Myo-inositol and selenium in subclinical hypothyroidism

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ABSTRACT — OBJECTIVE: *Here we report our experience of treatment with myo-inositol (Myo-Ins) in association with selenium (Se) in patients affected by subclinical hypothyroidism and autoimmune thyroiditis (AT).*

PATIENTS AND METHODS: *This is a retrospective evaluation of patients (n=26) with slight subclinical hypothyroidism [thyroid-stimulating hormone (TSH) between 3.5 and 6.5 mcIU/ml] treated with Myo-Ins 600 mg in association with Se (83 mcg) tablets, twice per day, in the last 4 years, with respect to a control group of patients (n=15) with slight subclinical hypothyroidism not treated in the same period. A complete thyroid assessment was done before the treatment, and after six months, in treated patients and controls.*

RESULTS: *After the treatment, TSH levels significantly declined with respect to basal values (5.12±0.87, vs. 3.93±1.19, mcIU/ml, respectively; p=0.002), in patients treated with Myo-Ins+Se, and in 46% of cases it reached the normal range. Furthermore, after the treatment, antithyroid autoantibodies levels declined. Moreover, the immune-modulatory effect was first confirmed by the fact that after the treatment chemokine (C-X-C motif) ligand (CXCL)10 levels declined, too. No significant modifications of TSH, thyroglobulin antibodies (AbTg), thyroid peroxidase antibodies (AbTPO), or CXCL10 levels, and of the other studied parameters, were observed in the control patients with subclinical hypothyroidism not treated.*

CONCLUSIONS: *The results of the present study show an improvement of thyroid function in patients with subclinical hypothyroidism and in presence of AT, treated with Myo-Ins in association with Se. After the treatment, TSH levels significantly declined with respect to basal values, and in 46% of cases it reached the normal range. We confirmed also 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 large population.*

KEYWORDS
Subclinical hypothyroidism, Autoimmune thyroiditis, Myo-inositol, Selenium, CXCL10, Antithyroglobulin antibody, Antithyroperoxidase antibody, Hashimoto's thyroiditis.

INTRODUCTION

Selenium (Se) and myo-inositol (Myo-Ins) play an important role in thyroid function, and autoimmunity. Se is a chemical element whose traces are present in the form of the amino acid selenocysteine in selenoproteins. The selenoproteins have many physiological effects on human health, many of which are involved in the regulation of the reduction-oxidation processes. Glutathione peroxidase (GPx) and thioredoxin reductase (TRx), that belong to the selenoenzyme families,

