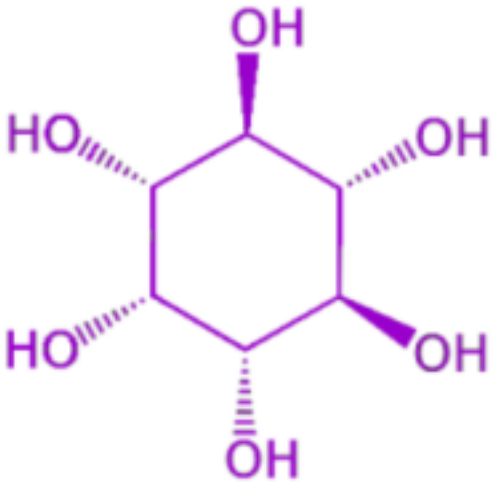
Myo-Inositol for Hashimoto's Thyroiditis

by Jeffrey Dach, MD | Dec 31, 2024
Post Categories: Hormone and Metabolic Health | Supplements | Thyroid Health

Mary has Hashimoto's thyroiditis, with elevated TSH of 10.2 and TPO antibody greater than 900. Free T3 and Free T4 levels are normal. Mary's primary care doctor prescribed a small dose of NP thyroid, 15 mg per day, yet Mary could not tolerate it, and stopped taking it. Mary would like to know if there is anything else she could take to reduce the TSH and the Antibody levels. Yes there is. It is called Myo-Inositol.

What is Myo-Inositol?

Myo-Inositol (vitamin B8) is a sugar-like molecule involved in cell signaling, making TSH signal more effective in the thyroid cells. This is useful in Hashimoto's Thyroiditis, where Myo-Inositol is given in combination with selenium and vitamin D3 for better effect. Myo-Inositol is present in food, and as a nutritional supplement available at most health food stores. Foods high in Myo-Inositol are: beans, peas, brown rice, wheat bran, nuts, cantaloupe, bananas, raisins, cabbage.[1-12]



Left upper image: Myo-Inositol Chemical Structure with the six carbon configuration at the courtesy of Wikimedia.

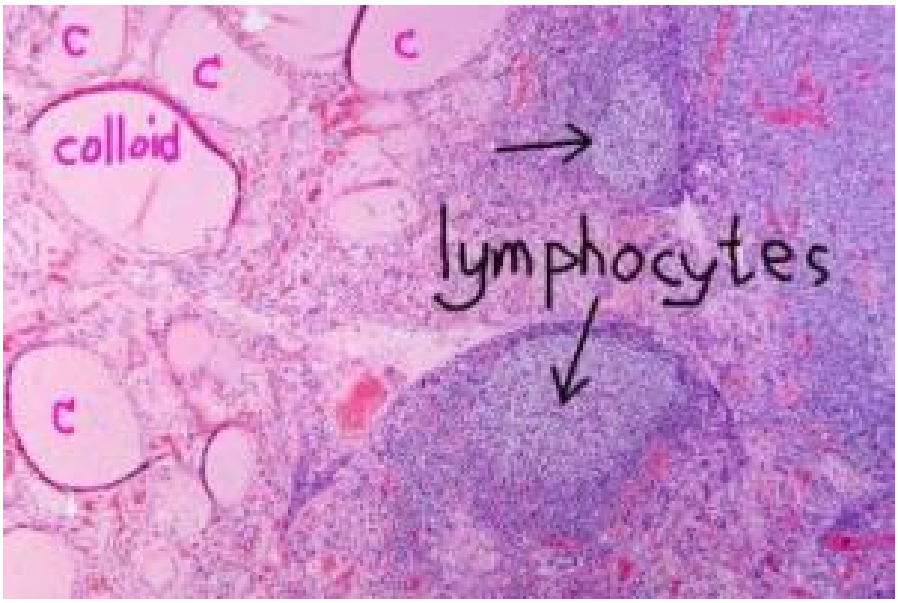
Hashimoto's Thyroiditis Elevated Antibodies

Hashimoto's thyroiditis is an autoimmune disease affecting 10% of females and 2% of males. It is usually detected by finding characteristic anti-thyroid antibodies, the TPO (Thyro-Peroxidase) and thyroglobulin antibodies on routine blood tests.[1-12]

Hashimoto's Microscopic Histology of Thyroid Gland

Hashimoto's Thyroiditis is characterized by diffuse lymphocyte and plasma cell infiltration, fibrous replacement, and eventual atrophy of the thyroid gland. Microscopic evaluation of the thyroid gland shows lymphocytic infiltration, plasma cell infiltration, fibrotic scarring, and over time, atrophic changes. In about 20% of patients with Hashimoto's Autoimmune Thyroiditis there is lymphocytic infiltration alone without the tell-tale elevation of TPO or thyroglobulin antibodies. This is called Seronegative Hashimoto's Thyroiditis. Decreased echogenicity of the

thyroid on ultrasound imaging is predictive of hypothyroidism in Hashimoto's with high probability. In 2002, Dr. Wolfgang Raber writes:



abnormal thyroid ultrasound [hypoechoic] patterns were highly indicative of autoimmune thyroiditis and allowed the detection of thyroid dysfunction [hypothyroidism] with 96% probability.[47-48C]

