related to female gender, a TSH value at a border line high level (though in the normal range), the presence of AbTPO positivity, and a small thyroid volume, according with what reported by other studies in the general population [16-18].

The significant differences between MC+HCV patients and controls, in the baseline thyroid parameters, may account for the higher incidence of hypothyroidism in the MC+HCV group, at least in part.

The association of autoimmune disorders is well known [21], even if its pathogenetic

base is still under investigation [22, 23].

A predominant Th1 immune pattern has been shown in target organs of patients with chronic AT, or Graves' ophthalmopathy, or type 1 diabetes, at the beginning of these diseases, as demonstrated by data reported from animal models and available in humans [24-26]. In the initial and active phase of MC+HCV, too, a prevalent Th1 immune reactivity is evident, that switches to a predominant Th2 immune response in the inactive phase [27, 28]. Such prevalence of the Th1 immune reactivity at the beginning of both MC+HCV, and AT, under the influence of genetic and environmental conditions, could cause the appearance of autoimmune phenomena involving different organs in the same subject [29, 30].

In conclusion, we demonstrate a high incidence of new cases of hypothyroidism, TD, AbTPO positivity, appearance of a small thyroid and a hypoechoic thyroid pattern in MC+HCV patients, overall in female gender with respect to control subjects. A TSH value at a border line high level (though in the normal range), the presence of AbTPO positivity, and a small thyroid volume, in female gender, are risk factors for the development of TD. The clinical profile in MC+HCV patients should involve thyroid function evaluation and ultrasonography. In female patients at high risk [a border line high (though in the normal range) TSH, positive AbTPO, hypoechoic and small thyroid] thyroid function follow-up and appropriate treatments should be evaluated periodically (approximately every year).

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**Table 1.** Demographic and clinico-serological features of 112 MC+HCV patients.

| | |
|---|---|
| Age (years) | 62 ± 15 |
| Men/Women | 26/86 |
| Disease duration with MC (years) | 14 ± 10 |
| Purpura | 86% |
| Active vasculitis | 41% |
| Weakness | 99% |
| Arthralgias | 92% |
| Arthritis | 15% |
| Raynaud's phenomenon | 47% |
| Sjogren's syndrome | 44% |
| Peripheral neuropathy | 77% |
| Renal involvement* | 11% |
| Aminotransferases elevation and/or histologic activity† | 85% |
| Cryocrit (%) | 4.6 ± 9.2 |
| CH50 (normal: 160-220 units) | 114 ± 45 |
| C3 (normal: 60-130 mg/dl) | 79 ± 44 |
| C4 (normal 20-55 mg/dl) | 12 ± 7 |
| Autoantibodies ‡ | 34% |

* Serum creatinine >1.5 mg/dl and/or proteinuria >0.5 gr/24h.
† Increase of the liver enzyme (alanine aminotransferase) and/or histological alterations.
‡ Presence of anti-nuclear and/or anti-mitochondrial and /or anti-smooth muscle and/or anti-extractable nuclear antigen autoantibodies.

**Table 2.** Comparison of thyroid status at the initial, or at the last evaluation, between MC+HCV patients and matched controls.

