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## Original article

# Improvement of chronic idiopathic urticaria with L-thyroxine: a new TSH role in immune response?

**Background:** The association between chronic idiopathic urticaria (CIU) and autoimmune thyroiditis (AT) is known, as well as major prevalence of antithyroid antibodies in the allergical subjects and other autoimmune diseases. We have evaluated the effects of L-thyroxine on clinical symptoms of CIU in AT patients suggesting the hypothesis of a new thyroid-stimulating hormone (TSH) role in immune system.
**Methods:** In 20 female patients with CIU + AT, both hypothyroid and euthyroid, we have investigated the therapeutic effects of L-thyroxine dosed to suppress the TSH. Free-T3, Free-T4, TSH, antithyroperoxidase and antithyroglobulin antibodies, total immunoglobulin (Ig)E, Rheuma test and eritro-sedimentation rate were monitored during treatment.
**Results:** In 16 patients a strong decrease of urticaria symptoms has happened after 12 weeks. The TPO Ab and HTG Ab clearly decreased in 14 patients. Furthermore, in two patients with rheumatoid arthritis and in two patients with pollen allergy a strong decrease of rheuma test titer and total IgE has happened.
**Conclusion:** The reason of AT is associated to CIU and others allergical and autoimmune diseases is poorly known. The exclusive hormonal therapy reduces the symptoms of CIU and inflammatory response in many chronic diseases associated to AT. We suggest a stimulatory effect of TSH able to produce considerable changes of the immune response and immune tolerance in patients with AT causing target organs damage.The causal mechanism involves immune, nervous and endocrine system, sharing a common set of hormones, cytokines and receptors, in a unique totally integrated loop (the neuro–immuno–endocrine axis).

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It is well known since ancient times that alterations of psycho-physical state may condition the biological organism response. Galeno, 2000 years ago, described the existence of relationships between immune function and emotional state.

Infective, inflammatory, surgical or other stress, in living organism initiate a number of complementary events involving the *immune*, *nervous* and *endocrine* system. Physiological studies seem to indicate that the *pituitary gland* plays a unique role in the physiologic integration of the *neuro–immuno–endocrine* axis. The pituitary, as the producer of throphic hormones, such as thyroid-stimulating hormone (TSH), ACTH, HPRL, GH, etc., regulates many endocrine and nonendocrine target tissues (1–4). The *cytokines* [Interleukines (IL), Monokines, etc.] secreted by immune cells, acting as humoral signs, may communicate to the neuro–endocrine system by a regulatory feedback loop (1–5).

The association between chronic idiopathic urticaria (CIU) [duration longer than 6 weeks (6)] and autoimmune thyroiditis (AT) (hypothyroid, euthyroid or hyperthyroid) is known long before, as well as major prevalence of antithyroid antibodies in the allergical subjects and the other autoimmune diseases, compared with healthy (7–16).

An autoimmunity disorder is often indicated like common reason of CIU, AT and other diseases associated with them.

### Aim of study

The aims of our study have been: to evaluate the effects of hormonal therapy with L-thyroxine on clinical symptoms of CIU and other chronic inflammatory disease in patient with AT; to suggest a new hypothesis, according to the symptoms improvement is strictly linked to the TSH suppression able to produce considerable changes of the immune tolerance and immune response.

## Materials and methods

We have selected 20 female patients with CIU + AT. Patients with AT had antithyroglobulin or antithyroperoxidase antibody levels >250 IU/ml from more than 6 months. The food skin prick test were negative in all subjects. The patients have been subdivided in two groups: eight hypothyroid (40%) with elevated TSH (>5 IU/ml); 12 (60%) euthyroid with normal TSH (0.3–3.0 IU/ml).

Two hypothroid patients presented rheumatoid arthritis (RA) with elevated rheuma test titer (>100 IU/ml) and two patients pollen allergy (PA) with elevated immunoglobulin (Ig)E (>200 IU/ml). One euthyroid was affected by RA with elevated rheuma test titer and one PA with elevated IgE (Table 1).

We have treated the patients with increasing doses of L-thyroxine until total suppression of TSH level (<0.3 μIU/ml), that happened about after 4 weeks.

Free triiodothyronine (FT3), free thyroxine (FT4), TSH, thyroglobulin (HTG), antithyroperoxidase antibodies (AntiTPO Ab), antithyroglobulin antibodies (AntiHTG Ab), total IgE, Rheuma test and eritro-sedimentation rate (ESR) are controlled before and during treatment. FT3, FT4, TSH, Anti-TPO Ab, AntiHTG Ab were measured by Luminometric Assay, IgE by Enzyme Immuno Assay, Rheuma test by Nephelometric method. All patients were treated after 2 weeks of antihistamine washout. Clinical response was evaluated by clinical score.

