Myoinositol (Myo) is a cyclic polyol with 6 hydroxyl groups. It is mainly derived from dietary intake while its endogenous production is generated from glucose by enzymatic reactions. Moreover, Myo is also synthesized de novo by catabolism of phosphatidylinositol (PI), phosphoinositides (PIP), and inositol phosphates (IP). Myo has a determinant role in thyroid function and autoimmune diseases as it regulates iodine organization and thyroid hormone biosynthesis by the formation of hydrogen peroxide (H₂O₂) in thyrocytes. Depletion of Myo that is involved in the thyroid stimulating hormone (TSH) signaling pathway, may cause the development of thyroid diseases such as hypothyroidism. TSH levels significantly decreased in patients with subclinical hypothyroidism, with or without autoimmune thyroiditis, after treatment with Myo plus Selenium (Myo+Se). In addition to TSH, antithyroid autoantibodies are reduced. This review summarizes the role of Myo in the thyroidal physiology and its role in the management of some thyroid diseases.

Keywords: myoinositol, autoimmune thyroiditis, hypothyroidism, CXCL10, chemokines

INTRODUCTION

In the past few years, medical and public attention on nutraceuticals has grown. Nutraceuticals, also known as dietary supplements, are considered complementary medicines, defined as a “food, or parts of a food, that provide medical or health benefits, including the prevention and treatment of disease”. Presently, they are contemplated for the prevention of different pathological conditions, including chronic thyroid diseases and associated disorders. In fact, beyond iodine, which is necessary for thyroid physiology, other dietary components are involved in thyroid homeostasis and for this reason their clinical use has been questioned and evaluated. Among these, Inositol (Ins) is one of the most studied and prescribed.
With this manuscript, we aim to review Ins and its derivates knowledge, in the light of their role in thyroid physiology and pathology, and their potential clinical impact focusing on in vitro and in vivo studies reported in previous scientific literature (1).

**MYOINOSITOL**

Ins is a cyclic polyol with 6 hydroxyl groups and exists in 9 possible isoforms. Myoinositol (Myo) is the first isof orm of Ins that has been described and the most commonly found (more than 99%) inside eukaryotic cells (2).

Myo is mainly derived from dietary intake: either as free form or as phytate (IP6). Vegetables are rich in IP6, while animal-derived foods are abundant of free Ins. The exogenous IP6 is converted by bacterial phytases in free Myo, orthophosphate, or Ins-phosphate metabolites (i.e., mono-, di-, tri-, tetra-, and penta-phosphate esters). Beans, citrus fruits (except lemons), nuts, and cereals have a high content of Ins (3).

Common Western diets account for an intake of about 1 g per day of Myo. Its gastro-intestinal absorption is guaranteed by two transporters [sodium/myo-inositol channels type 1 (SMIT1) and type 2 (SMIT2)], which are expressed on duodenum and jejunum mucosal cells (4).

In humans, Myo is also generated from glucose by enzymatic reactions: a) hexokinase convert glucose into glucose-6-phosphate (5), that is subsequently isomerized into inositol-3-phosphate (IP3) by an enzyme called D-3-myo-inositol-phosphate synthase (MIPS1, Ino1, or inositol synthase) (6). This enzymatic pathway up to 2 g Myo/day, are produced in each kidney, for a total of 4 g/day (5).

Moreover, Myo is also synthesized de novo by catabolism of phosphatidylinositol (PI), phosphoinositides (PIP), and inositol phosphates (IP) and afterward, the diacylglycerol-mediated reaction is used to build up new PIP (7). Finally, in mammals, Myo is degraded in the kidney (8, 9).

To summarize, the human body pool of Myo is determined by three distinct pathways: 1) enteral absorption and renal clearance; 2) recycling between plasma, interstitial, and intracellular compartments; and 3) endogenous production and catabolism.

