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Myo-inositol and selenium reduce the risk of developing overt hypothyroidism in patients with autoimmune thyroiditis

S.M. FERRARI[1], P. FALLAHI[1], F. DI BARI[2], R. VITA[2], S. BENVENGA[2,3], A. ANTONELLI[1]

[1]Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy
[2]Department of Clinical and Experimental Medicine, Endocrinology Section, University of Messina, Messina, Italy
[3]Interdepartmental Program of Molecular and Clinical Endocrinology, and Women's Endocrine Health, University Hospital, Policlinico G. Martino, Messina, Italy

Abstract. – OBJECTIVE: The beneficial effects obtained by myo-inositol in association with seleno-methionine in patients affected by subclinical hypothyroidism have been recently demonstrated. Here, we evaluate the immune-modulating effect of myo-inositol in association with seleno-methionine in patients with euthyroid autoimmune thyroiditis (AT).

PATIENTS AND METHODS: Twenty-one consecutive Caucasian patients with newly diagnosed euthyroid chronic AT were evaluated. All subjects were treated with myo-inositol in association with selenium (600 mg/83 μg) tablets, twice per day, for six months. A complete thyroid assessment was done before the treatment, and after six months.

RESULTS: After the treatment thyroid-stimulating hormone (TSH) levels significantly declined with respect to basal values, overall in patients with an initial TSH value in the high normal range (2.1<TSH<4.0), suggesting that the combined treatment can reduce the risk of a progression to hypothyroidism in subjects with autoimmune thyroid diseases (AITD). We found that after the treatment antithyroid autoantibodies levels declined. Moreover, the immune-modulatory effect was first confirmed by the fact that after the treatment CXCL10 levels declined, too.

CONCLUSIONS: We first show an immune-modulatory effect of myo-inositol in association with seleno-methionine in patients with euthyroid AT. Further studies are needed to extend the observations in a large population, to evaluate the effect on the quality of life, and to study the mechanism of the effect on chemokines.

Key Words:
Myo-inositol, Selenium, CXCL10, Chronic autoimmune thyroiditis, Hypothyroidism, AbTg, AbTPO.

Introduction

Myo-inositol and phosphatidylinositol(s) play an important function in many metabolic pathways, that, when impaired, exert negative effects in humans[1].

Myo-inositol (an isomer of a C6 sugar alcohol) is the precursor for the synthesis of phosphoinositides, that are involved in the phosphatidylinositol (PtdIns) signal transduction pathway[1], and it has a determinant role in different cellular processes.

For example, myo-inositol-PtdIns are responsible for the signal transduction across the plasma membrane, via the second messenger (inositol 1,4,5-triphosphate) that is involved in the intracellular Ca^{2+} release, and it is a docking site for many signal-transduction proteins[2].

Several experimental researches and clinical trials have shown that myo-inositol and phosphatidylinositol(s) are involved in physiological and pathological conditions of the thyroid gland. Phosphatidylinositol is important in the intracellular signaling associated with thyroid-stimulating hormone (TSH) signaling in the thyroid cells[3]. TSH intracellular signaling involves two different signals: a) on one side the signal cascade involves as second messenger cyclic AMP (cAMP), that is involved in T4, T3 secretion, and in cell growth and differentiation; b) the other branch is inositol dependent[4,5], and regulates H_2O_2 mediated iodination[4]. It has been demonstrated that low TSH concentrations can stimulate cAMP signaling cascade, while only 100-fold higher TSH concentrations can stimulate the inositol-mediated pathway[6].

Corresponding Author: Alessandro Antonelli, MD; e-mail: alessandro.antonelli@med.unipi.it

Phosphatidylinositol is involved in thyroid autoimmunity[7,8]. Moreover, phosphatidylinositol is influenced by the disorders in function of some receptors, such as those of TSH receptor (TSHR), insulin, or insulin-like growth factor-1 (IGF-1R), and it is connected with the association between hypothyroidism, and high serum TSH, on one side, and insulin resistance (IR), on the other side. Phosphatidylinositol dysfunctions have been shown in metabolic syndrome [diabetes, polycystic ovary syndrome (PCOS)], IR, autoimmunity and some kinds of cancer[9-16].

It has been shown that iodine and selenium have an important role in thyroid autoimmunity[17,18]. In regions with severe selenium deficiency, there is an increased prevalence of autoimmune thyroiditis (AT). This effect is due to a decreased activity of selenium-dependent glutathione peroxidase activity within thyroid cells; moreover, selenium-dependent enzymes are also important in regulating the immune system. Several studies[19-21] have demonstrated that even mild selenium deficiency may contribute to the development and maintenance of autoimmune thyroid diseases (AITD).

