

Thyroid hormones and complement parameters in hereditary angioedema with C1-inhibitor deficiency

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ABSTRACT

Background: Thyroid hormones control and up-regulate the synthesis of many plasma proteins.

Objective: To explore possible associations between thyroid hormone and complement levels in patients with hereditary angioedema resulting from the deficiency of the C1-inhibitor (C1-INH-HAE).

Methods: In this case-control study, serum thyrotropin, free triiodothyronine (FT₃), and free thyroxine (FT₄) levels, anti-thyroid peroxidase and antithyroglobulin antibody titers, and C1-INH concentrations were measured in 117 euthyroid patients with C1-INH-HAE and compared with their clinical properties. The control group comprised 150 healthy, age- and sex-matched, euthyroid individuals.

Results: The thyrotropin and antithyroglobulin levels were similar between the patients and the controls. Significantly lower FT₃ ($P < .001$) and FT₄ ($P = .002$) levels, as well as higher anti-thyroid peroxidase titers ($P < .001$), were seen in the patients with C1-INH-HAE. The proportion of patients with reduced C1-INH activity was greater among those with below-median FT₄ levels than among those with above-median values ($P = .02$). Patients who experienced more edematous attacks per year had lower FT₄ levels (within the normal range) than those afflicted by fewer episodes ($P = .01$). The FT₃ and FT₄ levels were significantly higher in patients undergoing long-term danazol therapy than in those who did not receive this drug ($P = .01$ and $P = .02$, respectively). The proportion of patients with FT₄ levels in the below-median range was higher in the subset with increased D-dimer concentration ($P = .009$).

Conclusion: Minor variations of the thyroid hormone levels (within the reference range) can influence the function of C1-INH in C1-INH-HAE. Our findings suggest a role for the endocrine system in the pathophysiology of C1-INH-HAE.

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Introduction

Hereditary angioedema resulting from the deficiency of the C1-inhibitor (C1-INH-HAE) is a rare, autosomal dominant disorder. The lack of C1-INH leads to the activation of plasma enzyme cascades (ie, of the complement, coagulation, kinin-kallikrein, and fibrinolytic systems), resulting in the formation of bradykinin.¹ This substance is a vasoactive mediator that enhances capillary permeability and the

outflow of plasma from the intravascular space into the extracellular compartment, thereby producing the characteristic symptom of the disorder—angioedema.² C1-INH-HAE is characterized by recurring, bradykinin-mediated edematous episodes, which may involve the subcutis and/or submucosal (gastrointestinal or upper airway) tissues.^{3,4} The severity of the disease varies greatly within and among individuals. The time of onset, severity, and location of the edematous episodes are unpredictable; their onset may depend on a variety of factors.^{5,6} In C1-INH-HAE, the baseline level of functional C1-INH (C1-INH_f) correlates with disease severity.⁷

Prophylaxis with antifibrinolytics, attenuated androgens, and C1-INH concentrate may reduce the frequency of these episodes. The exact mechanism of the action of attenuated androgens is unknown; their use is based on empirical data. However, these agents are thought to enhance the production of plasma proteins

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by the liver and the expression of C1-INH messenger RNA in peripheral blood mononuclear cells.^{8–11} Attenuated androgens reduce the level of thyroxine-binding globulin (the changes of the free hormone remain within the reference range), which is associated with an increase of basal metabolism. The mechanism of this effect has not yet been described.^{12–15}

Only a few publications provide data on the association between C1-INH-HAE and thyroid hormone (TH) levels.^{16,17} These articles focus on immunoregulatory disorders (including thyroiditis) or patients with hypothyroidism or hyperthyroidism. Through the activation of the classic pathway of the complement system, C1-INH deficiency may predispose patients to the onset of autoimmune disorders, and these disorders may worsen the symptoms of C1-INH-HAE.^{17–19} The treatment of thyroid disease with anti-thyroid agents or TH replacement resulted in the reduction of the number of angioedematous episodes also in C1-INH-HAE.¹⁷ The disorders accompanied by similar symptoms include angioedema in thyroiditis with associated chronic idiopathic urticaria.²⁰