Inositol Involved in TSH Signaling Cascade

In 2023, Dr. Sabrina Rosaria Paparo reviewed the role of inositol in the signaling cascade for TSH induced generation of hydrogen peroxide. TSH does not work directly; rather TSH signal activates two separate signaling cascades. One signaling cascade uses inositol phosphate to generate H202, used by TPO to organify iodine to thyroglobulin, thus producing thyroid hormone. The other TSH cascade uses cAMP to regulate cell growth and thyroid hormone secretion. Note that TSH activates both cascades, while TSH antibodies in Graves' Disease only the cAMP cascade, and not the H202 generating inositol phosphate cascade. Increasing TSH causes greater accumulation of myo-inositol phosphate within thyrocytes. Patients with hypothyroidism require higher levels of myo-inositol than controls. Myo-inositol improves iodine availability for organification, of benefit in the Hashimoto's patient who typically has an organification defect as demonstrated by the perchlorate discharge test. Dr. Sabrina Rosaria Paparo writes Myo-Inositol is essential for thyroid physiology:

Thyroid hormones (TH) homeostasis is controlled through both the PLC-dependent inositol phosphate Ca2+/DAG and the cyclic AMP (cAMP) cascade, both activated by the TSH and its receptor (TSHR) binding. The cAMP cascade regulates thyrocytes development and differentiation and TH secretion, while the PLC-dependent inositol phosphate Ca2+/DAG pathway results in enhanced H2O2 production, which is needed for iodine incorporation and TH synthesis. Therefore, Myo and its derivatives are essential in thyroid physiology, as demonstrated *in vitro*, by active accumulation of myo-inositol phosphate formation in thyrocytes under increased TSH level. Moreover, metabolomic studies indicate that hypothyroid patients require higher myo level than healthy subjects, suggesting that myo may limit thyroid functions' impairment by increasing iodine availability for thyrocytes.[3]

Inositol in Signaling Cascade for Many Other Hormones

As it turns out, inositol is a key player in many other signaling cascades transducing the cellular effects of hormones LH and FSH which stimulate ovarian function, and insulin involved in glucose uptake metabolism, thus playing a role in PCOS, obesity, and adult onset diabetes mellitus (AODM). In 2023, Dr. Sabrina Rosaria Paparo reviewed the role of inositol in signal transduction, opening calcium channels, writing:

Numerous hormones such as thyroid stimulating hormone (TSH), luteinizing hormone (LH), follicle stimulating hormone (FSH), and insulin, transmit their function through the PI [phospho-**inositol**] signal pathway where the phospholipase C (PLC) hydrolyzes phosphatidyl**inositol**-4,5-biphosphate (PIP2) in two second messengers: IP3, and diacylglycerol (DAG), which in turn, open Ca^{2+} channels of the smooth endoplasmic reticulum and mitochondria

membranes and induce protein kinase C (PKC), with subsequent cellular responses.[3]

Myo-Inositol and Selenium Reduce Antibodies and TSH

In 2013, Maurizio Nordio did a six month randomized, controlled trial (RCT) on the combined use of myo-inositol (600 mg/day) and selenomethionine (83mcg/day) in 46 women with Hashimoto's thyroiditis with high thyroglobulin antibodies (TgAb). After six months of combined use, both TPO and thyroglobulin antibodies were reduced about 40% from around 900 to 500 mIU/mL. Surprising, the elevated TSH normalized in the group taking both supplements, not achieved with selenium alone. Only in the combined use group, TSH levels decreased about 40% from 4.4 to 3.1 mIU/mL. Dr. Maurizio Nordio writes:

We demonstrated that the beneficial effects obtained by selenomethionine treatment on patients affected by subclinical hypothyroidism, likely due to the presence of autoantibody (TPOAb and TgAb), are further improved by co-treatment with myo-inositol. Conclusions: indeed, due to its action as TSH second messenger, myo-inositol treatment reduces TSH levels closer to physiological concentrations.[1]

TSH Suppression Beneficial for Hashimoto's

Our treatment plan for the Hashimoto's patient includes TSH suppression below the reference range with a suitable dosage of thyroid hormone medicine, preferably NDT (natural desiccated thyroid). The lower the TSH, the less stimulation of the thyroid gland to produce hydrogen peroxide, the damaging oxidant which causes inflammation in

the gland. This is discussed further in the chapter on Hashimoto's With Normal TSH, When to Treat.

Myo-Inositol and Selenium for SubClinical Hypothyroidism

In 2017, Dr Maurizio Nordio conducted a larger study including 85 Hashimoto's patients with subclinical hypothyroidism, with TSH between 3 and 6 mIU/L. The 85 patients had elevated antithyroid antibodies, and normal free T3 and Free T4 hormone levels. Again, the combined use of selenium and Myoinositol restored a normal TSH level, and increased Free T3 and Free T4 levels. The one hyperthyroid patient showed improvement in TSH which increased into the normal range. Dr. Nordio writes:

Patients were assigned to receive Myo-Ins-Se (myoinositol and selenium). TSH, TPOAb, and TgAb levels were significantly decreased in patients treated with combined Myo-Ins-Se after six months of treatment. In addition, a significant fT3 and fT4 increase, along with an amelioration of their quality of life, was observed…. **Remarkably, TSH values of the hyperthyroid patient increased from 0.14 µU/ml up to 1.02 µU/ml, showing a complete restoration of TSH values at a normal range.** In conclusion, the administration of Myo-Ins-Se is significantly effective in decreasing TSH, TPOAb, and TgAb levels, as well as enhancing thyroid hormones and personal wellbeing, therefore restoring euthyroidism in patients diagnosed with autoimmune thyroiditis.[2]

Note: this is the first and only reference I have seen reporting benefits of myo-inositol in Graves' Disease. This beneficial effect may be due to myo-inositol ability to reduce pro-inflammatory chemokines CXCL10 found in Graves' Disease (GD) and Hashimoto's Thyroiditis (HT). Chemokines stimulate movement of immune cells to a particular

location, perpetuating the autoimmune process. In 2019, Dr. Silvia Martina Ferrari writes:

In GD, recruited Th1 lymphocytes are responsible for enhanced IFN-γ [interferon gamma] and TNF-α [tumor necrosis factor alpha] production, which in turn stimulates Th1 chemokines release from thyrocytes, initiating and perpetuating the autoimmune process. Circulating levels of these chemokines are associated with the active phase of GD.[36]

In 2018, Dr. Silvia Martina Ferrari studied surgically removed tissue obtained after thyroidectomy from three Hashimoto's patients and three benign goiter patients. This *in vitro* thyrocyte study used cytokines to stimulate chemokine CXCL10 secretion in presence or absence of H2O2. Dr. Silvia Martina Ferrari found myo-inositol, but not selenium, decreased the secretion of CXCL10 chemokines, providing a protective effect, writing:

The secretion of CXCL10 chemokine induced by IFN-γ+tumor necrosis factor alpha (TNF)-α has been decreased by myo+ins, both in presence or absence of H2O2.[5]

In 2020 and 2021, Dr. Salvatore Benvenga showed myo-inositol combined with selenium had protective effects on cadmium induced thyroid toxicity in mice, reducing C cell hyperplasia and hypertrophy. Note: C cells produce calcitonin, and C cell hyperplasia is considered a precursor to medullary carcinoma of the thyroid.[57-58]

Myo-Inositol for Benign Thyroid Nodules

Thyroid nodules are quite common in the general population, prevalent in up to two thirds of patients when screened with thyroid ultrasound. Typically, these are benign, and of no clinical significance. In 2018, Dr. Nordio did a retrospective study of thyroid nodules detected by ultrasound in 34 of 642 patients with suspected hypothyroidism. Half

were treated with myo-inositol 600 mg plus selenium 83 mcg over six months. The other half served as controls. Final data in 34 patients showed significant reduction in size for 76% of thyroid nodules in the treated group, compared to only 38% in the untreated group. The treated group had a significant decrease in nodule diameter from 16.7 mm to 12.4 mm. However, in the control group nodule size reduction was not significant, from only 19.5 mm to 17.5 mm. In the treated group, TSH levels dropped from 4.2 to 2.1 mIU/L after six months. However, in the control group, TSH levels significantly increased after six months from 3.95 to 4.30 mIU/L.[7]

Management of Thyroid Nodule with Suppression of TSH

Results such as Dr. Nordio's 2018 study above can be improved by adding TSH suppression with thyroid hormone medication, as is commonly done by mainstream endocrinology using levo-thyroxine. In 2003, Dr. Mary Jo Welker writes in *American Family Physician*:

Use of TSH suppressive therapy with thyroxine to manage benign, solitary thyroid nodules remains controversial. The lack of universal efficacy makes such therapy optional in most patients. Some randomized, controlled studies suggest that short-term thyroxine therapy is not superior to placebo in patients with a solitary hypofunctioning colloid nodule. The efficacy of thyroxine is less certain for solitary nodules than for a diffuse or multinodular goiter. However, some patients may benefit, and suppressive therapy is considered an appropriate alternative as long as the patient is followed carefully at six-month intervals.[59-62]

Nodules are carefully followed with serial ultrasound for any change in size. Enlarging nodules are referred for biopsy, and/or surgery. For large nodules which protrude from or cause bulging in the neck, referral for

surgical removal is usually justified. For further discussion of thyroid nodule management see, the chapter on the thyroid nodule epidemic.

Inhibition of Secretion of Chemokines

Thyroid Tumor Prevention, and Iodine Deficiency

One might object to an intervention such as myo-inositol which makes TSH signaling more effective and increases hydrogen peroxide generation in the thyroid. Yet paradoxically, such an intervention with myo-inositol is protective of thyrocytes by reducing chemokines. In 2019 and 2023, Dr. Daniele Barbaro suggested myo-inositol was useful in treatment of auto-immune thyroiditis, prevention of thyroid tumors, and in treatment of iodine deficiency, writing:

As myo-inositol plays a crucial role in the regulation of iodine organification, supplementation may promote faster recovery from ID [iodine deficiency]. Indeed, H2O2 generated under the stimulus of myo-inositol is available for iodine incorporation inside the thyroid. Such activity makes myo-inositol very appealing as a novel molecule to increase iodine availability…myo-inositol when administered with selenium in patients affected by autoimmune thyroiditis contributes to restore the euthyroid status, to reduce the titer of the autoantibodies, and to prevent the progression of SCH [subclinical hypothyroidism] to overt hypothyroidism. This positive activity of myo-inositol is further demonstrated in cases of hypothyroidism during pregnancy. Moreover, preliminary evidence on the role of myo-inositol on thyroid cancer has also been investigated, and the data on thyroid nodules appear promising. Also, animal studies suggest a protective effect of myo-inositol against proliferation of cancer cells and indirectly by inhibition of secretion of chemokines….[34,46]

PCOS – Polycystic Ovary Syndrome

PCOS affects 6-18% of adolescent girls. The two main features of PCOS are:

1) Irregular, anovulatory menstrual cycles

2) Hyperandrogenism causing hirsutism and acne.

In the thyroid gland, inositol acts as a second messenger to TSH. Similarly in the ovary, myo-inositol acts as a second messenger to FSH (follicle stimulating hormone) which induces ovulation. Myo-inositol is very effective in PCOS (polycystic ovary syndrome), improving insulin sensitivity, reducing acne and hirsutism, restoring ovulation, normal cycling and fertility.[15-25]

In 2013, Dr. Paolo Giovanni Artini did a randomized study in 50 overweight PCOS patients using myo-inositol 2 grams/day plus folic acid 200 mg/day. After 12 weeks, the LH (luteinizing hormone), prolactin, and insulin levels were reduced. Insulin sensitivity improved, and normal menstrual cycles were restored in all subjects.[17]

Alpha Lactalbumin Added to Myo-Inositol

Myo-inositol has been effective in restoring ovulation in women with PCOS. However some women are resistant. In 2018, Dr. Mario Montanino Oliva used myo-inositol to treat 37 anovulatory women with PCOS. Two thirds of the women ovulated with myo-inositol treatment, while one third were resistant and did not ovulate. However, by adding 50 milligrams of α-LA (alpha lactalbumin) to 2 g of myo-inositol twice a day, ovulation was restored in 86% of inositol-resistant women.[15]

Myo-inositol combined with D-chiro-inositol in a 40:1 ratio improved efficacy for restoring ovulation in PCOS.[56]

In 2022, Dr. Fedyeh Haghollahi writes:

A systematic study has shown that lifestyle modifications such as exercise and weight loss remain the first-line treatment for adolescents with PCOS…. Taking vitamin D supplements, as well as other supplements such as the combination of myo-inositol and α-lipoic acid [alpha-lactalbumin] have been also recommended for treating adolescent girls with this syndrome…. Lifestyle modifications can be added to first-line medications, including metformin, oral contraceptives (OCs), or anti-androgens.[33]

Normal Androgenic Phenotype D, the Exception in PCOS

In 2023, Dr. Vittorio Unfer reviewed the various phenotypes of PCOS. Although inositol has been successfully used in PCOS for 20 years, inositol may be inappropriate in the PCOS patients with normal androgen level, and normal metabolic profile, writing:

The efficacy of inositol supplementation in PCOS scenarios has been endorsed worldwide for more than 20 years, but interestingly, therapy with inositols is not appropriate for patients exhibiting phenotype D PCOS, since they are not affected by hyperandrogenism and do not always experience dysmetabolism.[75]

Panic Disorder, Depression, and OCD

Myo-inositol is also effective for panic disorder. A small study published in 2001 showed it was more effective than SSRI antidepressants. Large doses, up to 16 grams per day, were used. It may also be effective for depression and OCD (obsessive compulsive disorder), thought to be beneficial as second messenger for dopamine, serotonin and/or norepinephrine receptors in the brain.[13,14,28,28B]

In 2002, Dr. Brian Harvey writes:

Despite a mode of action that remains illusive, MI [myo-inositol] has demonstrated therapeutic efficacy in obsessive-compulsive disorder (OCD), putative OCD-spectrum disorders, as well as panic and depression.[28C]

In 2023, Dr. Carmen Concerto writes:

Combination tablets courtesy of Export India Web Site.

> The interest in inositol as a possible antidepressant molecule began in 1978 when Barkai and colleagues showed a reduced concentration of inositol in the CSF of patients with mood disorders. Afterward, several studies measured levels of myo-inositol in different brain areas of patients with major depressive disorder (MDD) and bipolar disorder (BD), highlighting how low levels of inositol were associated with depressive symptoms, while high levels with (hypo) manic symptoms…. It has been suggested that the therapeutic activity of inositol may be related to the modulation of serotonin and/or norepinephrine receptors and to an effect on the signal transduction pathway. Indeed, from the data available in the literature, inositol acts as a precursor of the inositol phosphate-phosphoinositide (IPP) cycle…. The IPP cycle and its derived second messengers are involved in several receptor systems, including noradrenergic (α-1), serotonergic (5-HT2A and 5-HT2C), cholinergic (muscarinic), and dopaminergic (D1) receptors…. [96,97] Overall, encouraging results seem to emerge for inositol in panic disorders, likely through its peculiar second messenger characteristics, which are different from the transmitter-receptor mechanism of SSRIs used for this disorder…findings have been

demonstrated in animal models…to date, literature evidence on the efficacy of inositol in the treatment of psychiatric disorders is still controversial…partly due to the heterogeneity of supporting studies. … systematic use of inositol in routine clinical practice cannot be recommended yet….[42]

Myo-Inositol for Type Two Diabetes, Metabolic Syndrome and Obesity

Myo-inositol is a second messenger for insulin, and has an insulin sensitizing effect similar to metformin. For convenience, a number of products are available with both Metformin and myo-inositol in the same packaging (left image).