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are indeed able to act as antioxidants then preserving cells from oxidative damage. Another group of selenoproteins are the iodothyronine deiodinase enzymes (DIO), that regulate thyroid hormones metabolism by catalyzing the conversion of thyroxine (T4) in triiodothyronine (T3)[1]. Because of the pivotal role covered by Se in GPx, TRx and DIO, its concentration in thyroid tissue are higher respect to that present in other districts of the body. A deficiency of Se is linked with sub-optimal thyroid function and has been demonstrated to be a risk factor for Graves' disease (GD) and Hashimoto's thyroiditis (HT). Several studies have shown that a therapy with Se could be useful in reducing thyroid antibodies, however few data is available about its impact on clinical outcomes. Se also has a useful role in altering disease progression and in ameliorating ophthalmic symptom in GD, and in particular in Graves' ophthalmopathy (GO)[2,3]. Myo-Ins is the precursor for the synthesis of phosphoinositides, involved in the phosphatidylinositol (PtdIns) signal transduction pathway[4], and it plays a decisive role in several cellular processes. For instance, Myo-PtdIns leads to the signal transduction across the plasma membrane, via the second messenger (inositol 1,4,5-triphosphate) that causes an intracellular Ca^{2+} release, and it is a docking site for several proteins involved in the signal-transduction[5]. Myo-Ins and PtdIns exerted a significant role in several metabolic pathways, that if impaired have a negative effects in humans[4]. The involvement of Myo-Ins and PtdIns in the physiological and pathological conditions of the thyroid gland has been demonstrated by many experimental researches and clinical trials. In the thyroid cells PtdIns is involved in the intracellular signaling associated with thyroid-stimulating hormone (TSH) signaling[6]. Two different signals are related to the TSH intracellular signaling, one involving a second messenger cyclic AMP (cAMP) that is implicated in T4, T3 secretion, and in cell growth and differentiation; the other is inositol dependent[7,8], regulating H_2O_2 mediated iodination[7]. It has been shown that cAMP signaling cascade is stimulated by low TSH concentrations, whereas the inositol-mediated pathway is stimulated by 100-fold higher TSH concentrations[9]. PtdIns is involved in thyroid autoimmunity[10, 11]. In addition, PtdIns is influenced by the disorders in function of some receptors, for instance those of TSH receptor (TSHR), insulin, or insulin-like growth factor-1 (IGF-1R), and it is linked with the association between hypothyroidism, and high serum TSH, on one side, and insulin resistance (IR), on the other side. PtdIns dysfunctions have been demonstrated in several disorders including the metabolic syndrome [diabetes, polycystic ovary syndrome (PCOS)], IR, autoimmunity and some types of cancer[12-15]. The beneficial effects achieved by Myo-Ins plus Se have been recently showed in patients with subclinical hypothyroidism[16], as well as their immune-modulating effect in patients with euthyroid autoimmune thyroiditis (AT)[17]. Here we report our experience of treatment with Myo-Ins in association with Se in patients affected by subclinical hypothyroidism and AT.

PATIENTS AND METHODS

Design of the Study

This is a retrospective evaluation of patients with slight subclinical hypothyroidism treated with Myo-Ins+Se in the last 4 years, with respect to a control group of patients with slight subclinical hypothyroidism not treated in the same period.

Patients Treated with Myo-Ins+Se

Twenty-six consecutive Caucasian outpatients with recently diagnosed subclinical hypothyroidism and chronic AT (Table 1) were treated with Myo-Ins+Se. The diagnosis of AT has been made according to the clinical presentation including the presence of a firm goiter, varying 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)[18,19]. A slight subclinical hypothyroidism was diagnosed in presence of TSH circulating values comprised between 3.5 and 6.5 mcIU/ml, normal free thyroxine (FT4), and free triiodothyronine (FT3) levels (Table 1). All subjects were treated with Myo-Ins 600 mg in association with Se (83 mcg) tablets, twice per day, for six months.

Controls

Fifteen consecutive Caucasian outpatients with recently diagnosed subclinical hypothyroidism and chronic AT (Table 1) were not treated. A slight subclinical hypothyroidism was diagnosed in presence of TSH circulating values comprised between 3.5 and 6.5 mcIU/ml, and normal FT4, and FT3 levels. The diagnosis of AT was established as previously reported[18,19] (Table 1).

Exclusion Criteria for Patients and Controls

Subjects were excluded from the study if having anti-TSH receptor antibodies or a clinical history of hyperthyroidism; if in therapy with drugs interfering with immune system, [such as cytokines, interferon (IFN), corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), amiodarone, lithium]; in case of pregnancy and lactation over the previous 6 months; and in the presence of acute or chronic systemic diseases and of infectious diseases in the last three months.

Table I. Thyroid status of patients treated with Myo-Ins+Se, and controls.

	Myo-Ins+Se	Controls	*p*
n	26	15	
Age (years)	55 ± 14	59 ± 15	ns
Gender (M/F)	5/21	2/13	ns
Thyroid volume (ml)	10 ± 7	12 ± 9	ns
Hypoechoic (%)	78	81	ns
Hypervascular (%)	42	35	ns
Serum TSH (mcIU/ml)	5.12 ± 0.87	4.86 ± 0.92	ns
AbTPO (IU/ml)	318 ± 324	289 ± 435	ns
AbTg (IU/ml)	295± 391	314 ± 371	ns
TRAb (IU/ml)	0	0	ns
AbTPO positivity (%)	87	79	ns
AbTg positivity (%)	74	71	ns
CXCL10 (pg/ml)	152 ± 57	163± 76	ns

Antithyroperoxidase antibody = AbTPO; Antithyroglobulin antibody = AbTg; Thyroid-stimulating hormone = TSH.