Thyroid function tests and the determination of antibody titers are now routinely performed during the diagnostic evaluation of idiopathic urticaria with angioedema. Treatment with thyroxine does not necessarily have a positive influence on manifestations, but it can achieve the resolution of symptoms in many cases.^{21,22}

The systemic effects of THs stimulate the synthesis of certain proteins.²³ According to Zhang et al.,²⁴ serum triiodothyronine levels correlate with total complement activity, and a positive association exists between free thyroxine (FT₄) and C4 in multiple sclerosis and neuromyelitis optica. It has been suggested that THs may play diverse roles in modulating complement activation in different diseases.

Several work groups have investigated the association among THs, coagulation, and the fibrinolytic system.^{25–27} Because both enzyme cascades play leading roles in the pathomechanism of C1-INH-HAE, the clinical manifestations of the latter might be influenced by possible interactions between THs and these systems.

This study investigated whether TH levels differ between patients with C1-INH-HAE and healthy individuals, as well as whether there is any association between TH and complement levels. Furthermore, it explored possible associations among the parameters of thyroid function and attack frequency, as well as any correlation with attenuated androgen therapy.

In our belief, TH levels might influence, even in the settings of normal thyroid function, the synthesis of complement proteins in individual patients and could thereby modulate the pathomechanism of C1-INH-HAE. The beneficial effects of the attenuated androgens used for the therapy of this disorder could affect also the synthesis of THs by augmenting the synthesis of complement proteins. THs might contribute to the finetuning or to the changes of the equilibrium among the the plasma systems involved in the pathomechanism of C1-INH-HAE.

Methods

In 2011, we conducted a case-control study at the Hungarian Angioedema Center. All 146 patients had C1-INH-HAE established by pedigree analysis and by the evaluation of the clinical manifestations and complement parameters (antigenic C1-INH [C1-INH_a], C1-INH_f, C1q, C4). Using the entries of patient diaries, we ascertained the annual numbers and locations of the attacks experienced, along with the types of therapy received, by our patients with C1-INH-HAE.

At the regular control visits (when the patients were symptom free), we determined the levels of THs (thyrotropin, FT₄, free triiodothyronine [FT₃]), the titers of thyroid antibodies (antithyroglobulin [anti-TG], anti-thyroid peroxidase [anti-TPO]),

complement levels (C4, C1-INH_a, and C1-INH_f levels), and, in a limited number of patients with C1-INH-HAE, the levels of fibrinogen, D-dimer, and prothrombin fragments 1 and 2 (F1+2). In healthy controls, we measured the levels of THs (thyrotropin, FT₄, FT₃), anti-TG, and anti-TPO. Patients younger than 16 years (*n* = 16) and those with autoimmune or clinical thyroid disease (*n* = 13) were excluded from further analysis because these patients had been discussed in a previous publication by our work group.¹⁷ Only patients and controls with TH levels within the reference range for age and clinical status were analyzed.

Thus, we studied 117 euthyroid patients with C1-INH-HAE. A total of 107 had type 1 and 10 had type 2 disease, 52 (44.4%) were male, 65 (55.6%) were female, and their mean age was 39.7 years (range, 16–81 years). All patients were free of dysalbuminemia or hyperglobulinemia or hypoglobulinemia. None of them took antidepressants, anticonvulsants, oral contraceptives containing estrogens, or anabolic steroids (except danazol) or received hormone replacement therapy. There were no pregnant women in this group.

The age- and sex-matched control group comprised 150 healthy, euthyroid individuals (70 males [46.7%] and 80 females [53.3%], with a mean age of 38.5 years [range, 16–73 years]). All the study participants had been referred for routine medical checkup and volunteered for the study by giving informed consent. The controls did not have any known disease or had not received medicinal products at the time of blood sampling. C1-INH deficiency was excluded by complement testing in all healthy individuals. The study protocol adhered to the tenets of the Declaration of Helsinki, and all participants gave written informed consent.