Cell membranes of all body tissues are made of phospholipids of which Ins is a constitutive element, and Myo is its most widespread isof orm. Ins is involved in different physiological processes including in the neuronal transmission, shuttling of phospholipids, other fatty acid groups between cell membranes, intracellular effects of insulin, and intracellular calcium homeostasis. The central nervous system is the main Myo recipient, where it seems to promote emotional and mental wellness. Furthermore, in women, it exerts key functions in preserving ovarian wellbeing and glucose tolerance (10).

PIPs, IP, glycosylphosphatidylinositol (GPIs), IP3, inositol-phosphoglycans (IPGs), and PI derive from Myo-containing phospholipid and they play a role in the biochemical cascade which transmits a chemical signal through a cell as a series of molecular events called signal transduction (5, 11). In particular, numerous hormones such as thyroid stimulating hormone (TSH), luteinizing hormone (LH), follicle stimulating hormone (FSH), and insulin, transmit their function through the PI signal pathway where the phospholipase C (PLC) hydrolyzes phosphatidylinositol-4,5-biphosphate (PIP2) in two second messengers: IP3, and diacylglycerol (DAG), which in turn, open Ca²⁺ channels of the smooth endoplasmic reticulum and mitochondria membranes and induce protein kinase C (PKC), with subsequent cellular responses (12).

As a result, Myo homeostasis impairment could potentially affect several physiological cellular mechanisms that may translate to a broad range of disorders, ranging from thyroid diseases, fertility impairment, polycystic ovary syndrome (PCOS), neurological diseases, and diabetes (13).

Thyroid hormones (TH) homeostasis is controlled through both the PLC-dependent inositol phosphate Ca²⁺/DAG and the cyclic AMP (cAMP) cascade (14), both activated by the TSH and its receptor (TSHR) binding. The cAMP cascade regulates thyrocytes development and differentiation and TH secretion (15), while the PLC-dependent inositol phosphate Ca²⁺/DAG pathway results in enhanced H₂O₂ production, which is needed for iodine incorporation and TH synthesis (16, 17). Therefore, Myo and its derivates are essential in thyroid physiology, as demonstrated in vitro, by active accumulation of Myo and by inositol phosphate formation in thyrocytes under increased TSH level (18, 19). Moreover, metabolomic studies indicate that hypothyroid patients require higher Myo level than healthy subjects (20), suggesting that Myo may limit thyroid functions impairment by increasing iodine availability for thyrocytes (21).

**AUTOIMMUNE THYROID DISEASES (AITD)**

Autoimmune thyroid diseases (AITD) include the chronic autoimmune thyroiditis [Hashimoto’s thyroiditis (HT)], which is the most common cause of hypothyroidism in iodine-sufficient areas, along with Grave’s disease (GD), a syndrome that consists in hyperthyroidism, goiter, thyroid eye disease, and occasionally pretibial dermopathy. Both of these disorders are considered the result of the combination of genetic susceptibility with environmental factors and they are characterized by the presence of high serum levels of autoantibodies against one or more thyroid antigens, along with a diffuse lymphocytic infiltration of the thyroid tissue, which includes predominantly thyroid-specific T cells and especially, in HT, and B cells (22, 23). However, AITD can be present even in the absence of circulating antithyroid autoantibodies (24).

Women have a higher risk of developing AITD than men (25). The prevalence of AITD is higher in iodine-sufficient areas (25) and where there is an increased iodine intake (26).

AITD are very common in the general population and it shows an increased association with other autoimmune diseases, particularly with connective tissue disease [i.e., systemic sclerosis (SSc), Sjogren syndrome (SS), vitiligo, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and sarcoidosis] (27–29).
Genetic predisposition for AITD includes the familial clustering of the disease, a concordance rate in monozygotic twins (20-40%), and a sibling risk ratio of approximately 17 (30).

Approximately 70% of the genes associated with the risk of AITD take part in T cell functions, underlying the role of these cells in AITD pathogenesis (31).