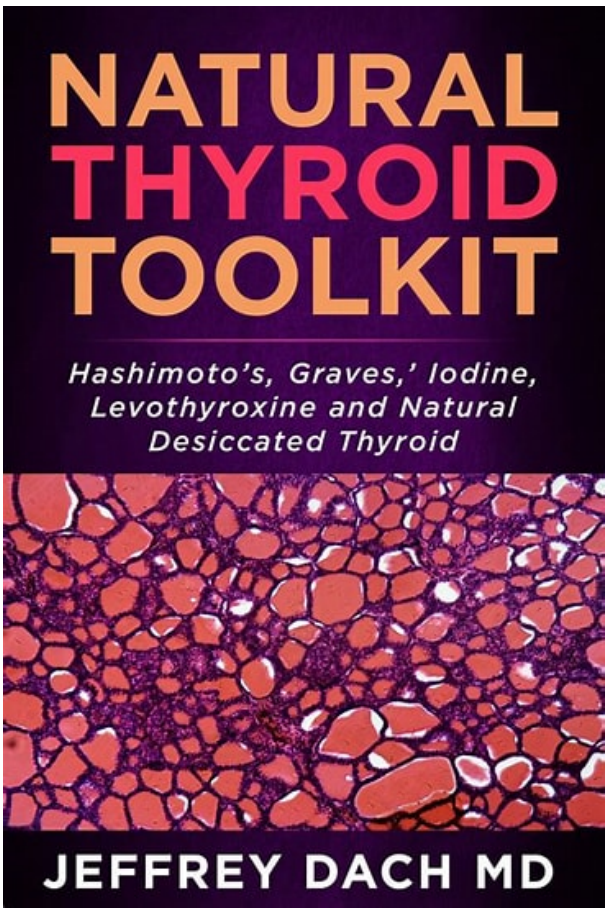
Studies have shown beneficial effects in Adult Onset Diabetes Mellitus (AODM, Type 2) and Metabolic Syndrome with improvement in insulin sensitivity, reduction in blood glucose and HgbA1C levels after 12-26 weeks of Myo-inositol, 2 grams/day, also found useful in prevention of gestational diabetes. (24)(30)(73-86)

Myo-Inositol Broad Spectrum Anti-Cancer Effects

In 2016, Dr. Mariano Bizzarri reviewed inositol and inositol hexaphosphate (InsP6) as broad spectrum anticancer agents writing:

Further investigation demonstrated that InsP6 [inositol-6-phosphate] had unequivocal apoptotic effects on both solid and haematogenous tumors. Indeed, InsP6 has been shown to trigger programmed cell death both *in vitro* and *in vivo* in numerous cancer cell lines including Kaposi's sarcoma and prostate, breast, cervical, pancreas, melanoma, and colon cancer. This apoptotic effect is frequently associated with growth inhibition…[Note: apoptosis is programmed cell death].[50-52, 87-93]

In Conclusion



Myoinositol is an effective tool in the treatment of Hashimoto's Thyroiditis, normalizing TSH and antibody levels. Efficacy is improved when combined with selenium and vitamin D3. As a signaling molecule in various cascades, Myoinositol plays a role in multiple areas of human health. In 2023, Dr Paparo writes:

Myo [myo-inositol] 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.[3]

Buy Supplements from Pure Encapsulations:

Myo-Inositol Complex capsules
myo-inositol 550 mg – D-chiro inositol 150 mg
take 2 capsules, 2 times daily, with meals. (2200 grams/d)
3.6:1 ratio of myo-inositol to d-chiro inositol

Myo-inositol Powder (as myo-inositol) (2 scoops= 4.1 g)
2 scoops, 1-3 times per day, with or between meals.

If you liked this article, you might like my new book, Natural Thyroid Toolkit available on Amazon. If you purchase a book, remember to leave a favorable review. That would be much appreciated.

Articles with Related Interest:

Hashimotos Thyroiditis with Normal TSH, When To Treat?

All Hashimotos Articles

PCOS Part One

PCOS Part Two

PCOS Part three

U. of Wisconsin Integrative Med Myo-Inositol Dosing Chart

References:

1. Nordio, Maurizio, and Raffaella Pajalich. Combined treatment with Myo-inositol and selenium ensures euthyroidism in subclinical hypothyroidism patients with autoimmune thyroiditis. *Journal of Thyroid Research* 2013 (2013).
2. Nordio, Maurizio, and Sabrina Basciani. Treatment with myo-inositol and selenium ensures euthyroidism in patients with autoimmune thyroiditis. *International Journal of Endocrinology* 2017 (2017).

Clinical evidence has highlighted the efficacy of myo-inositol and selenium in the treatment of autoimmune thyroiditis. Aim of this study was to further analyze the role of myo-inositol plus selenium (Myo-Ins-Se) in restoring a normal thyroid function of Hashimoto's patients with subclinical hypothyroidism.