Because of the pathogenetical link of AITD with environmental conditions that may trigger intrathyroidal oxidative stress[22] and because of the antioxidant property of selenium[19], some studies[19] have been conducted on AITD patients supplemented with sodium selenite or selenomethionine using the decrease of AbTPO levels as the outcome.

Recently, it has been demonstrated the beneficial effects obtained by myo-inositol in association with seleno-methionine in patients affected by subclinical hypothyroidism[23].

Here, we evaluate the immune-modulating effect of myo-inositol in association with seleno-methionine in patients with euthyroid AT.

Patients and Methods

Patients

We enrolled 21 consecutive Caucasian outpatients with recently diagnosed euthyroid chronic AT (Table I). General doctors and other hospitals directed to our attention the patients with serum thyroid autoantibodies, or clinical suspicion of a thyroid disorder. The clinical presentation (presence of a firm goiter, that varies from a small to a very large size, and with a lobulated surface), thyroid hormones and autoantibodies levels, and/or thyroid ultrasonography (decreased, dyshomogeneous echogenicity) permitted to establish the diagnosis of AT[24-26]. Almost all subjects showed a normal thyroid volume, some had a goiter (24%) or hypotrophic thyroiditis (5%). Fine-needle aspiration (FNA) was performed in few patients (5%) to rule out the presence of thyroid cancer or lymphoma, and cytology confirmed a lymphocytic infiltration.

Exclusion Criteria for Patients

Exclusion Criteria: a) the presence of anti-TSH receptor antibodies; b) clinical history of hyperthyroidism or hypothyroidism; c) evidence of infectious diseases in the last three months; d) therapy with drugs interfering with immune system, as cytokines, interferon (IFN), corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), amiodarone, lithium; e) pregnancy and lactation over the previous 6 months; f) presence of acute or chronic systemic diseases.

The study was approved by the local Ethical Committee and the patients gave their informed consent to it.

All subjects were treated with myo-inositol in association with selenium (600 mg/83 μg) tablets, twice per day, for six months.

A complete thyroid assessment was done before the treatment, and after six months.

Ultrasonography of the Neck and FNA

Neck ultrasonography was done with a probe (Esaote, Florence, Italy; AU5 with a sectorial 7.5 MHz transducer) by the same operator, who did not know the levels of thyroid hormones, autoantibodies and CXCL10. Thyroid volume was determined by the ellipsoid formula[26]. Hypoechoic and dyshomogeneous echogenicity was arbitrarily ranked according to: (0=normal echogenicity; 1=slight hypoechoic and dyshomogeneous; 2=se-

Table I. Thyroid status of patients with autoimmune thyroiditis.

Thyroiditis	
n	21
Age (years)	48 ± 12
Gender (M/F)	5/16
Thyroid volume (mL)	13 ± 11
Hypoechoic (%)	74
Hypervascular (%)	32
Serum TSH (μIU/mL)	2.01 ± 0.86
AbTPO (IU/mL)	360 ± 339
AbTg (IU/mL)	361 ± 459
Serum CXCL10 (pg/mL)	144 ± 54

Thyroid peroxidase antibodies, AbTPO; thyroglobulin antibodies, AbTg; thyroid-stimulating hormone, TSH.

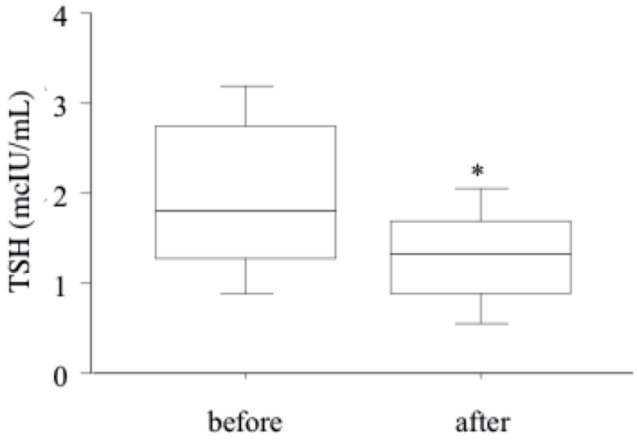

Figure 1. After the treatment TSH levels significantly declined with respect to basal values (1.355±0.703, vs. 2.010±0.867, μIU/mL, respectively) (ANOVA, $p<0.05$). The box indicates the lower and upper quartiles and the central line is the median value; the horizontal lines at the end of the vertical lines are the 2.5% and 97.5% values.

verely hypoechoic and dyshomogeneous) to investigate structural thyroid abnormalities linked to thyroid autoimmunity[26]. The presence of thyroid nodules was registered, and ultrasonography-guided FNA was done by the same operator in the ones with a diameter >10 mm, by a free-hand method[26].