AITD occurrence is associated with environmental factors in about 20% of cases. The external insult causes a cellular/tissue damage that switches on the innate immune system leading to the progression of an AITD in the presence of a genetic susceptibility (27, 32).

Radiation exposure, infection, sex steroids, stress, pregnancy, and iodine intake are the known possible precipitating environmental factors for AITD. Fetal microchimerism within the maternal thyroid is also a possibility (26). Smoking is a risk factor for Graves’ hyperthyroidism and even a stronger risk factor (33, 34) for Graves’ Ophthalmopathy.

The thyroidal tissue expresses specific selenoproteins and the lack of selenium is involved in the onset of thyroid autoimmunity, whereas its supplementation protects from radiation exposure, infection, sex steroids, stress, pregnancy, and iodine intake are the known possible precipitating environmental factors for AITD. Fetal microchimerism within the maternal thyroid is also a possibility (26). Smoking is a risk factor for Graves’ hyperthyroidism and even a stronger risk factor (33, 34) for Graves’ Ophthalmopathy.

The thyroidal tissue expresses specific selenoproteins and the lack of selenium is involved in the onset of thyroid autoimmunity, whereas its supplementation protects from AITD (35).

Among infections, people with hepatitis C virus (HCV) infection showed (26–38) higher prevalence of AITD thyroid autoantibodies levels.

The immune cells infiltrate the AITD thyroid and it includes CD4+ and CD8+ T cells, CD19+ B cells, macrophages, and plasma cells. B lymphocytes also act as antigen presenting cells (APCs), activating naïve autoreactive CD4+ T cells by presenting thyroid autoantigens (Tg and TPO) making the gland the major site of thyroid antibody secretion against Tg and TPO antigen (39).

SUBCLINICAL HYPOTHYROIDISM

The PLC-dependent inositol phosphate Ca²⁺/DAG pathway regulates the biosynthesis of H₂O₂ which is needed for iodine organification and TH biosynthesis making Myo-containing phospholipids derivates (IP3, PI, PIP, IPGs and GPs) impairment an element of disruption for thyroid physiology with subsequent potential development of hypothyroidism (40, 41). Recently, several studies have explored the possible role of Myo in the management of subclinical hypothyroidism (SCH) associated with AITDs (SCH-AITD). In 2013, the authors of another study, in order to evaluate oral Myo in women with SCH-AITD, uniformly randomized 48 women with TSH values with the interval of 4.01-9.99 mIU/L and with antithyroglobulin (AbTg), and antithyroid peroxidase (AbTPO) positivity in two harms: in one group, 600 mg of Myo plus 83 mcg of selenium (Myo+Se) were administrated for 6 months, while in the other, only 83 mg of selenium (Se) was administered the same period of time. At the end of the study, the Myo+Se group showed 31% of TSH drop and a 44% and 48% reduction of AbTPO and AbTg, respectively (p<0.01), while the Se group demonstrated only lower antibodies with no significant variation in the TSH level (42).

Later, 86 patients (men and women) suffering from SCH and HT, were managed with Myo+Se, showing significant reduction in TSH values (p ≤ 0.001) after 6 months of therapy and a clear amelioration in their quality of life, after being assessed with a subjective examination form (43). In 2017, another study evaluated 168 patients affected by HT with TSH within the 3 and 6 mIU/mL range, dividing them in two groups in which Myo +Se, or only Se (83 µg) were prescribed. After 6 months, the researchers noticed a compelling recovery in the thyroid functions test with Myo+Se therapy (44). Following data confirmed these findings (45), even in a different clinical setting. In fact, in 2018, the efficacy and the safety of Myo+Se supplementation was examined in pregnant women with TSH levels laying between 1.6-2.5 µIU/ml (600 mg Myo plus 83 µg Se, daily throughout pregnancy) observing more patients with normal TH in the treated group than in the control group (94.1% vs 68.7%) (46). Moreover, Morgante et al. reported that after 6 months, in insulin resistant PCOS patients on Ins +metformin therapy vs. metformin alone, TSH dropped significantly (p<0.05) in the Ins-combined treatment group (47). There are further results supporting beneficial Myo impact on patients with SCH and HT in a time-dependent manner with TSH declined, over a treatment period of three months, by 21% (48) and even more steadily when the administration is prolonged for a 1 year (40).

