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Evaluation of thyroid nodule characteristics in subclinical hypothyroid patients under a myo-inositol plus selenium treatment

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Abstract. – OBJECTIVE: The anticancer effect of myo-inositol (MI) is catching researchers' attention worldwide. Thyroid nodules (TNs) have been detected by ultrasound (US) in up to 76% of the general population and, although most of them are benign, thyroid cancer is the most common malignancy of the endocrine system.

PATIENTS AND METHODS: A retrospective, observational study was conducted in 642 patients with suspected hypothyroidism undergoing US. The analysis was addressed exclusively to patients with subclinical hypothyroidism (SCH) or thyroid-stimulating hormone (TSH) levels borderline associated to TNs classified as class I and II; 1 group (control, no. 16) no treatment was prescribed; the other group (treated, no. 18) underwent treatment with 1 tablet containing MI plus selenium (Se) every day, for six months. Clinical data were collected to evaluate the nodular size, number, and elasticity, as well as TSH levels.

RESULTS: Final data were analyzed from 34 patients: in 76% of mixed TNs was observed a significant reduction of their size and 56% of them significantly regressed nodule stiffness following oral supplementation with MI plus Se. The mean number of mixed nodules for patient shifted from 1.39 ± 0.16 to 1.05 ± 0.15 ($p \leq 0.05$). TSH levels dropped from 4.2 ± 0.21 mIU/L at baseline to 2.1 ± 0.20 mIU/L post-treatment ($p < 0.001$). In the control group, 38% of TNs reduced their diameter but TSH levels significantly increased up to the threshold after six months (from 3.95 ± 0.18 mIU/L to 4.30 ± 0.22 mIU/L, $p \leq 0.05$).

CONCLUSIONS: In SCH patients undergoing treatment with MI plus Se, a reduction of the size, number and elasticity score of TNs as well as TSH levels was observed. Further studies are required, either *in vitro* and *in vivo*, to investigate the use of MI plus Se for the management of TNs.

Key Words:

Myo-inositol, Thyroid nodule, TSH, Subclinical hypothyroidism, Ultrasound.

Introduction

Epidemiological studies[1-3] have shown that thyroid nodules (TNs) are prevalent in up to 76% of screened people for thyroid diseases. A greater incidence is found in female and elderly people. About 4-7% of women and 1% of men living in iodine-sufficient regions present TNs at high-resolution ultrasound (US)[2]. The US is considered as the first-line diagnostic tool for nodular disorders of the thyroid. The American Association of Clinical Endocrinologists (AACE), American College of Endocrinology (ACE) and Associazione Medici Endocrinologi (AME) Guidelines recommend US to patients having palpable TNs or goiter, neck lymphadenopathy as well as who are at risk for thyroid malignancy[4]. It is useful for identifying nodules too small to be palpated, and ascertaining whether the nodule is solitary or dominant, solid, cystic or mixed, as well as size and lymph node status. The US provides other specific nodular features which can suggest malignancy such as diameter, vascularity, microcalcifications, the absence of a halo and irregular margins. A novel and promising tool for assessing the malignant potential of TNs is the elastography, by evaluating the tissue stiffness[5-8]. Through an external force, it measures the degree of tissue distortion. Its diagnostic evaluation of TNs ranges between 96%-100% of specificity and 82%-97% of sensitivity[9]. However, large-scale prospective studies of elastographic technique evaluating TNs are further required.

Most diagnosed nodules are benign, asymptomatic, requiring only observation and follow-up[10,11]. Thyroidectomy might be performed in case of local compressive symptoms such as shortness of breath, hoarseness, dysphagia, choking or pain. Asymptomatic TNs can be sub-

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jected to fine needle aspiration (FNA) biopsy, when abundant colloid is present or to verify the nature of the nodule, such as cytological features of malignancy. This has increased the diagnosis and treatment of papillary thyroid microcarcinomas[4]. Progression to thyroid cancer occurs in 7%-15% of cases, exacerbated by different factors such as radiation exposure[12], elderliness, sex or family history of thyroid disease[10]. Nodular size and morphology are the most important criteria, although only the last one is considered predictive of malignancy risk[13-16]. The risk of cancer is not correlated with the number of nodules[17,18]. Indeed, observational studies and meta-analysis have shown that a single nodule has a higher likelihood of being malignant than multiple nodules[17,19]. The association between malignancy and Hashimoto's thyroiditis (HT) has been extensively investigated but is still controversial[20-25]. Different researches have not found a statistical significance; however, the risk of developing thyroid carcinoma might be considered, as most of the pathological studies reported high prevalence rate of papillary thyroid carcinoma in HT patients[26]. The AACE/ACE/AME Guidelines outline the risk of malignancy of thyroid lesion in 3 different classes: I) low-risk thyroid lesion, II) intermediate-risk thyroid lesion and III) high-risk thyroid lesion. The expected risk of malignancy is about 1% in class I, 5% to 15% in class II and 50% to 90% in class III nodules[4].