3. Paparo, Sabrina Rosaria, et al. Myoinositol in autoimmune thyroiditis. *Frontiers in Endocrinology* 13 (2022).

PIPs, IP, glycosylphosphatidylinositols (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 Ca^{2+} channels of the smooth endoplasmic reticulum and mitochondria membranes and induce protein kinase C (PKC), with subsequent cellular responses (12).

Thyroid hormones (TH) homeostasis is controlled through both the PLC-dependent inositol phosphate Ca^{2+}/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 Ca^{2+}/DAG pathway results in enhanced H_2O_2 production, which is needed for iodine incorporation and TH synthesis (16, 17). Therefore, myo and its derivatives are essential in thyroid physiology, as demonstrated *in vitro*, by active accumulation of myo-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).

The PLC-dependent inositol phosphate Ca^{2+}/DAG pathway regulates the biosynthesis of H_2O_2 which is needed for iodine organification and TH biosynthesis making myo-containing phospholipid derivatives' (IP3, PI, PIP, IPGs and GPIs) impairment an element of disruption for thyroid physiology with subsequent potential development of hypothyroidism (40, 41).

Pregnant Women: 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).

PCOS Patients: 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% and even more steadily when the administration is prolonged for a 1 year (40).

Preliminary *in vitro* studies performed on blood mononuclear cells (PBMC), taken from either HT and normal controls and subjected to H_2O_2-induced oxidative stress, revealed that Myo+Se reduced the burden of several cytokines, including CXCL10, CCL2, CXCL9, and the H_2O_2-mediated genotoxicity (51–53).

Benign Thyroid Nodules: 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).

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 (1).

Myo has a determinant role in thyroid function and autoimmune diseases as it regulates iodine organification 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.

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

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]

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.

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Our results confirm:

1) the toxic effect of H_2O_2 in primary thyrocytes that leads to an increase of the apoptosis, to a decrease of the proliferation, and to a slight reduction of cytokines-induced CXCL10 secretion;

2) the secretion of CXCL10 chemokine induced by IFN-γ+tumor necrosis factor alpha (TNF)-α has been decreased by Myo+Ins, both in presence or absence of H_2O_2;

3) no effect has been shown by the treatment with Se. Therefore, a protective effect of myo-ins on thyroid cells has been suggested by our data, which exact mechanisms are at the basis of this effect need to be further investigated.

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Many clinical studies have shown that after treatment with myo-inositol plus selenium (MYO+Se), TSH levels significantly decreased in patients with subclinical hypothyroidism with or without autoimmune thyroiditis. The TSH reduction was accompanied by a decline of antithyroid autoantibodies. Moreover, myo-inositol supplementation seemed to be involved also in the management of thyroidal benign nodules, with a possible effect in the size reduction.

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MyoInositol for OCD, Panic

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Administration of MI has been found to be therapeutic for obsessive-compulsive disorder and panic disorder…DCI may be considered a therapeutic agent against metabolic syndrome, endothelial dysfunction, and erectile dysfunction in diabetes patients (Nacimento et al., 2006), and MI may act as alternative of metformin, the most popular oral antidiabetic drug, because it interacts directly with insulin target tissues; however, it does not show the side effects of the drug.… In women with PCOS, administration of DCI improves clinical features of the syndrome (Baillargeon et al., 2010). Moreover, combined therapy of MI and DCI improves the metabolic profile of obese PCOS patients, reducing the risk of CVD.

14. Palatnik, Alex, et al. Double-blind, controlled, crossover trial of inositol versus fluvoxamine for the treatment of panic disorder. *Journal of Clinical Psychopharmacology* 21.3 (2001): 335-339.

Only 70% of patients respond to current treatments for panic disorder, and many discontinue drugs because of side effects. Myo-inositol, a natural isomer of glucose and a precursor for the second-messenger phosphatidyl-inositol system, has previously been found superior to placebo in the treatment of depression, panic disorder, and obsessive-compulsive disorder (OCD), but a direct comparison with an established drug has never been performed. A double-blind, controlled, random-order crossover study was undertaken to compare the effect of inositol with that of fluvoxamine in panic disorder. Twenty patients completed one month of inositol up to 18 g/day and one month of fluvoxamine up to 150 mg/day. Improvements on Hamilton Rating Scale for Anxiety scores, agoraphobia scores, and Clinical Global Impressions Scale scores were similar for both treatments. In the first month, inositol reduced the number of panic attacks per week (mean and SD) by 4.0 (2) compared with a reduction of 2.4 (2) with fluvoxamine ($p = 0.049$). Nausea and tiredness were more common with fluvoxamine (p

= 0.02 and p = 0.01, respectively). Because inositol is a natural compound with few known side effects, it is attractive to patients who are ambivalent about taking psychiatric medication. Continuing reports of inositol's efficacy in the treatment of depression, panic disorder, and OCD should stimulate replication studies.

Myo-inositol plus alpha-lactalbumin for PCOS

15. Montanino Oliva, Mario, et al. Effects of myo-inositol plus alpha-lactalbumin in myo-inositol-resistant PCOS women. *Journal of Ovarian Research* 11.1 (2018): 1-7.