Thyroid Blood Flow (TBF)

Color-flow Doppler (CFD) was investigated in all subjects[26] and classified into: normal (or type 0), TBF limited to peripheral thyroid arteries; type I, TBF mildly increased; type II, TBF clearly increased; or type III, TBF markedly increased[26]. No relation between TBF and the thyroid status was evidenced in AT patients; 58% of subjects had TBF type 0, 34% type I, 8% type II, while none had type III CFD pattern[27].

Laboratory Evaluation

Thyroid function and autoantibodies were evaluated[26]. Serum free triiodothyronine (FT3), free thyroxine (FT4) were assayed by commercial RIA kits (AMERLEX-MAB FT3/FT4 Kit; Amersham Biosciences, Little Chalfont, UK). Serum TSH (DiaSorin, Saluggia, Italy), thyroid peroxidase antibodies (AbTPO) and thyroglobulin antibodies (AbTg) (ICN Pharmaceuticals, Costa Mesa, CA, USA) were measured by IRMA assay. Positivity for AbTg and AbTPO was established at >50 and >50 IU/mL, respectively[28].

Serum CXCL10

Serum CXCL10 was measured by a quantitative sandwich immunoassay [enzyme-linked immunosorbent assay (ELISA); R&D Systems, Inc., Minneapolis, MN, USA]: sensitivity 0.41-4.46 pg/mL; mean minimum detectable dose 1.67 pg/mL; intra- and inter-assay coefficients of variation 3.0% and 6.9%[29,30]. The reference range in the normal population was 90±51 pg/mL[29].

Statistical Analysis

Values are expressed as mean±SD for normally distributed variables, otherwise as median and [interquartile range]. Mean group values were compared by one-way analysis of variance (ANOVA) for normally distributed variables, or Mann-Whitney U or Kruskal-Wallis test. X^2-test was used to compare proportions, while the Bonferroni-Dunn test for post-hoc comparisons on normally distributed variables.

Results

The demographic and clinical features of patients are reported in Table I. All patients had TSH, *FT3*, FT4, in the euthyroid range, all had circulating antithyroid autoantibodies, and most of them a thyroid hypoechogenicity. The mean CXCL10 level was significantly high (with respect to the reference range of the normal population)[29].

After the treatment, TSH levels significantly declined with respect to basal values (1.355±0.703, *vs.* 2.010±0.867, μIU/mL, respectively; ANOVA, $p<0.05$) (Figure 1). The decline was higher in AT patients with an initial TSH value in the high normal range (2.1<TSH<4.0), than in patients with a low normal TSH (0.8<TSH<2.0) (ANOVA, $p<0.05$).

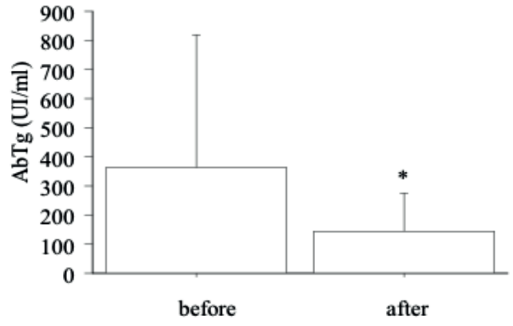

Figure 2. After the treatment AbTg levels significantly declined with respect to basal values (141±136, vs. 361±459, IU/mL, respectively; ANOVA, $p<0.05$).

FT4 and FT3 levels were not significantly changed ($p>0.05$) after, *vs.* before, the treatment in the whole group, such as in AT subgroups with an initial TSH value in the high normal range (2.1<TSH<4.0), or in patients with a low normal TSH (0.8<TSH<2.0).

After the treatment, AbTg levels significantly declined (Figure 2) with respect to basal values (141±136, *vs* 361±459, IU/mL, respectively; ANOVA, $p=0.041$). Also in this case, the decline was higher in AT patients with a higher initial AbTg value (AbTg>200 UI/mL), than in patients with a lower AbTg level (AbTg<199 UI/mL) ($p<0.05$).

After the treatment, AbTPO levels (Figure 3) declined, too, even if not significantly ($p>0.05$), with respect to basal values (197±251, *vs.* 360±339, IU/mL, respectively; ANOVA, $p=0.849$). The decline was not significantly different in AT patients with a higher initial AbTPO value (AbTPO>200 IU/mL), than in patients with a lower AbTPO level (AbTPO<199 IU/mL).