In this retrospective observational study the nodular size, number, elasticity, vascularity, presence of calcifications were evaluated, as well as the serum thyroid-stimulating hormone (TSH) levels in patients with subclinical hypothyroidism (SCH) undergoing myo-inositol (MI) plus selenium (Se) treatment.

Patients and Methods

Patients

Over a period of 2 years, from February 2015 to April 2017, a total of 642 patients with suspected hypothyroidism (475 females and 167 males) underwent US. Among these patients 309 did not require any therapy, 184 followed a treatment with MI + Se, and 149 underwent other therapeutic aids. For this retrospective observational study, only patients with SCH or TSH levels borderline associated to TNs classified as class I and II (following the 2016 Update Appendix of the AACE/ACE/AME Guidelines[3]) were included (slightly hypoechoic or isoechoic nodules with ovoid-to-round shape and smooth or ill-defined margins, intranodular vascularization, macro- or continuous rim calcifications and elevated stiffness at elastography). Only TNs larger than 5 millimeters (mm) in diameter were monitored. Data from two groups were analyzed; 1 group (control group: no. 16) no treatment was prescribed; the treated group (no. 18) was taking 1 tablet containing 600 mg MI plus 83 μg Se (Tiroxil®, LO.LI. Pharma S.r.l., Rome, Italy) every day, for six months. Patients with evident malignancy, follicular neoplasia or Hurthle cell hyperplasia, or taking any drug as hormonal agents, insulin sensitizers, oral contraceptives, anti-androgens, glucocorticoids, and corticosteroids during the six months of follow-up were excluded from the investigation. Patient's age, sex, family history of thyroid cancer and exposure to radiation were surveyed.

The main outcome of interest was the nodule size (diameter). Secondary outcomes were: total number of mixed nodules, presence of calcifications, nodule vascularity, elasticity score (ES) and levels of TSH. The study designed as a retrospective observational study was conducted in accordance with the ethical principles of the Declaration of Helsinki and national laws. For this type of study, formal consent is not required. All data were anonymized and held securely in the outpatient care center.

Laboratory and Technical Investigations

The US examinations of the thyroid and neck were performed with high-resolution US (MYLAB 70 XVG; Esaote S.p.A., Genova, Italy) with a 5-13 MHz transducer, at the beginning and the end of the study by an independent investigator. The US technician had at least 10 years' experience in thyroid and neck ultrasonography. The study-related investigations were done by the same operator. Elastography was performed for the TNs on longitudinal plane by using a freehand technique. Briefly, a semi-quantitative approach has been used, acquiring data corresponding to tissue composition before the deformation, in a neutral situation, and right after exerting an appropriate compression of the selected area. To minimize the intra-observer variability, the freehand compression applied on the appropriate neck area was standardized by real-time measurement displayed on a numeric

scale (graded 1-5) and an intermediary level of compression was considered as optimal. The elastosonographic evaluations classified the different tissue stiffness depending on the elasticity score (ES) of each nodule (ES 1: elasticity throughout the examined area; ES 2: elasticity in most of the examined area; ES 3: hardness in most of the examined area, ES 4: completely inelastic nodules). The thyroid US and elastography data were recorded in the database at first visit and after 6 months of treatment. An initial evaluation of the patient's characteristics as well as the type of nodules was accurately performed including features like size, shape, vascularity of lesion and calcifications. The total number of mixed TNs and the mean number of mixed nodules among patients were calculated. Serum TSH levels were measured at baseline and after 6 months, by an enzyme immunometric assay (Byk-Sangtec Dietzenbach, Germany).

Statistical Analysis

Data were tested for significant differences using the Student's T-Test (GraphPad Software, La Jolla, CA, USA). The means of the two groups were compared using the Independent Samples *t*-test, and the means from the same group at different times were compared using the Paired *t*-test. Data are reported as mean ± standard error of the mean (SEM). Percentage (%) was also calculated. A p-value ≤ 0.05 was considered statistically significant.