MYOINOSITOL AND CXCL10

Previous studies showing antithyroid autoantibodies levels decline together with reduction in TSH values (42, 45), and hypothesized an immune-modulatory effect originated by Myo-based therapy. This has been further supported by the measurement, before and after treatment, of C-X-C motif chemokine ligand 10 (CXCL10) levels. The CXCL10, also known as IFN-γ-inducible protein 10 (IP-10), through its receptor [chemokine (C-X-C motif) receptor 3 (CXCR3)], implicated in the immune-pathogenesis of numerous autoimmune diseases, (i.e., GD and orbitopathy, type 1 diabetes, mixed cryoglobulinemia, SLE, SS, or SSc) (49, 50).

Beyond CD4+, CD8+, and natural killer (NK), it has also been demonstrated that thyrocytes are able to release CXCL10 under the stimulant effect of IFN-γ. Indeed, AITD patients, especially if complicated by hypothyroidism and ultrasonographic hypechochogenicity of the gland (sign of a more lymphomonocytic infiltration), show high serum CXCL10. Hence, CXCL10 in peripheral fluids could be a marker of T helper (Th)1 type immunity, whose circulating levels directly correlate with the intensity and magnitude of thyroid auto-inflammatory state (45).

In 2017 Ferrari SM et al., studied the effect of the association of Myo and Se (600 mg/83 mcg), given twice per day for a 6-month period, on 21 patients with newly diagnosed autoimmune thyroiditis (AT). After the treatment period, besides the significant reduction in TSH and AbTg levels, they also reported a decline, even if not statistically significant, of CXCL10 levels compared to initial values (114 ± 46, vs. 144 ± 54, pg/mL, respectively; p=0.061) (45).
The exact mechanisms through which Myo and Se can influence the immune-response are still unknown, demanding further investigations. However, preliminary in vitro studies performed on blood mononuclear cells (PBMC), taken from either HT and normal controls and subjected to H₂O₂-induced oxidative stress, revealed that Myo+Se reduced the burden of several cytokines, including CXCL10, CCL2, CXCL9, and the H₂O₂-mediated genotoxicity (51–53).

Finally, Myo deficiency has also been associated with an increased thyroid cancer risk. In fact, preliminary metabolomic studies which examined samples of normal thyroids in comparison with those of glands carrying benign nodular diseases, follicular adenoma, and thyroid carcinoma reported lower Myo thyroid tissue amount with malignancy (54). Conversely, in 2018, a retrospective investigation examined the effects, after 6 months, of 600 mg Myo plus 83 mcg Se supplementation on benign thyroid nodules [class I and II defined by AACE/ACE/AME Guidelines (55)] in patients with SCH. Observations were a reduction of the size (16.72 ± 1.32 vs 12.44 ± 1.81), number (1.39 ± 0.16 vs 1.05 ± 0.15), and elasticity score (1.80 ± 0.13 vs 1.24 ± 0.18) of thyroid nodules (56).

CONCLUSIONS

Former in vitro and in vivo studies revealed a potential favorable impact of Myo supplementation on subclinical hypothyroidism and autoimmune thyroiditis, emphasizing the crucial role of Myo in the homeostasis of the endocrine system, including the thyroid and other organs. In fact, as a source of second messengers, such as IP3, Myo is involved in the TH biosynthesis and metabolism and thyrocytes need physiological levels of Myo to ensure the euthyroid status. Moreover, reduced levels of thyroid antibodies, pro-inflammatory chemokines (i.e., CXCL10), and oxidative stress observed after Myo employment advocate for the immune-modulatory effect of the compound that could be clinically relevant to prevent euthyroid AT and SCH patients to develop overt thyroid dysfunctions. While these results need to be confirmed by larger studies and clinical trials, and also to further elucidate the biochemical mechanisms, Myo treatment turns out to be a compelling approach on the management of subclinical AT and hypothyroidism.