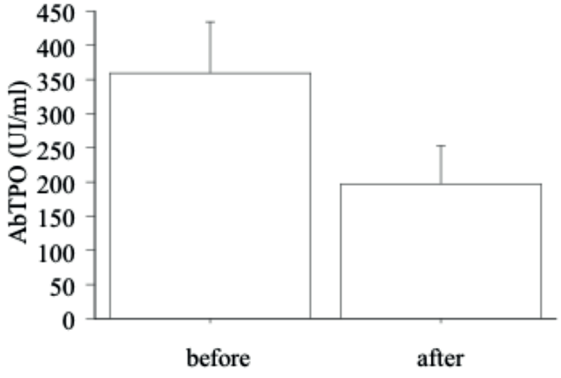

Figure 3. After the treatment AbTPO levels declined, even if not significantly, with respect to basal values (197±251, vs. 360±339, IU/mL, respectively; ANOVA, $p=0.849$).

After the treatment, CXCL10 levels (Figure 4) declined, too, even if not significantly, with respect to basal values (114±46, *vs.* 144±54, pg/mL, respectively; $p=0.061$). The decline was not significantly different in AT patients with a higher initial CXCL10 value (CXCL10>150 pg/mL), than in patients with a lower CXCL10 (CXCL10<149 pg/mL).

No significant differences were noticed considering the presence of goiter, atrophic thyroiditis, or the presence of hypoechogenicity, or hypervascularity, before and after the treatment (data not shown).

Discussion

This study demonstrates that myo-inositol and selenium reduce the risk of developing overt hypothyroidism in patients with AT, and it first shows an immune-modulatory effect of myo-inositol in association with seleno-methionine in patients with euthyroid AT. After the treatment, TSH levels significantly declined with respect to basal values, overall in patients with an initial TSH value in the high normal range (2.1<TSH<4.0). FT4 and FT3 levels were not significantly changed. Moreover, after the treatment, AbTg levels significantly declined with respect to basal values, and AbTPO levels declined, too, even if not significantly. The immune-modulatory effect was confirmed by the fact that, after the treatment, CXCL10 levels declined, too.

Several studies[31] found decreased serum selenium levels in Hashimoto thyroiditis, Graves' disease and in thyroid-associated ophthalmopathy patients, the levels being related to the outcome. Furthermore, other studies[32] (with low numbers of cases) indicate that selenium supplementation in autoimmune thyroiditis and mild Graves' disease improves clinical scores and reduces the titer of AbTPO. However, published results are still conflicting.

Our results were in agreement with the observation of other studies. Nordio et al[23] aimed to investigate the effectiveness of the combination of myo-inositol and seleno-methionine, in patients with subclinical hypothyroidism, in a double-blind randomized controlled trial. Forty-eight women with subclinical hypothyroidism and high circulating AbTg (>350 IU/mL) were treated. Patients were randomized: 1- group A comprised 24 subjects administered with oral 83 μg selenium/day, in soft gel capsule; 2- group B was consti-

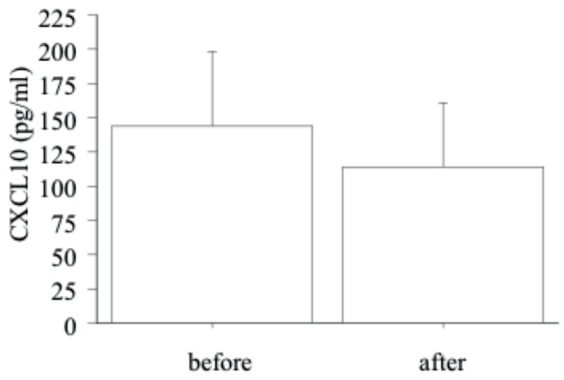

Figure 4. After the treatment CXCL10 levels declined, even if not significantly, with respect to basal values (114±46, vs. 144±54, pg/mL, respectively; ANOVA, p=0.061).

tuted by 24 patients receiving a combined treatment myo-inositol 600 mg plus 83 μg selenium (oral soft gel capsule, for 6 months). Outcome measures were TSH, AbTPO and AbTg levels, myo-inositol, and selenium plasma concentration. It was shown that the good action derived from the therapy with seleno-methionine in patients with subclinical hypothyroidism, probably due to the presence of AbTPO and AbTg, is strongly improved by the combination with myo-inositol. TSH levels significantly declined in-group B by 31% (4.4±0.9 *vs.* 3.1±0.6 mIU/mL, p<0.01), while no change was observed in-group A. AbTPO and AbTg levels significantly declined in both groups. AbTg declined below the threshold in 11 patients in therapy with myo-inositol plus seleno-methionine, *vs.* 3 patients in group A. In these subjects, the thyroid ultrasonography evidenced a normalized echogenicity[23].