Laboratory Methods

We determined the levels of C1-INH_a and of C4 by radial immunodiffusion and C1-INH_f activity with an enzyme immunoassay kit (Quidel, San Diego, California). The fibrinogen level was determined with the Clauss method. We used the Liaison chemiluminescence immunoassay and a paramagnetic microparticle solid phase analyzer (Diasorin S.p.A., Saluggia, Italy) to determine thyrotropin, FT₄, FT₃, anti-TPO, and antithyroglobulin levels. Commercial kits were used to determine the concentrations of F1+2 (Enzygnost) and D-dimer (Innovance D-dimer kit) according to the manufacturer's instructions.

Statistical Analyses

Calculations were performed with the SPSS statistical software, version 20 (SPSS Inc, Chicago, Illinois). Because many variables had a nongaussian distribution, we used nonparametric tests. Independent groups were compared with the Mann-Whitney *U* test. We used the Spearman ρ coefficient to calculate correlations. In addition, χ^2 tests or Fisher exact tests were performed. All statistical analyses were 2-tailed, and *P* < .05 was considered statistically significant.

Results

Thyroid Parameters in Patients With C1-INH-HAE and in Healthy Controls

The TH levels of the 117 patients with C1-INH-HAE and of the controls are summarized in Table 1. Only individuals with TH levels within the reference range for their age and clinical status were analyzed. Thyrotropin and antithyroglobulin levels of the patients and of the controls were similar. The levels of FT₄ and FT₃ were significantly lower, whereas anti-TPO levels were significantly higher (but still within the reference range) in patients with C1-INH-HAE than in healthy controls.

Table 1
TH Levels in Patients With C1-INH-HAE and Healthy Controls

TH parameter (reference range)	Median (IQR)		Mann-Whitney U test P value
	Controls (n = 150)	Patients with C1-INH-HAE (n = 117)	
Thyrotropin, mU/L (0.3–3.6 mU/L)	1.6 (1.0–2.2)	1.5 (1.0–2.2)	.72
FT ₄ , pmol/L (10.9–21.9 pmol/L)	15.2 (13.3–17.1)	14 (12.5–16.0)	.002
FT ₃ , pmol/L (3.4–6.5 pmol/L)	5.1 (4.5–5.7)	4.6 (4.2–5.0)	<.001
Antithyroglobulin, IU/mL (5–100 IU/mL)	6 (2.0–13.5)	5 (5.0–5.3)	.22
Anti-TPO, IU/mL (1–16 IU/mL)	1.5 (0.3–4.2)	2.5 (1.5–5.2)	<.001

Abbreviations: anti-TPO, anti-thyroid peroxidase; C1-INH-HAE, hereditary angioedema due to C1-inhibitor deficiency; FT₃, free triiodothyronine; FT₄, free thyroxine; IQR, interquartile range; TH, thyroid hormone.

Association of Thyroid and Complement Parameters in Patients With C1-INH-HAE

The associations between thyroid and complement parameters detected in the same blood samples were analyzed with χ^2 tests in 115 patients with C1-INH-HAE. In the year of the study, C1-INH_f activity was unknown for 2 patients. We determined the proportion of patients with a below-median (30%) C1-INH_f level in the subset of individuals with normal, below-, or above-median FT₄ levels. The proportion of patients with a low C1-INH_f concentration was higher among those with below-median FT₄ levels than in the above-median cohort (37/58 and 24/57; $P = .02$; Pearson $\chi^2_1 = 5.429$) (Fig 1). In particular, the risk of a reduced C1-INH_f level was 2.4 times greater than that seen in patients with C1-INH-HAE with above-median FT₄ levels (odds ratio = 2.42; 95% confidence interval, 1.14–5.13). Furthermore, comparing C1-INH_a and free TH levels did not reveal any correlation ($P = .97$). We detected only a

marginal association between C4 and FT₄ levels ($P = .054$; Pearson $\chi^2_1 = 3.726$).