AUTHOR CONTRIBUTIONS

SRP, SMF, AP, FG, SB, AA, and PF conceived the paper. All authors reviewed and approved the final version of the manuscript.

FUNDING

The cost of the publication has been sustained by LoLi Pharma.

REFERENCES

1. Benvenega S, Ferrari SM, Elia G, Ragusa F, Patrizio A, Paparo SR, et al. Nutraceuticals in Thyroidology: A Review of in Vitro, and in Vivo Animal Studies. *Nutrients* (2020) 12:1337. doi: 10.3390/nu12051337
2. Downes CP, Macphee CH. Myo-Inositol Metabolites as Cellular Signals. *Frontiers in Endocrinology*. 2022;13:9307564.

11. Bizzarri M, Fuso A, Dinicola S, Cacina A, Bevilacqua A. Pharmacodynamics and Pharmacokinetics of Inositol(1) in Health and Disease. *Expert Opin Drug Metab Toxicol* (2016) 12:1181–96. doi: 10.1080/17425255.2016.1206887

12. Benvenega S, Antonelli A. Inositol(1) in Thyroid Function, Growth and Autoimmunity. *Rev Endocr Metab Disord* (2016) 17:471–84. doi: 10.1007/s11154-016-9370-3

13. Frej AD, Clark J, Le Roy CI, Lilla S, Thomason PA, Otto GP, et al. The Inositol-3-Phosphate Synthase Biosynthetic Enzyme Has Distinct Catalytic and Metabolic Roles. *Mol Cell Biol* (2016) 36:1464–79. doi: 10.1128/MCB.00039-16

14. Fallahi P, Ferrari SM, Elia G, Ragusa F, Paparo SR, Caruso C, et al. Myo-Inositol in Autoimmune Thyroiditis, and Hypothyroidism. *Rev Endocr Metab Disord* (2018) 19:349–54. doi: 10.1007/s11154-018-9477-9

15. Benvenega S, Nordio M, Lagana AS, Unfer V. The Role of Inositol in Thyroid Physiology and in Subclinical Hypothyroidism Management. *Front Endocrinol (Lausanne)* (2021) 12:662582. doi: 10.3389/fendo.2021.662582

16. Chen G, Pekary AE, Sugawara M, Hershman JM. Effect of Exogenous Hydrogen Peroxide on Iodide Transport and Iodine Organic Transport During the Growth and Differentiation of Thyrocytes: A Link With Thyroid-Stimulating Hormone-Induced Phospholipase A2 Activity. *Biochem J* (1987) 247:519. doi: 10.1042/bj19870519

17. Fong P. Thyroid Iodide Efflux: A Team Effort? *J Physiol* (2011) 589:5929–39. doi: 10.1113/jphysiol.2011.218594

18. Grafton G, Baxter MA, Sheppard MC, Eggo MC. Regulation of Myo-Inositol Transport During the Growth and Differentiation of Thyrocytes: A Link With Thyroid-Stimulating Hormone-Induced Phospholipase A2 Activity. *Biochem J* (1995) 309:667–75. doi: 10.1042/bj3090667

19. Field JB, Ealey PA, Marshall NJ, Cockcroft S. Thyroid-Stimulating Hormone Stimulates Increases in Inositol Phosphates as Well as Cyclic AMP in the FRTL-5 Rat Thyroid Cell Line. *Biochem J* (1987) 247:519–24. doi: 10.1042/ijb2470519

20. Piras C, Pibiri M, Arisci N, et al. Analysis of Metabolomics Profile in Hypothyroid Patients Before and After Thyroid
Hormone Replacement. *J Endocrinol Invest* (2021) 44:1309–19. doi: 10.1007/s40618-020-01434-7