The study was conducted in accordance with the Ethical principles of the Declaration of Helsinki and national laws; the patients gave their informed consent[20].

Timing

A complete thyroid assessment was done for patients and controls at the first observation, and after six months, by the following procedures.

Ultrasonography of the Neck and Fine Needle Aspiration

A single operator performed the neck ultrasonography using a probe (Esaote, Florence, Italy; AU5 with a sectorial 7.5 MHz transducer). The operator did not know the levels of thyroid hormones, autoantibodies and chemokine (C-X-C motif) ligand (CXCL)10 of the subjects. The volume of the thyroid was obtained by the ellipsoid formula[19]. Hypoechoic and dyshomogeneous echogenicity were randomly ranked (as follows: 0=normal echogenicity; 1=slight hypoechoic and dyshomogeneous; 2=severely hypoechoic and dyshomogeneous) to focus on thyroid abnormalities associated with thyroid autoimmunity[19]. The presence of thyroid nodules was documented, and the same operator carried out an ultrasonography-guided fine needle aspiration (FNA), by a free-hand method, in nodules having a diameter >10 mm.

Laboratory Evaluation

Thyroid function and autoantibodies were investigated[21]. Commercial radioimmunoassay (RIA) kits (AMERLEX-MAB FT3/FT4 Kit; Amersham Biosciences, Little Chalfont, UK) have been used to determine serum FT3, FT4. Immunoradiometric assay (IRMA) assay has been performed to measure serum TSH (DiaSorin, Saluggia, Italy), thyroid peroxidase antibodies (AbTPO) and thyroglobulin antibodies (AbTg) (ICN Pharmaceuticals, Costa Mesa, CA, USA). AbTg and AbTPO values were considered positive if >50 IU/mL[22].

Serum CXCL10

A quantitative sandwich immunoassay [enzyme-linked immunosorbent assay (ELISA); R&D Systems, Inc., Minneapolis, MN, USA] has been used to measure serum CXCL10 levels. The assay has a sensitivity of 0.41-4.46 pg/ml; a mean minimum detectable dose of 1.67 pg/ml; and intra- and inter-assay coefficients of variation of 3.0% and 6.9%[23,24]. The reference range in the normal population was 90±51 pg/ml[23].

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. A *p*-value was considered significant when $p<0.05$.

RESULTS

The demographic and clinical features of patients are reported in Table 1. Patients and controls were not significantly different in relation to age, gender, TSH, and thyroid ultrasonography, or thyroid autoantibodies. The mean CXCL10 level was significantly high in both groups with respect to the reference range of the normal population[23]. In patients treated with Myo-Ins+Se, after the treatment, TSH levels significantly declined with respect to basal values (5.12±0.87, *vs.* 3.93±1.19, mcIU/ml, respectively; ANOVA, $p=0.002$) (Figure 1). TSH declined below 3.5 mcIU/ml, in 12/26 patients (46%). No significant changes were observed between FT4, or FT3, values pre-and post-treatment ($p>0.05$) (data not shown). After the treatment, AbTPO levels (Figure 2) decreased, too, significantly ($p=0.012$), with respect to basal values (318±324, *vs.* 137±154, IU/ml, respectively; ANOVA). The decline was not significantly different in patients with a higher ini-