Results

Among the patients included in the investigation and diagnosed with TNs Class I and II by US at baseline, 5 dropouts occurred. One of these patients had a gynecological surgery, two got pregnant and two had no follow-up information available. Therefore, tests for significance were performed from 34 patients. They were 16 females (88%) and 2 men (22%) with mean age 40.56 ± 2.80 years in the treated group and 15 females (93.75%), 1 man (6.25%) with mean age 41.19 ± 2.89 years in the control group. Patients' characteristics are reported in Table I. In total the 61% of patients had family history of nodular thyroid disease. The range of nodules size was 8-32 mm in the treated group and 7-28 mm in the control group. All patients had a 6-month follow-up. No cases of thyroid cancer were found, and 5 patients had a multinodular goiter with a thyroid gland enlarged containing multiple TNs very small, only a few mm in size (< 5 mm) (Table II). The number of mixed nodules in respect to the total number of TNs dropped from 64% to 49% after 6-months treatment with MI + Se and from 72% to 61% in the control group (Table II). The mean number of mixed TNs among patients was significantly reduced after MI + Se supplementation (1.39 ± 0.16 to 1.05 ± 0.15, $p < 0.01$) and in controls (1.63 ± 0.15 to 1.38 ± 0.20, $p \leq 0.05$). The diameter of nodules significantly decreased from 16.72 ± 1.32 mm to 12.44 ± 1.81 mm ($p \leq 0.05$) in the treated group, whereas in the control group reduction was not significant (from 19.52 ± 1.05 mm to 17.52 ± 1.63 mm) (Table II). No differences on the vascularization of nodules as well as the presence of calcifications were observed in either group. The nodules elasticity score (ES) ameliorated significantly after 6 months of MI + Se: data reported a mean score of 1.80 ± 0.13 at baseline and 1.24 ± 0.18 post-treatment ($p < 0.001$) (Table II). In the control group, ES was reduced but not significantly (from 1.69 ± 0.11 to 1.54 ± 0.17). TSH levels dropped significantly from 4.2 ± 0.21 mIU/L at baseline to 2.1 ± 0.20 mIU/L post-treatment ($p < 0.001$), whereas controls had a significant increase of TSH levels (from 3.95 ± 0.18 mIU/L to 4.30 ± 0.22 mIU/L, $p \leq 0.05$) (Table II).

Table I. Clinical characteristics of subclinical hypothyroid patients (no. = 34) with thyroid nodules at baseline.

Characteristics	Control (no. = 16)	Treated (no. = 18)	*p*-value
Age (years)	41.19 ± 2.89	40.56 ± 2.80	NS
Females, no. (%)	15 (93.75)	16 (88)	
Men, no. (%)	1 (6.25)	2 (22)	
BMI (kg/m^2)	25.81 ± 0.65	26.17 ± 0.58	NS
Family history of nodular thyroid disease, no. (%)	9 (56)	12 (68)	
Type of TNs	Class I and II (Mixed TNs)	Class I and II (Mixed TNs)	
Range of the diameter TNs (mm)	7-28	8-32	

Thyroid Nodules (TNs); Number (no.); Percentage (%); Body Mass Index (BMI). Data are expressed as mean ± SEM.

Table II. Clinical characteristics of subclinical hypothyroid patients with thyroid nodules at baseline and after 6 months of treatment MI + Se (treated group) or no treatment (control).

Characteristics	Control (16)		Treated (18)	
	T0	T1	T0	T1
Total number of mixed TNs, no. (%)	26 (72)	22 (61)	25 (64)	19 (49)
Mean no. of mixed TNs for patients	1.63 ± 0.15	1.38 ± 0.20[§]	1.39 ± 0.16	1.05 ± 0.15**
Diameter of TNs (mm)	19.52 ± 1.05	17.52 ± 1.63	16.72 ± 1.32	12.44 ± 1.81*[†]
Multiple TNs, no. of patients (%)	3 (11)	3 (11)	2 (9)	2 (9)
Thyroid cancer, no. (%)	0 (0)	0 (0)	0 (0)	0 (0)
Exposure to radiation, no. (%)	0 (0)	0 (0)	0 (0)	0 (0)
Presence of calcifications, no. (%)	0 (0)	0 (0)	0 (0)	0 (0)
Nodule vascularity, no. (%)				
Mixed	6 (23)	5 (23)	5 (20)	4 (21)
Peripheral	19 (73)	17 (77)	16 (64)	13 (68)
Absent	1 (4)	0 (0)	4 (16)	2 (11)
Elasticity Score, (ES)	1.69 ± 0.11	1.54 ± 0.17	1.80 ± 0.13	1.24 ± 0.18***
TSH (mIU/L)	3.95 ± 0.18	4.30 ± 0.22[§]	4.2 ± 0.21	2.1 ± 0.20***[†††]

Baseline (T0); end-of-study 6-months (T1); Thyroid-stimulating hormone (TSH); Thyroid Nodules (TNs); Number (no.); Percentage (%); Elasticity score (ES) = ES 1: elasticity throughout the examined area; ES 2: elasticity in most of the examined area; ES 3: hardness in most of the examined area, ES 4: completely inelastic nodules. Data are expressed as mean ± SEM. *p*-value < 0.05 was considered statistically significant. Statistical differences: control group baseline- vs. end-of-study ([§]), treated group pre- *vs.* post-treatment (*), control group *vs*. treated group at end-of-study (T1) (†). *p*-value: [§]≤ 0.05; [§§]< 0.01; [§§§]< 0.001. *p*-value: *≤ 0.05; ** < 0.01; *** < 0.001. *p*-value: [†] ≤ 0.05; [††] < 0.01; [†††] < 0.001.