Barba D, Orrù E, Unver F. Iodine and Myo-Inositol: A Novel Promising Combination for Iodine Deficiency. *Front Endocrinol (Lausanne)* (2019) 10:457. doi: 10.3389/fendo.2019.00457

Romagnani S. The Th1/Th2 Paradigm and Allergic Disorders. *Allergy* (1998) 53:12–2. doi: 10.1111/j.1398-9995.1998.tb04951.x

Orgiazzi J. Thyroid Autoimmunity. *Presse Med* (2012) 41:e611–25. doi: 10.1016/j.pjpm.2012.10.002

Rotondi M, Coperchini F, Magri F, Chiavato L. Serum-Negative Autoimmune Thyroiditis: What’s in a Name? *J Endocrinol Investig* (2014) 37:589–91. doi: 10.1007/s40618-014-0083-8

Antonelli A, Ferrari SM, Corrado A, Di Domenicantonio A, Fallahi P. Autoimmune Thyroid Disorders. *Autoimmun Rev* (2015) 14:174–80. doi: 10.1016/j.autrev.2014.10.016

Ferrari SM, Fallahi P, Antonelli A, Benvenga S. Environmental Issues in Thyroid Diseases. *Front Endocrinol (Lausanne)* (2017) 8:650. doi: 10.3389/fendo.2017.00050

Fallahi P, Ferrari SM, Ruffilli I, Elia G, Bricotti M, Vita R, et al. The Association of Other Autoimmune Diseases in Patients With Autoimmune Thyroiditis: Review of the Literature and Report of a Large Series of Patients. *Autoimmun Rev* (2016) 15:1125–8. doi: 10.1016/j.autrev.2016.09.009

Ferrari SM, Fallahi P, Ruffilli I, Elia G, Ragusas F, Benvenga S, et al. The Association of Other Autoimmune Diseases in Patients With Graves’ Disease: (With or Without Ophthalmopathy): Review of the Literature and Report of a Large Series. *Autoimmun Rev* (2019) 18:287–92. doi: 10.1016/j.autrev.2018.10.001

Antonelli A, Ferri C, Fallahi P, Colaci M, Giuggioli D, Ferrari SM, et al. Th1 and Th2 Chemokine Serum Levels in Systemic Sclerosis in the Presence or Absence of Autoimmune Thyroiditis. *J Rheumatol* (2008) 35:1809–11.

Brix TH, Hegedüs L. Twin Studies as a Model for Exploring the Aetiology of Autoimmune Thyroid Disease. *Clin Endocrinol (Oxf)* (2012) 76:457–64. doi: 10.1111/j.1365-2265.2011.04318.x

Simmonds MJ. GWAS in Autoimmune Thyroid Disease: Redefining Our Understanding of Pathogenesis. *Nat Rev Endocrinol* (2013) 9:277–87. doi: 10.1038/nrendo

Kawashima A, Tanigawa K, Akama T, Yoshihara A, Ishii N, Suzuki K. Innate Immune Activation and Thyroid Autoimmunity. *J Clin Endocrinol Metab* (2011) 96:3661–71. doi: 10.1210/jc.2011-1568

Perricone C, Versini M, Ben-Ami D, Gertel S, Watad A, Segel MJ, et al. Smoke and Autoimmunity: The Fire Behind the Disease. *Autoimmun Rev* (2016) 15:358–74. doi: 10.1016/j.autrev.2016.01.001

Neri S, Boraschi P, Antonelli A, Falaschi F, Baschieri L. Pulmonary Function, Smoking Habits, and High Resolution Computed Tomography (HRCT) Early Asbestos. *Am J Ind Med* (1996) 30:588.

Ferrari SM, Fallahi P, Antonelli A, Benvenga S, et al. Myo-Inositol and Selenium Reduce the Risk of Developing Overt Hypothyroidism in Patients With Autoimmune Thyroiditis. *Eur Rev Med Pharmacol Sci* (2017) 21:36–42.