The study by Montanino and colleagues indicated that adding 50 milligrams of α-LA to 2 g of myo-Inositol twice a day restored ovulation in 86% of inositol-resistant women with PCOS.

This treatment involved 2 g MI, taken twice per day by oral route, for three months. The Homeostasis Model Assessment (HOMA) index and MI plasma levels were measured. In the main phase, previously selected MI-resistant patients received the same daily amount of MI plus 50 mg α-LA twice a day, for a further three months. Ovulation was assessed using ultrasound examination on days 12, 14 and 20 of the cycle. The HOMA index, lipid, hormone and MI plasma levels were detected at baseline and at the end of this phase.

Thirty-seven anovulatory PCOS subjects were included in the study. Following MI treatment, 23 of the 37 women (62%) ovulated, while 14 (38%) were resistant and did not ovulate. In the latter group, MI plasma levels did not increase. These MI-resistant patients underwent treatment in the main phase of the study, receiving MI and α-LA. After this combined treatment, 12 (86%) of them ovulated. Their MI plasma levels were found to be significantly higher than at baseline; also, a hormone and lipid profile improvement was recorded.

The combination of MI with α-LA allowed us to obtain significant progress in the treatment of PCOS MI-resistant patients. Therefore, this new formulation was able to re-establish ovulation, greatly increasing the chances of desired pregnancy.

16. Mendoza, Nicolas, et al. Comparison of the effect of two combinations of myo-inositol and D-chiro-inositol in women with polycystic ovary syndrome undergoing ICSI: a randomized controlled trial. *Gynecological Endocrinology* (2019).

This was a multicenter controlled, randomized, double-blind parallel group study with two MYO-DCI formulations for 12 weeks. The study group (SG) was administered 550 mg of MYO + 150 mg of DCI twice daily; the control group (CG) was administered 550 mg of MYO + 13.8 mg of DCI twice daily. The participants comprised 60 women with PCOS undergoing ICSI. At baseline, no differences were found between the two groups regarding age, BMI, HOMA-IR or testosterone levels. The pregnancy and live birth rates were significantly higher in the SG than in the CG (65.5 vs. 25.9 and 55.2 vs. 14.8, respectively) [risk ratio (RR) = 0.4; 95%CI (0.2, 0.79); p = .003 and RR = 0.27; 95%CI (0.10, 0.70); p = .002 respectively]. The risk of ovarian hyperstimulation syndrome (OHSS) was lower in the SG (3.44 vs. 18.5%, p = .07). The combination of MYO-DCI at high doses of DCI improves the pregnancy rates and reduces the risk of OHSS in women with PCOS undergoing ICSI.

17. Artini, Paolo Giovanni, et al. Endocrine and clinical effects of myo-inositol administration in polycystic ovary syndrome. A randomized study. *Gynecological Endocrinology* 29.4 (2013): 375-379.

To evaluate the effects of the administration of myo-inositol (MYO) on hormonal parameters in a group of polycystic ovary syndrome (PCOS) patients.

Design: Controlled clinical study. Setting: PCOS patients in a clinical research environment. Patients: 50 overweight PCOS patients were enrolled after informed consent. Interventions: All patients underwent hormonal evaluations and an oral glucose tolerance test (OGTT) before and after 12 weeks of therapy (Group A (n¼10): MYO 2 g plus folic acid 200 mg every day; Group B (n¼10): folic acid 200 mg every day). Ultrasound examinations and Ferriman-Gallwey score were also performed. Main outcome measures: Plasma LH, FSH, PRL, E2, 17OHP, A, T, glucose, insulin, C peptide concentrations, BMI, HOMA index and glucose-to-insulin ratio.

Results: After 12 weeks of MYO administration plasma LH, PRL, T, insulin levels and LH/FSH resulted significantly reduced. Insulin sensitivity, expressed as glucose-to-insulin ratio and HOMA index resulted significantly improved after 12 weeks of treatment. Menstrual cyclicity was restored in all amenorrheic and oligomenorrheic subjects. No changes occurred in the patients treated with folic acid. Conclusions: MYO administration improves reproductive axis functioning in PCOS patients reducing the hyperinsulinemic state that affects LH secretion.

18. Unfer, V., et al. Effects of myo-inositol in women with PCOS: a systematic review of randomized controlled trials. *Gynecological Endocrinology* 28.7 (2012): 509-515.

Polycystic ovary syndrome (PCOS) affects 5%-10% of women in reproductive age, and it is the most common cause of infertility due to ovarian dysfunction and menstrual irregularity. Several studies have reported that insulin resistance is common in PCOS women, regardless of the body mass index. The importance of insulin resistance in PCOS is also suggested by the fact that insulin-sensitizing compounds have been proposed as putative treatments to solve the hyperinsulinemia-induced dysfunction of ovarian response to endogenous

gonadotropins. Rescuing the ovarian response to endogenous gonadotropins reduces hyperandrogenemia and re-establishes menstrual cyclicity and ovulation, increasing the chance of a spontaneous pregnancy. Among the insulin-sensitizing compounds, there is myo-inosiol (MYO). Previous studies have demonstrated that MYO is capable of restoring spontaneous ovarian activity, and consequently fertility, in most patients with PCOS. With the present review, we aim to provide an overview on the clinical outcomes of the MYO use as a treatment to improve ovarian function and metabolic and hormonal parameters in women with PCOS.