Presence of symptoms was scored daily on a diary card by the patient, with a scale from 0 (none) to 3 (max) for erythema, wheals, itching and interference with sleep. Clinical check was evaluated every 4 weeks for 3 months.

### Statistical analysis

We used Student's *t*-test for paired samples to calculate *P*-values related to blood tests and clinical score. The comparison was with values before the start of therapy. *P*-value of <0.05 was considered to indicate statistical significance. All *P*-values were two-tailed.

## Results

In 16 (80%) patients (all eight patients with hypothyroidism) a strong decrease of urticaria symptoms has happened after 12 weeks. The AntiHTG Ab are significantly decreased when compared before and after treatment (401.8 ± 339.2 *vs* 199.0 ± 204.1; $P = 0.0016$), also Anti-TPO Ab (840.7 ± 900.8 *vs* 366.7 ± 501.3; $P = 0.0010$) and ESR (21.6 ± 10.9 *vs* 11.3 ± 3.4; $P = <0.0001$) (Table 2).

Two patients reported an improvement with poor decrease of antithyroid antibodies, while four euthyroid patients showed poor improvement within 12 weeks with persistent elevated antibodies. The clinical score showed a significant improvement of all symptoms as itching (2.150 ± 0.587 *vs* 1.000 ± 0.324; $P < 0.0001$), erythema (1.100 ± 0.447 *vs* 0.200 ± 0.410; $P < 0.0001$), wheals (0.350 ± 0.489 *vs* 0.000 ± 0.000; $P = 0.0047$) and interference with sleep (1.300 ± 0.571 *vs* 0.600 ± 0.503; $P < 0.0001$) (Table 3).

We have observed an important correlation between clinical improvement and decrease of ESR values and antithyroid antibodies levels.

Two patients had a recurrence of symptoms after a spontaneous stopping treatment, which resolved after treatment was restarted. Furthermore, in two patients with rheumatoid arthritis and in two with PA, both with hypothiroidism, we have observed improvement of symptoms with a strong decrease of rheuma test titer and total IgE, although the decrease of rheuma test titer has not statistical significance likely short numbers of patients (Table 2).

Table 1. Base-line characteristic of 20 patients

| Characteristic | Value |
|---|---|
| Age (years) | 36.8 ± 11.9 |
| Hypothyroid group (*n*) | 8 (40%) |
| Euthyroid group (*n*) | 12(60%) |
| Subgroups | |
| Hypothyroid with RA (*n*) | 2 |
| Hypothyroid with PA (*n*) | 2 |
| Euthyroid with RA (*n*) | 1 |
| Euthyroid with PA (*n*) | 1 |

RA, rheumatoid arthritis; PA, pollen allergy.

Table 2. Sierologic tests – mean and SD before and after 12 weeks of treatment with l-thyroxine

| | | Before | | After | | |
|---|---|---|---|---|---|---|
| Test (normal levels) | *n* | Mean | SD | Mean | SD | *P*-value |
| FT3 (1.9–3.4 pg/ml) | 20 | 2.187 | 0.185 | 2.744 | 0.304 | <0.0001* |
| FT4 (0.7–1.8 ng/dl) | 20 | 0.906 | 0.139 | 1.435 | 0.210 | <0.0001* |
| TSH (0.3–3.0 μIU/ml) | 20 | 5.298 | 3.944 | 0.173 | 0.089 | <0.0001* |
| HTG (<75 IU/ml) | 20 | 10.060 | 19.530 | 7.583 | 8.308 | 0.5447 |
| AntiHTG (<35 IU/ml) | 20 | 401.800 | 339.208 | 199.005 | 204.198 | 0.0016* |
| AntiTPO (<16 IU/ml) | 20 | 840.735 | 900.864 | 366.795 | 501.385 | 0.0010* |
| Rheuma test (<15 IU/ml) | 3 | 154.333 | 90.091 | 23.633 | 20.448 | 0.1691 |
| IgE (<20 IU/ml) | 20 | 66.800 | 91.524 | 28.820 | 26.407 | 0.0321* |
| ESR (<15 mm) | 20 | 21.650 | 10.999 | 11.300 | 3.450 | <0.0001* |

*Statistical significance.
TSH, thyroid-stimulating hormone; HTG, thyroglobulin; AntiHTG, antithyroglobulin; AntiTPO, antithyroperoxidase; IgE, immunoglobulin E; ESR, eritro-sedimentation rate.

Table 3. Clinical score – mean and SD before and after 12 weeks of treatment with l-thyroxine

| | | Before | | After | | |
|---|---|---|---|---|---|---|
| | *n* | Mean | SD | Mean | SD | *P*-value |
| Itching | 20 | 2.150 | 0.587 | 1.000 | 0.324 | <0.0001* |
| Erythema | 20 | 1.100 | 0.447 | 0.200 | 0.410 | <0.0001* |
| Wheals | 20 | 0.350 | 0.489 | 0.000 | 0.000 | 0.0047* |
| I.W-Sleep | 20 | 1.300 | 0.571 | 0.600 | 0.503 | <0.0001* |

*Statistical significance.