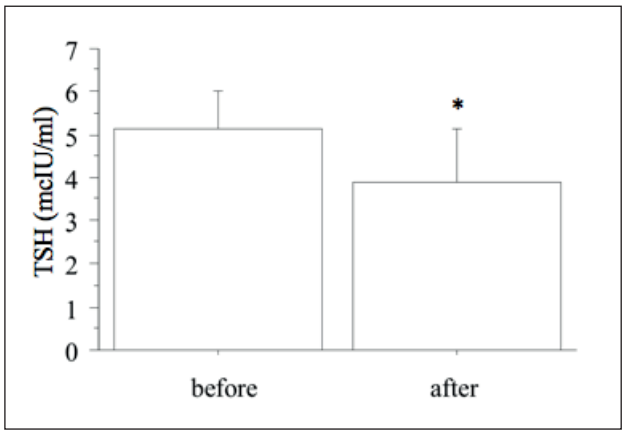

Figure 1. After the treatment, TSH levels significantly declined with respect to basal values (mean±SEM, mcIU/ml; ANOVA, p=0.002).

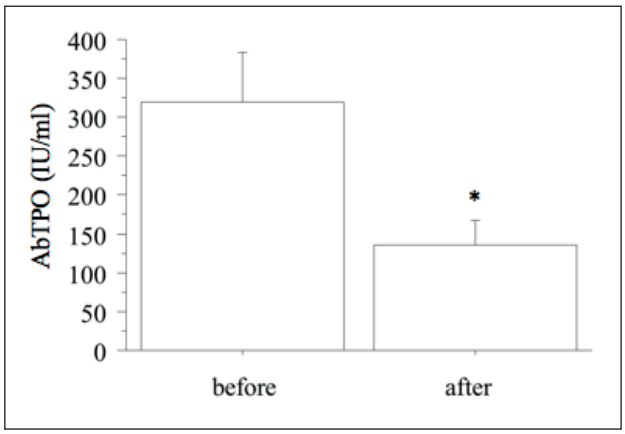

Figure 2. After the treatment, AbTPO levels significantly declined with respect to basal values (mean±SEM, IU/ml; ANOVA, p=0.012).

tial AbTPO value (AbTPO>200 IU/ml) than in patients with a lower AbTPO level (AbTPO<199 IU/ml). After the treatment, also AbTg levels declined (Figure 3), even if not significantly, with respect to basal values (295±391, *vs.* 137±126, IU/ml, respectively; ANOVA, p=0.055). Also in this case the decline was not significantly different in patients with a higher initial AbTg value (AbTg>200 IU/ml) than in patients with a lower AbTg level (AbTg<199 IU/ml). After the treatment, CXCL10 levels (Figure 4) were also declined, with respect to basal values (152±57, *vs.* 121±51, pg/ml, respectively; p=0.050). The reduction 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 changes were observed in patients treated with Myo-Ins+Se considering the presence of goiter, atrophic thyroiditis, or the presence of hypoechogenicity, or hypervascularity, before and after the treatment (data not shown). TSH declined below 3.5 mcIU/ml, in 1/15 patients (6.6%). No significant modifications of TSH, AbTg, AbTPO, or CXCL10 levels, and of the other studied parameters, were observed in the control group with subclinical hypothyroidism (Table 2).

DISCUSSION

This study demonstrates that Myo-Ins and Se correct slight subclinical hypothyroidism in patients with AT, reducing the levels of circulating thyroid autoantibodies, and of serum CXCL10. After the treatment, TSH levels significantly declined with respect to basal values. FT4 and FT3 levels were not significantly changed. Moreover, after the treatment, AbTPO levels significantly declined with respect to basal values, and AbTg levels declined, too, even if not significantly. The immune-modulatory effect was confirmed by the fact that, after the treatment, CXCL10 levels declined, too. A decrease of Se serum levels