TH Levels of Patients with C1-INH-HAE by Number of Attacks

On the basis of the median annual attack number experienced by the 117 patients with C1-INH-HAE (median, 4 episodes per year; interquartile range, 0.5–9.0), we divided this group into 2 subsets experiencing 4 or fewer or more than 4 attacks per year. Then we analyzed the TH levels in these subsets with the Mann-Whitney U test. As indicated in Table 2, we found lower FT₄ levels in patients experiencing more (>4) attacks per year than in the other subset (≤ 4 attacks per year). Using the contingency table and the χ^2 test, we examined the proportions of patients with below- or above-median normal FT₄ levels within these 2 subsets. We found that the proportion of patients with below-median FT₄ levels (still within the reference range) was greater among those experiencing more than 4 attacks per year than among those sustaining fewer attacks (34/54 and 26/63; $P = .02$; Pearson $\chi^2_1 = 5.477$). The comparison with FT₃ levels also revealed significant differences (36/54 and 27/62; $P = .01$; Pearson $\chi^2_1 = 6.216$), whereas thyro-

TH Levels in Patients With C1-INH-HAE Treated vs Not Treated With Danazol

Among the 117 patient with C1-INH-HAE, we compared those not treated with danazol ($n = 63$) with those receiving long-term danazol prophylaxis ($n = 54$) (Table 3). The levels of FT₄ and FT₃ were significantly higher in danazol-treated patients than in those not receiving danazol (Mann-Whitney U test; $P = .02$ and $P = .01$). We also found a significant difference between the FT₄ and FT₃ levels of patients not taking danazol and of the healthy controls ($P < .001$, Fig 2). On the other hand, FT₄ and FT₃ levels were similar in danazol-treated patients and healthy controls ($P = .41$ and $P = .08$; Fig 2).

The anti-TPO levels of danazol-treated vs nontreated patients with C1-INH-HAE were significantly higher than those of the controls ($P = .001$ for both comparisons). For the levels of other TH parameters, we did not detect significant differences between patients treated or not treated with danazol.

Association Among TH Levels, D-Dimer, F1+2, and Fibrinogen in Patients With C1-INH-HAE

We measured D-dimer and F1+2 and fibrinogen levels in blood samples obtained during the symptom-free period of the same year

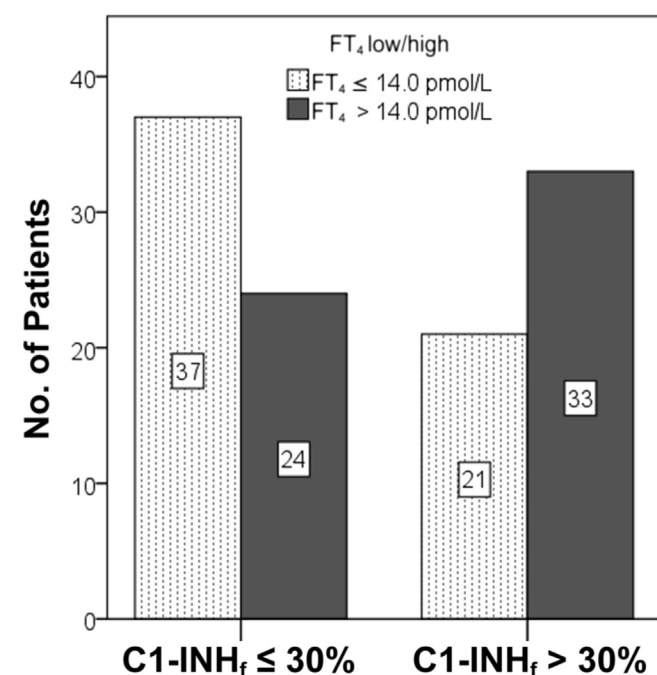


Figure 1. Below-median functional C1-inhibitor (C1-INH_f) levels in a greater proportion of patients with below-median (normal) free thyroxine (FT₄) levels.