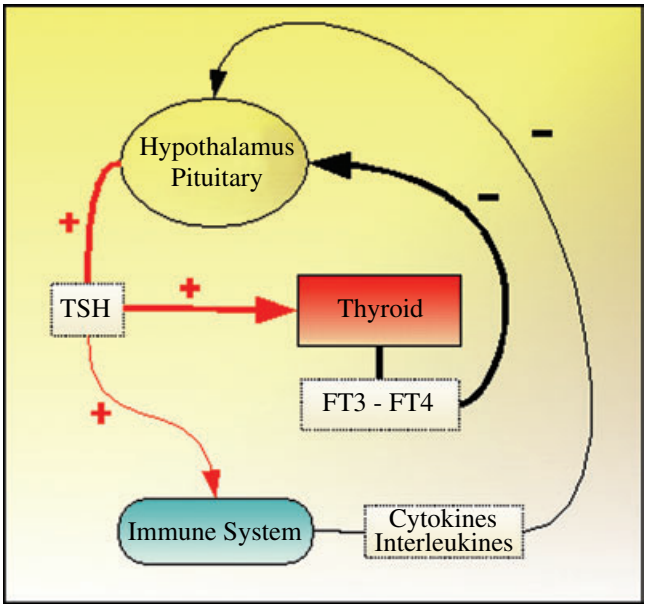


*Figure 1.* Feedback in healthy subject (*Red lines = stimulatory – Black lines = inhibitory – Line thickness = stimulatory or inhibitory grade*).

## Discussion

It is already clearly documented the bidirectional relation between *immune* and *neuro–endocrine* system. The two systems are a totally integrated loop, sharing a common set of *hormones*, *cytokines* and *receptors* (1, 2, 4–5, 7–17).

Several cytokines [IL-1, IL-2, IL-6, TNFα, INFγ, Thimic hormones, leukotrienes (LT), prostaglandins (PG), etc.] are able to modulate the secretion and the release of hormones by hypothalamus, pituitary and peripheral tissues, where specific receptors for these cytokines are present (1–4, 18–19).

On the contrary, immune cells [T and B lymphocytes, dendritic cells (APC), monocytes, thymocytes and splenocytes] express receptors for various kinds of messengers, such as: hormones (TRH, TSH, ACTH, GH, HPRL, sex hormone, corticosteroids), neuro-transmitters, cytokines, growth factors modulating their trophism and cytokines secretion (1–4).

Several authors have documented in their studies:

1. the expression of TSH, TRH, HPRL and other hormone receptors on the cellular components of the immune system (1–4),