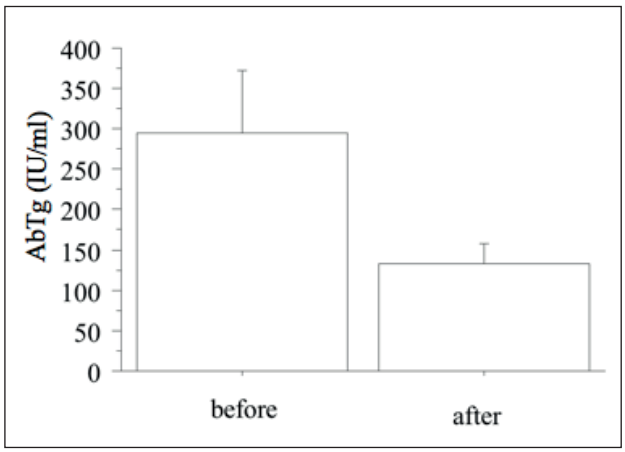

Figure 3. After the treatment, AbTg levels declined, even if not significantly, with respect to basal values (mean±SEM, IU/ml; ANOVA, p=0.055).

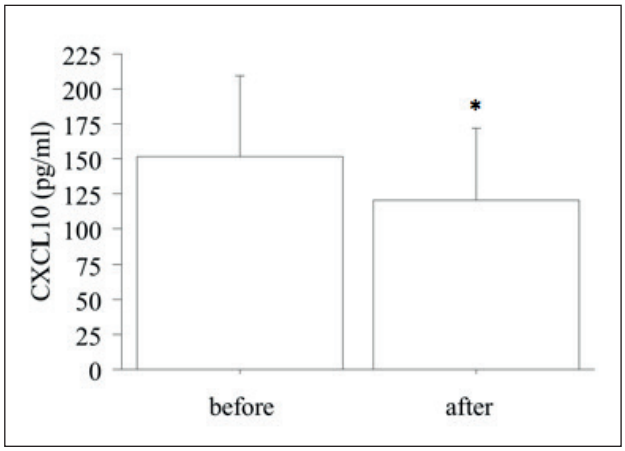

Figure 4. After the treatment, CXCL10 levels declined with respect to basal values (mean±SEM, pg/ml; ANOVA, p=0.050).

Table II. TSH, thyroid autoantibodies, and CXCL10 in controls before, and after 6 months.

	Before	After	*p*
Serum TSH (mcIU/ml)	4.86 ± 0.92	5.31 ± 0.89	ns
AbTPO (IU/ml)	289 ± 435	324 ± 465	ns
AbTg (IU/ml)	314 ± 371	289 ± 405	ns
CXCL10 (pg/ml)	163 ± 76	154 ± 65	ns

Antithyroperoxidase antibody = AbTPO; Antithyroglobulin antibody = AbTg; Thyroid-stimulating hormone = TSH.