Discussion

This retrospective observational study evaluated the TNs modification in terms of size, number, and elasticity after treatment with MI + Se for 6 months. In the 76% of mixed TNs was observed a significant reduction of the diameter and the remaining 24% had no modification or showed a larger size. The control group showed a reduction of diameter only in 38% of nodules and the remaining 62% had not changed or increased their diameter. In total 6 TNs in the treated group and 4 in controls completely disappeared, due to the whole shrinkage of their diameter. Thyroid elastography revealed that the elasticity from mostly soft or mostly hard at baseline shifted to entirely soft after treatment. In particular, 56% of mixed TNs significantly reduced their stiffness and 44% had not changed. Predominantly, the nodules that after six months of treatment resulted smaller had also a variation in their elasticity. Elastography is a noninvasive technique for evaluating TNs that reduces the misinterpretation of US results due to over- or under-compression by operators[6]. Thyroid elastography reveals the range from elasticity in the entire examined area to no elasticity in the nodules; however, nodules mostly liquid or fully calcified are difficult to be evaluated by the elastographic method[27]. In this study, only mixed TNs, with the presence of both solid and cystic components, were considered. The management of mixed nodules with no suspicious features can rely on US, as they generally have low rate of malignancy[28]. So far, no specific treatment is available and mainly FNA biopsy is recommended in case of growth of the solid component.

MI is one of the nine stereoisomers of inositol, a cyclic carbohydrate, the most distributed form naturally occurring. Its role in biochemical pathways regulating glucose metabolism, cell proliferation, morphogenesis, and fertility has been extensively demonstrated[29-31]. A meta-analysis[32] reported its beneficial effect in improving the metabolic profile of women with polycystic ovary syndrome, concomitantly reducing their hyperandrogenism. Increasing evidence indicates its involvement in thyroid diseases[33-35]. Indeed, MI acts as a second messenger regulating the activities of TSH[36]. In different studies it has been shown that administration of MI + Se significantly decreases the levels of TSH, thyroid peroxidase antibody, and thyroglobulin antibody as well as significantly improves quality of life in patients with autoimmune thyroiditis. The anticancer effect of inositol and inositol-hexakisphosphate, another stereoisomer, has been investigated as adjuvants to chemotherapy in a number of studies[37-39], showing an improvement of patients' quality of life. Other *in vitro* studies have explored the intrinsic actions of MI on the cytoskeleton, reporting that

inositol-monophosphate and -biphosphate induce actin synthesis[40] and the F-actin ring formation[41]. Preliminary results on breast cancer cell line have shown a reduction of vimentin expression in cells and a stabilization of cortical F-actin by the MI action[42], suggesting that MI facilitates the stabilization of cell structure and suppresses motility and invasiveness of cancer cells. Of note, it has been reported that the advancement of thyroid carcinoma to metastases has been associated to the epithelial-to-mesenchymal transition, which comprises the rearrangement of the cytoskeleton as well as the loss of cell-cell adhesion[43]. Treatment of cancer cells with inositol decreased the levels of fascin, which is involved in cytoskeleton remodeling. Lower levels of fascin result in a reduction of cell projections, proliferation as well as cancer cells invasiveness[44,45]. Another aspect to consider is the association between levels of TSH and thyroid malignancy. Indeed, recent studies have found a correlation with higher serum TSH levels and the advanced stages of thyroid cancer[46,47]. Therefore, TSH seems to play a crucial role in the onset and/or progression of thyroid carcinomas[48].

Conclusions

In this study, a decrement of the size, the number and stiffness of nodules in patients with SCH undergoing a MI + Se treatment was observed. Throughout the study few limitations can be summarized: firstly, the small number of subjects, and secondly, the partial comprehension and reporting of MI action on TNs.

Further studies are required, either *in vitro* and *in vivo*, in order to have a better understanding of the different MI activities in the thyroid cells. Extending the treatment to larger cohorts and double-blind control trials would also be necessary to define the use of MI plus Se for the management of TNs.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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