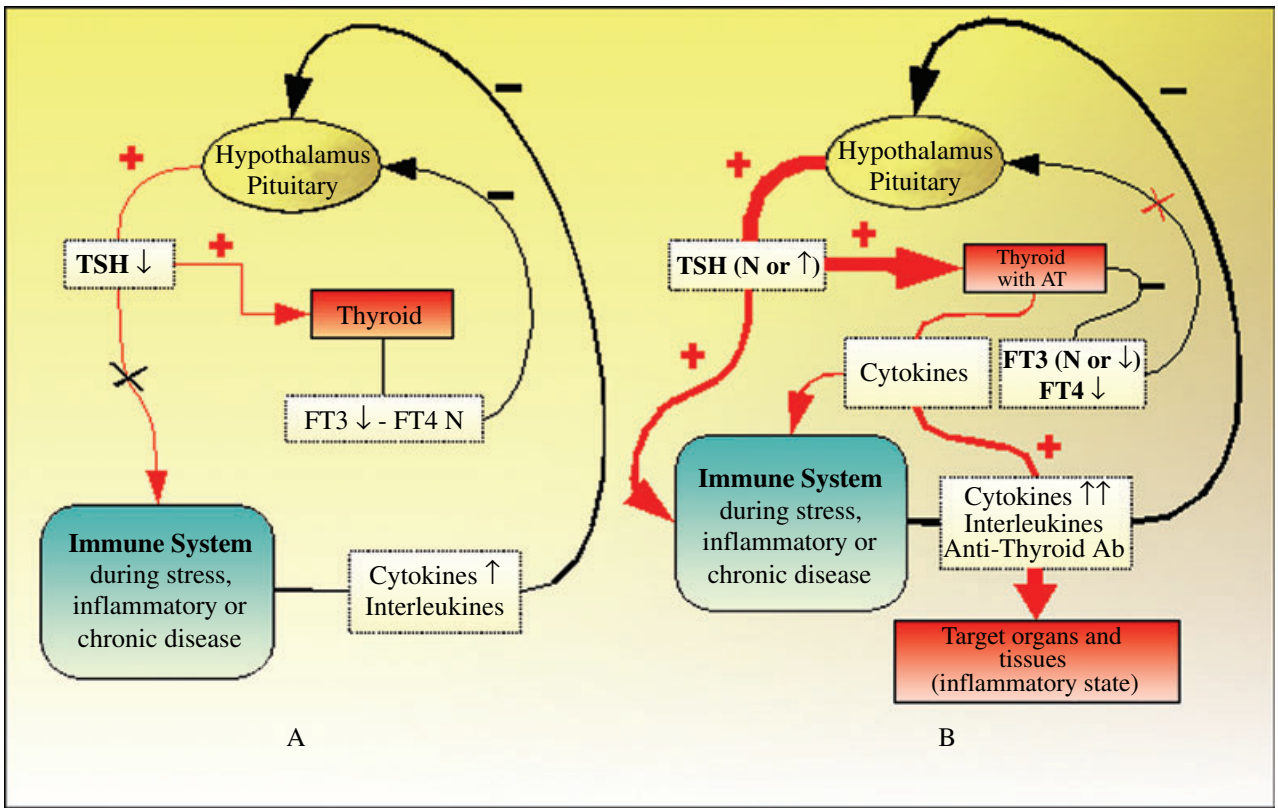


*Figure 2.* (A) Feedback in subject with inflammatory stress or chronic disease (*nonthyroidal illness – euthyroid sick syndrome*) (B) A normal feedback in same subject with autoimmune thyroiditis (*Red lines = stimulatory – Black lines = inhibitory – Line thickness = stimulatory or inhibitory grade*).

2. the capability of human peripheral mononuclear cells, monocytes, splenocytes to release a high amount of TSH treated with TRH (1, 2, 4),
3. the expression of cytokines receptors (especially IL-1, IL-2, IL-6, TNFα, INFγ, LT, PG) in CNS hypothalamic–pituitary axis with TRH-TSH inhibitory effects and CRH-ACTH stimulatory effects (1–4, 17, 18, 20–22) and
4. the proof of TSH (dose-dependent) and also HPRL stimulatory effect on the interleukines(IL-1, IL-2, IL-6, IL-12) and other messengers release by lymphocytes and dendritic cells (especially IL-2), involved in the amplification of immune response. IL-2 has shown multiple immunoregolatory properties. It is known as a major T cell growth factor, enhances natural killer cell (NK) and lymphokine-actived killer cell (LAK) activities (2–4, 23–26).

These evidences suggest that TSH has many of qualities of a cytokine and can regulate the immune response mainly by a direct T cell, B cell and dendritic cell activation (2–4, 27, 28). This stimulatory effect, amplified in AT patients, determines the continual release in circulation of various interleukines and cytokines (especially IL-2) by immune cells both of inflamed thyroid and other tissues, that could cause an inflammatory state of target organs such as skin, muscles, nervous system, heart, joints, eyes and bone marrow.

These data suggest that the IL and other cytokine receptors of CNS hypothalamic–pituitary axis could be normally the central site of a long feedback between cytokines and TSH (Fig. 1).

In many diseases or situations of inflammatory and noninflammatory stress (cardiac, renal, postsurgical, etc.) with healthy thyroid (nonthyroidal illness, euthyroid sick syndrome), this feed-back determines a (29–32) decrease of TSH and FT3, because of inhibition of hypothalamic–pituitary–thyroid (HPT) axis (Fig. 2A) and at same time the stimulation of hypothalamic–pituitary–adrenal (HPA) axis.

While in same patients with also AT, both hypothyroid (TSH increase) and euthyroid (inclined to increase TSH – subclinical hypothyroidism), the stimulation of TSH and also HPRL towards cytokines overcomes the inhibition of cytokines towards TSH, mainly because of thyroid hormones deficit (Fig. 2B). This altered feedback could cause CIU and other organs damage by means of immuno-tolerance alteration.

## Conclusion

Many clinical and experimental studies and also our observations suggest an important association between the CNS–hypothalamic–pituitary–thyroid function and the immune state. Therefore, the thyroid functionality and antithyroid antibodies, including antiTSH-receptor Ab, should be evaluated in all patients with CIU and other autoimmune or chronic inflammatory diseases. The thyroid hormonal therapy, mainly by a TSH suppression, can result effective to reduce the symptoms of CIU and inflammatory response in many chronic disease associated to AT in hypothyroid and euthyroid patients (33–35).

Further studies are required to evaluate the role of the other CNS–hypothalamic–pituitary hormones involved in immune response.

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