has been demonstrated by several studies in HT, GD and in thyroid-associated ophthalmopathy patients; the levels being linked to the outcome[25]. In addition it has been observed by other studies (with low numbers of cases) that Se supplementation improved the clinical scores and reduced AbTPO levels in patients with AT, and mild GD. Nevertheless, published results are still conflicting[26]. Our findings were in line with the other studies. A double-blind randomized controlled trial has been conducted by Nordio et al[16] in order to evaluate the efficacy of Myo-Ins and Se combination in patients with subclinical hypothyroidism. They enrolled 48 women having subclinical hypothyroidism and high circulating AbTg (>350 IU/ml). Patients were randomly divided in group A including twenty-four subjects treated with oral 83 mcg Se/day; and in group B with twenty-four patients taking a combined treatment Myo-Ins 600 mg plus 83 mcg Se for six months. Therefore TSH, AbTPO and AbTg levels, Myo-Ins, and Se plasma concentration were measured showing the good action derived from the therapy with Se in patients affected by subclinical hypothyroidism, that is strongly improved by the combination with Myo-Ins. In group B, a significant decline of TSH levels has been observed, by 31% (4.4±0.9 *vs.* 3.1±0.6 mcIU/ml, $p<0.01$), whereas no change was observed in group A. AbTPO and AbTg levels significantly declined in both groups. AbTg levels below the threshold have been found in 11 patients of group B, in treatment with Myo-Ins plus Se, *vs.* 3 patients of the group A. In these subjects, thyroid ultrasonography evidenced a normalized echogenicity[16]. Another research by Morgante et al[27] investigated on the prevalence of subclinical thyroid dysfunction in infertile PCOS patients and also evaluated if insulin sensitizers in insulin resistant PCOS patients could ameliorate, after 6 months of treatment, the thyroid function. A significant high prevalence of subclinical thyroid dysfunction has been observed in PCOS patients, overall in that overweight, obese and with IR. A treatment of six months with inositol well-known as insulin sensitizer reduced also the TSH levels in insulin resistant PCOS patients, in a significant manner. More recently, one hundred and sixty-eight patients with HT and TSH levels between 3 and 6 mcIU/ml were evaluated by Nordio et al[28]. Patients were randomly divided into 2 groups; in one group they were treated with Myo-Ins+Se and in the other with only Se. Treatment with Myo-Ins+Se leads to a significative decrease of TSH, AbTPO and AbTg levels, and also to an enhancement of thyroid hormones and personal wellbeing, as also shown by Briguglia et al[29]. Moreover, we have conducted a study enrolling twenty-one Caucasian patients with newly diagnosed euthyroid chronic AT; they were treated with Myo-Ins plus Se tablets (600 mg/83 mcg, administrated twice/day for six months). We have observed a reduction of TSH levels after the treatment; therefore, this leads to hypothesize that the combined treatment is effective in reducing the risk to develop hypothyroidism in subjects affected by autoimmune thyroid diseases (AITD). We also found that anti-thyroid autoantibodies decreased after treatment, as well as CXCL10 levels, thus confirming the immune-modulatory effect exerted by the treatment[17]. Myo-Ins exerts a beneficial effect on TSH thanks to its biological role in the TSH hormone signaling. It is indeed able to regulate the H_2O_2-mediated iodination[7] and it has been shown that the impairment of inositol-depended TSH signaling pathway can lead to TSH resistance, and hypothyroidism[8]. Therefore, the treatment may increase the amount of the second messenger, and improve the TSH sensitivity. We confirm here a reduction of anti-thyroid autoantibodies following the treatment. In addition the immune-modulatory effect is sustained by the reduction, after treatment, of CXCL10 levels. IFN-γ-inducible protein 10 (IP-10), also known as CXCL10, was initially identified as IFN-γ-induced chemokine. CXCL10 binds to the chemokine (C-X-C motif) receptor 3 (CXCR3), promoting the pathogenesis of different autoimmune diseases, systemic (such as systemic lupus erythematosus, systemic sclerosis, mixed cryoglobulinemia, or Sjogren syndrome), or organ specific (such as GD and GO, Type 1 diabetes)[30-32]. IFN-γ stimulates CXCL10 secretion through CD4+, CD8+, and natural killer (NK), and also by thyrocytes. High CXCL10 levels in peripheral fluids are, then, a marker of a T helper (Th)1 orientated immune response. CXCL10 serum levels are high in patients affected by AT, particularly in those having a hypoechoic ultrasonographic pattern, that is a sign of a more severe lymphomonocytic infiltration, and in patients with hypothyroidism. Hence, CXCL10 may be a marker of a more aggressive and stronger inflammatory response in the thyroid gland, which causes thyroid damage and thyroid dysfunction[23,33-39]. The immune-modulatory effect exerted by the combination of Myo-Ins and Se on CXCL10 suggests that they are capable of modulating the Th1 immune response, then these findings prompt to investigate on autoimmune diseases associated with the predominant Th1 immune response; the mechanisms need to be further explored[40,41].

CONCLUSIONS

The results of the present study show an improvement of thyroid function in patients with subclinical hypothyroidism and in presence of AT. After treatment with Myo-Ins+Se, TSH levels significantly declined with respect to basal values, and in 46% of cases it reached the normal range. We confirmed also 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 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.

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Nothing to declare.

Conflicts of interest:
The Authors declare that there are no conflicts of interest.

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