Morgante et al[33] evaluated the prevalence of subclinical thyroid dysfunction in infertile PCOS patients, and whether insulin sensitizers in insulin resistant PCOS patients may improve thyroid function after 6 months of treatment. PCOS patients had a significantly higher prevalence of subclinical thyroid dysfunction, overall overweight and obese PCOS patients, as insulin resistant PCOS patients. Six months treatment with insulin sensitizers significantly reduced TSH levels in insulin resistant PCOS patients.

Our results are in agreement with the above-mentioned studies, and suggest that myo-inositol in association with seleno-methionine in patients with euthyroid AT, reduces TSH levels significantly with respect to basal values, overall in patients with an initial TSH value in the high normal range. It is well known that a TSH value in the high normal range is an important risk factor for the development of a subsequent hypothyroidism; so our results suggest that the combined treatment can reduce the risk of a progression to hypothyroidism in subjects with AITD.

The myo-inositol beneficial effect on TSH is explained by its biological role in the TSH hormone signaling. In fact, inositol regulates the H_2O_2-mediated iodination[4] and it has been demonstrated that the impairment of inositol-depended TSH signaling pathway can cause TSH resistance, and hypothyroidism[5]. For this reason, the therapy can increase the amount of the second messenger, improving the TSH sensitivity.

We also confirmed that, after the treatment, antithyroid autoantibodies levels declined. Moreover, the immune-modulatory effect was confirmed by the fact that, after the treatment, CXCL10 levels declined, too.

The IFN-γ-inducible protein 10 (IP-10, also called CXCL10) was at first recognized as an IFN-γ-induced chemokine. CXCL10 binds to chemokine (C-X-C motif) receptor 3 (CXCR3), contributing to the pathogenesis of various autoimmune diseases, organ specific (i.e. Graves' disease and ophthalmopathy, type 1 diabetes), or systemic (i.e. mixed cryoglobulinemia, systemic lupus erythematosus, Sjogren syndrome, or systemic sclerosis). The secretion of CXCL10 by CD4+, CD8+, and natural killer (NK) depends on IFN-γ. Stimulated by IFN-γ, CXCL10 is secreted by thyrocytes. Hence, high CXCL10 levels in peripheral fluids is a marker of a T helper (Th)1 orientated immune response. Patients with AT have high serum CXCL10, in particular, it is significantly higher in the ones with a hypoechoic ultrasonographic pattern (a sign of a more severe lymphomonocytic infiltration), and in those with hypothyroidism. Therefore, it is assumed that CXCL10 could be a marker of a stronger and more aggressive inflammatory response in the thyroid, causing then thyroid destruction and hypothyroidism[29,34-39].

The immune-modulatory effect of the combination on CXCL10 suggests that myo-inositol and selenium are able to modulate the Th1 immune response, and advocates for future studies in autoimmune disorders associated with a predominant Th1 immune response; mechanisms remain to be investigated[40,41].

Interestingly, it has been recently shown that Th2 cytokines increase the release of inflammatory cytokines in bronchial epithelial cells, in the presence of rhinovirus infection. This increase was independent of effects of virus replication.

Moreover, inhibition of the PI3K pathway inhibited CXCL10 expression[42].

Conclusions

We first show the myo-inositol beneficial, and immune-modulatory, effect in patients with euthyroid AT. After the treatment, TSH levels significantly declined with respect to basal values, overall in patients with an initial TSH value in the high normal range (2.1<TSH<4.0), suggesting that the combined treatment can reduce the risk of a progression to hypothyroidism in subjects with AITD. We also confirmed that, after the treatment, antithyroid autoantibodies levels declined. Moreover, the immune-modulatory effect was first confirmed by the fact that after the treatment CXCL10 levels declined, too. Further studies are needed to extend the observations in a large population, and to evaluate the effect on the quality of life. Furthermore, other studies are needed to study the mechanism of the effect on chemokines.

Disclosure

S.B. has been an invited speaker for Lo.Li Pharma. Lo.Li Pharma provided us with pure myo-inositol, but had no role in the design, conduction of the experiments, their interpretation and writing of the manuscript.

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Nothing to declare

Conflict of interest

The authors declare no conflicts of interest.

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