Table 2

TH Levels of Patients With C1-INH-HAE Experiencing 4 or Fewer vs More Than 4 Attacks per Year

TH parameter (reference range)	Median (IQR)		Mann-Whitney U test P value
	Patients with ≤4 attacks per year (n = 63)	Patients with >4 attacks per year (n = 54)	
Thyrotropin, mU/L (0.3–3.6 mU/L)	1.5 (1.0–2.3)	1.4 (0.9–2.0)	.28
FT ₄ , pmol/L (10.9–21.9 pmol/L)	15.2 (12.8–16.5)	13.3 (12.1–15.0)	.01
FT ₃ , pmol/L (3.4–6.5 pmol/L)	4.8 (4.2–5.1)	4.5 (4.2–4.9)	.08
Antithyroglobulin, IU/mL (5–100 IU/mL)	5 (5.0–5.0)	5 (5.0–5.5)	.20
Anti-TPO, IU/mL (1–16 IU/mL)	2.4 (1.6–5.7)	2.6 (1.5–5.1)	.54

Abbreviations: anti-TPO, anti-thyroid peroxidase; C1-INH-HAE, hereditary angioedema due to C1-inhibitor deficiency; FT₃, free triiodothyronine; FT₄, free thyroxine; IQR, interquartile range; TH, thyroid hormone.

Table 3

TH Levels in the Subsets of Patients With C1-INH-HAE Treated vs Not Treated With Danazol

TH parameter (reference range)	Median (IQR)		Mann-Whitney U test P value
	Patients not treated with danazol (n = 63)	Patients treated with danazol (n = 54)	
Thyrotropin, mU/L (0.3–3.6 mU/L)	1.3 (0.9–2.2)	1.5 (1.1–2.2)	.36
FT ₄ , pmol/L (10.9–21.9 pmol/L)	13.4 (12.2–15.3)	15 (12.7–16.8)	.02
FT ₃ , pmol/L (3.4–6.5 pmol/L)	4.5 (4.0–4.9)	4.8 (4.3–5.2)	.01
Antithyroglobulin, IU/mL (5–100 IU/mL)	5 (5.0–5.1)	5 (5.0–5.4)	.61
Anti-TPO, IU/mL (1–16 IU/mL)	2.3 (1.5–4.5)	2.8 (1.6–6.2)	.60

Abbreviations: anti-TPO, anti-thyroid peroxidase; C1-INH-HAE, hereditary angioedema due to C1-inhibitor deficiency; FT₃, free triiodothyronine; FT₄, free thyroxine; IQR, interquartile range; TH, thyroid hormone.

from 31 of our 117 patients. Spearman correlation revealed a significant inverse association between FT₄ and D-dimer levels ($P = .02$; $R = -0.406$). Next, we examined the distribution of patients with below- or above-median FT₄ levels in subgroups divided at a 0.5- $\mu\text{g/mL}$ (upper limit of normal) D-dimer level (median, 0.6 $\mu\text{g/mL}$). According to our findings, the proportion of patients with below-median FT₄ was significantly greater among those with a high D-dimer level and the other way around (14/16 and 2/11; $P = .009$; Fisher exact test).

Grouping the patients by the levels of F1+2 and FT₄ did not reveal any significant difference. Nevertheless, the trend of the values suggests that lower FT₄ levels belong to higher F1+2 levels and vice versa. We could not find any association between fibrinogen and free TH levels, possibly because of the small number of the subjects.

Discussion

The evaluation of TH levels is complicated by many factors, as well as by their complex and diverse roles in metabolism. The symptoms of C1-INH-HAE may depend on a variety of factors. This delicate balance is maintained by the joint influence of several components. This finding is suggested by the fact that edema formation is not present permanently, and the occurrence of the edematous episodes appears unpredictable. In general, the onset of thyroid disease may lead to the worsening of the symptoms of

C1-INH-HAE, whereas its control may result in improvement.¹⁷ Therefore, checking TH levels and the periodic monitoring for antithyroid antibodies might prove useful in the follow-up of these patients.