| | Initial thyroid status | | | Last evaluation | | |
|---|---|---|---|---|---|---|
| | MC+HCV | Controls | *P* | MC+HCV | Controls | *P* |
| N° | 112 | 112 | | 112 | 112 | |
| Age, y (SD) | 62 ± 15 | 61 ± 17 | ns | 68 ± 14 | 68 ± 16 | ns |
| Gender (Men/Women) | 26/86 | 26/86 | ns | 26/86 | 26/86 | ns |
| TSH, μU/mL (SD) | 2.0 (0.6)[b] | 1.2 (0.7) | 0.037[a] | 2.8 (3.9)[b] | 1.4 (1.0) | 0.012[a] |
| FT4, pmol/L (SD) | 110 (5.0) | 121 (3.3) | ns | 108 (5.4) | 120 (3.6) | ns |
| FT3, pmol/L (SD) | 4.3 (1.9) | 4.9 (1.2) | ns | 4.2 (2.0) | 4.8 (1.1) | ns |
| AbTg, IU/mL (SD) | 101 (163) | 19 (65) | 0.034 | 132 (271) | 28 (87) | 0.022 |
| AbTPO, IU/mL (SD) | 87 (203)[b] | 17 (32) | 0.019[a] | 154 (311)[b] | 31 (61) | 0.011[a] |
| Subclinical hypothyroidism | 0% | 0% | ns | (9)9.8% | (2)1.8% | 0.101[c] |
| Clinical hypothyroidism | 0% | 0% | ns | (2)1.8% | (1)0.8% | ns |
| Subclinical hyperthyroidism | 0% | 0% | ns | (8)7.1% | (3)2.6% | ns |
| Graves' disease | 0% | 0% | ns | 0% | 0% | ns |
| Thyroid dysfunctions | 0% | 0% | ns | (19)17% | (5)4.5% | 0.002[c] |
| $AbTg^+$ | (10)8.9% | (5)4.5% | ns | (14)12.5% | (7)6.2% | ns |
| $AbTPO^+$ | (21)18.7% | (11)9.8% | 0.056[c] | 32(28.6%) | (13)11.6% | 0.001[c] |
| Hypoechoic pattern | (23)20.5% | (14)12.5% | 0.105[c] | (35)31.2% | (17)15.1% | <0.004[c] |
| Thyroid autoimmunity | (23)20.5% | (15)13.3% | 0.154[c] | (37)33% | (18)16.1% | <0.032[c] |
| Thyroid volume, mL (SD) | 12 (11) | 13(14) | ns | 10 (12) | 13 (12) | ns |
| Thyroid volume > 20 mL | 10% | 12% | ns | 9% | 12% | ns |
| Thyroid volume < 6 mL | (10)8.9% | (4)3.6% | 0.097[c] | (19)17% | (5)4.4% | 0.001[c] |

TSH = thyroid stimulating hormone; AbTPO = anti-thyroperoxidase antibody; $AbTPO^+$ = anti-thyroperoxidase antibodies >100 IU/ml; AbTg = anti-thyroglobulin antibody; $AbTg^+$ = anti-thyroglobulin antibodies >100 IU/ml; FT3 = free triiodothyronine; FT4 = free thyroxine; $AbTg^+$ or $AbTPO^+$ or ultrasonographic diagnosis of thyroiditis = thyroid autoimmunity. [a] = ANOVA. [b] = TSH levels and AbTPO titers were significantly higher in MC+HCV than in controls. [c] = $\chi^2$.

**Table 3.** New cases and incidence [c] of thyroid disorders in MC+HCV patients at the last evaluation.

| | MC+HCV patients number new cases (incidence) | Controls number new cases (incidence) | $P$ [b] |
|---|---|---|---|
| Subclinical hypothyroidism | 9 (14.4 [c]) | 2 (2.7 [c]) | 0.030 |
| Clinical hypothyroidism | 2 (3.2 [c]) | 1 (1.4 [c]) | ns |
| Hypothyroidism | 11 (17.5 [c]) | 3 (4.1 [c]) | 0.027 |
| Subclinical hyperthyroidism | 8 (12.8 [c]) | 3 (4.1 [c]) | 0.122 |
| Graves' disease | 0 (0) | 0 (0) | ns |
| Hyperthyroidism | 8 (12.8 [c]) | 3 (4.1 [c]) | ns |
| Thyroid dysfunction | 19 (30.3 [c]) | 6 (8.2 [c]) | 0.005 |
| $AbTg^+$ | 5 (8 [c]) | 2 (2.7 [c]) | ns |
| $AbTPO^+$ | 11 (17.5 [c]) | 2 (2.7 [c]) | 0.010 |
| Hypoechoic pattern | 12 (19.1 [c]) | 3 (4.1 [c]) | 0.011 |
| Thyroid autoimmunity | 14 (22.3 [c]) | 3 (4.1 [c]) | 0.055 |
| Thyroid volume > 20 mL | 0 (0) | 1 (1.4 [c]) | ns |
| Thyroid volume < 6 mL | 9 (14.4 [c]) | 1 (1.4 [c]) | 0.009 |

[a] Incidence is reported in parenthesis. Incidence = [incidence = number of new cases / patients (112) x years of follow-up (67 months = 5.6 years) = number of new events / 627 patients per year)] and matched controls [incidence = number of new cases / subjects (112) x years of follow-up (78 months = 6.5 years) = number of new events / 728 patients per year)].

[b] = $\chi^2$ (number of new cases).

[c] = with respect to 1000 patients with MC+HCV per year.

AbTPO = anti-thyroperoxidase antibody; $AbTPO^+$ = anti-thyroperoxidase antibodies >100 IU/mL; AbTg = anti-thyroglobulin antibody; $AbTg^+$ = anti-thyroglobulin antibodies >100 IU/mL.