Porcaro G, Angelozzi P. Myo-Inositol and Selenium Prevent Subclinical Hypothyroidism During Pregnancy: An Observational Study. *IJMADAT* (2018) 1:e164.

Morgante G, Musacchio MC, Orvieto R, Massaro MG, De Leo V. Alterations in Thyroid Function Among the Different Polycystic Ovary Syndrome Phenotypes. *Gynecol Endocrinol* (2013) 29:967–9. doi: 10.3109/09535930.2013.829445

Bruglia G. Time-Dependent Efficacy of Myo-Inositol Plus Selenium in Subclinical Hypothyroidism. *IJMADAT* (2018) 1:e108.

Antonelli A, Rotondi M, Fallahi P, Grosso M, Boni G, Ferrari SM, et al. Iodine-131 Given for Therapeutic Purposes Modulates Differently Interferon-Gamma-Inducible Alpha-Chemokine CXCL10 Serum Levels in Patients With Active Graves’ Disease or Toxic Nodular Goiter. *J Clin Endocrinol Metab* (2007) 92:1485–90. doi: 10.1210/jc.2006.1571

Antonelli A, Fallahi P, Rotondi M, Ferrari SM, Romagnani P, Grosso M, et al. Increased Serum CXCL10 in Graves’ Disease or Autoimmune Thyroiditis is Not Associated With Hyper- or Hypothyroidism Per Se, But is Specifically Sustained by the Autoimmune, Inflammatory Process. *Eur J Endocrinol* (2006) 154:651–8. doi: 10.1530/eje.1.02137

Benvenga S, Vicchio T, Di Bari F, Vita R, Fallahi P, Ferrari SM, et al. Favorable Effects of Myo-Inositol, Selenomethionine or Their Combination on the Hydrogen Peroxide-Induced Oxidative Stress of Peripheral Mononuclear Cells From Patients With Hashimoto’s Thyroiditis: Preliminary In Vitro Studies. *Eur Rev Med Pharmacol Sci* (2017) 21:89–101.

Ruffilli I, Ferrari SM, Colaci M, Ferri C, Politti U, Antonelli A, et al. CXCR3 E CXCL10 Nella Tiroide Autoimmune [CXCR3 and CXCL10 in Autoimmune Thyroiditis]. *Clin Ter* (2014) 165:e237–42. doi: 10.7417/CT.2014.1727

Ferrari SM, Elia G, Ragusas F, Ruffilli I, Paparo SR, Caruso C, et al. Myo-Inositol and Selenium in Subclinical Hypothyroidism. *IJMADAT* (2018) 1:e166.

Deja S, Dawiskiba T, Balcerzak W, Orczyk-Pawlowsa M, Glod M, Pawelka D, et al. Follicular Adenomas Exhibit a Unique Metabolic Profile. *H NMR Stud Thyroid Lesions PLoS One* (2013) 8:e84637. doi: 10.1371/journal.pone.0084637

Gharib H, Papini E, Garber JR, Duick DS, Harrell RM, Hegedüs L, et al. American Association of Clinical Endocrinologists, American College of Endocrinology, and Associazione Medici Endocrinologi Medical Guidelines for Clinical Practice for the Diagnosis And Management of Thyroid Nodules—2016 Update. *Endocr Pract* (2016) 22:622–39. doi: 10.4158/EP161208.GL

Nordio M, Bascian S. Evaluation of Thyroid Nodule Characteristics in Subclinical Hypothyroid Patients Under a Myo-Inositol Plus Selenium Treatment. *Eur Rev Med Pharmacol Sci* (2018) 22:2153–9. doi: 10.26355/eu1revr_201804_14749

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**Publisher’s Note:** All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in
this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Paparo, Ferrari, Patrizio, Elia, Ragusa, Botrini, Balestri, Guarneri, Benvenga, Antonelli and Fallahi. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.