Accordingly, we chose to study individuals with normal thyroid function. We found lower free TH levels in patients with C1-INH-HAE than in healthy controls. The reason for this observation is yet unknown. The level of anti-TPO was significantly elevated, possibly because of the enhanced humoral immune response in patients with C1-INH-HAE.^{17,28,29} On the other hand, we cannot rule out the possibility that high anti-TPO level might predict the future development of an autoimmune disorder.¹⁶

In patients with C1-INH-HAE, above-median FT₄ and FT₃ levels were associated with a reduced number of edematous episodes. Our study found above-median C1-INH_f activity in a greater proportion of patients with above-median FT₄ levels. As revealed by our previous study, C1-INH_f activity correlates with the severity of C1-INH-HAE.⁷

Our observation that patients with below-median free TH levels experience more angioedematous attacks may indicate, among other things, the activation of the fibrinolytic system, as suggested by elevated D-dimer levels. This finding is in agreement with the findings of Chadarevian et al,²⁷ who found that low-normal levels of FT₄ are associated with a hypercoagulable state and found a negative correlation between FT₄ and D-dimer.

We ascertained in our patients with C1-INH-HAE that FT₄ and FT₃ levels increase during treatment with danazol. However, the observed, danazol-induced elevation of FT₄ or FT₃ levels did not exceed the normal FT₄ or FT₃ values characteristic of the healthy controls. In the management of HAE, long-term prophylaxis with attenuated androgens is usually associated with the elevation of total protein and of various plasma protein levels, including those of some complement components.^{10,11,30} The free TH levels increase during treatment with danazol, possibly because of the anabolic effect of this drug.

We assume that the levels of free THs (which were within the reference range too) might contribute, by virtue of a subtle modulatory effect, to individual differences in the severity of C1-INH-HAE manifestations. Nevertheless, we suspect a complex association between the levels of circulating THs and of the complement or of the fibrinolytic system. Furthermore, our findings suggest a role for the endocrine system in the pathophysiology of C1-INH-HAE. Of course, additional, larger-scale, multicenter studies would greatly contribute to a more accurate characterization of the effects of THs in C1-INH-HAE, as well as to the exploration of their effect on angioedematous manifestations.

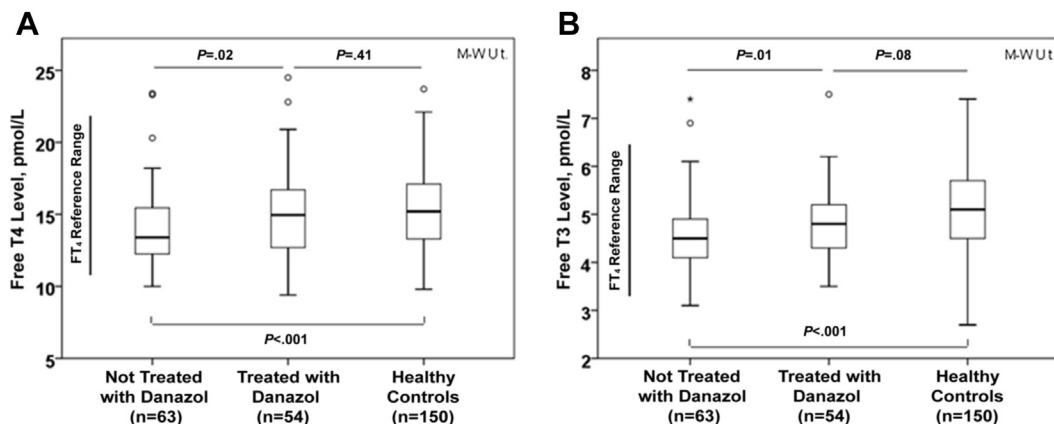


Figure 2. Thyroid hormone (free thyroxine [FT₄], free triiodothyronine [FT₃]) levels in patients treated vs not treated with danazol. The FT₄ and FT₃ levels were significantly higher in patients treated with danazol. M-W U-t indicates Mann-Whitney U test.

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