19. Genazzani, Alessandro D., et al. Differential insulin response to myo-inositol administration in obese polycystic ovary syndrome patients. *Gynecological Endocrinology* 28.12 (2012): 969-973.

Polycystic ovary syndrome (PCOS) is characterized by hyperandrogenism, chronic anovulation, polycystic ovaries at ultrasound evaluation, and quite frequently by insulin resistance or compensatory hyperinsulinemia. Attention has been given to the role of inositol-phosphoglycan (IPG) mediators of insulin action and growing evidences suggest that a deficiency of D-chiro-inositol (DCI) containing IPG might be at the basis of insulin resistance, frequent in PCOS patients. On such basis, we investigated the efficacy on insulin sensitivity and hormonal parameters of 8 weeks treatment with myo-inositol (MYO) (Inofert, ItalPharmaco, Milano, Italy) at the dosage of 2 g day in a group (n = 42) of obese PCOS patients,. After the treatment interval body mass index (BMI) and insulin resistance decreased together with luteinizing hormone (LH), LH/FSH and insulin. When subdividing the patients according to their fasting insulin levels, Group A (n = 15) insulin below 12 μU/ml and Group B (n = 27) insulin above 12 μU/ml, MYO treatment induced similar changes in both groups but only patients of Group B showed the significant decrease of both fasting insulin plasma levels (from 20.3 ± 1.8 to 12.9 ± 1.8 μU/ml, $p < 0.00001$) and of area

under the curve (AUC) of insulin under oral glucose tolerance test (OGTT). In conclusion, our study supports the hypothesis that MYO administration is more effective in obese patients with high fasting insulin plasma levels.

Hirsutism, Acne and Pattern Alopecia

20. Zacchè, Martino M., et al. Efficacy of myo-inositol in the treatment of cutaneous disorders in young women with polycystic ovary syndrome. *Gynecological Endocrinology* 25.8 (2009): 508-513.

Polycystic ovary syndrome (PCOS) is the most common endocrine cause of hirsutism, acne and pattern alopecia, often characterized by ovulation disorders (usually manifested as oligo- or amenorrhea). In addition, 30-40% of women with PCOS have impaired glucose tolerance, and a defect in the insulin signaling pathway seems to be implicated in the pathogenesis of insulin resistance. For this reason, insulin-lowering medications represent novel approach in women with PCOS. The aim of this study was to evaluate the effects of myo-inositol (MYO), an isoform of inositol, belonging to the vitamin B complex, in the treatment of cutaneous disorders like hirsutism and acne.

Methods: Fifty patients with PCOS were enrolled in the study. BMI, LH, FSH, insulin, HOMA index, androstenedione, testosterone, free testosterone, hirsutism and acne were evaluated at the baseline and after receiving MYO therapy for 6 months.

Results: After 3 months of MYO administration, plasma LH, testosterone, free testosterone, insulin and HOMA index resulted significantly reduced; no significant changes were observed in plasma FSH and androstenedione levels. Both hirsutism and acne decreased after 6 months of therapy.

Discussion: MYO administration is a simple and safe treatment that ameliorates the metabolic profile of patients with PCOS, reducing hirsutism and acne.

21. Roxas, Mario. Myo-inositol in patients with polycystic ovary syndrome: a novel method for ovulation induction. *Alternative Medicine Review* 12.4 (2007): 381-382.

Polycystic ovary syndrome (PCOS) is often characterized by chronic oligo- or anovulation (usually manifested as oligo- or amenorrhea), and hyperandrogenism. In addition, 30-40% of PCOS women have impaired glucose tolerance, and a defect in the insulin signaling pathway (inositol-containing phosphoglycan mediators) seems to be implicated in the pathogenesis of insulin resistance. PCOS patients are subfertile as a consequence of such ovulatory disorders and often need drugs, such as clomiphene citrate or follicle-stimulating hormone, for ovulation induction, which increases the risk of multiple pregnancy and ovarian hyperstimulation syndrome. We hypothesized that the administration of an isoform of inositol (myo-inositol), belonging to the vitamin B complex, would improve the insulin-receptor activity, restoring normal ovulatory function.

Materials and Methods: Twenty-five PCOS women of childbearing age with oligo- or amenorrhea were enrolled in the study. Ovulatory disorder due to PCOS was apparently the only cause of infertility; no tubal defect or deficiency of male semen parameters was found. Myo-inositol combined with folic acid (Inofolic) 2 g twice a day was administered continuously. During an observation period of 6 months, ovulatory activity was monitored with ultrasound scan and hormonal profile, and the numbers of spontaneous menstrual cycles and eventually pregnancies were assessed.

Results: Twenty-two out of the 25 (88%) patients restored at least one spontaneous menstrual cycle during treatment, of whom 18 (72%)

maintained normal ovulatory activity during the follow-up period. A total of 10 singleton pregnancies (40% of patients) were obtained. Nine clinical pregnancies were assessed with fetal heartbeat at ultrasound scan. Two pregnancies evolved in spontaneous abortion.

Conclusion: Myo-inositol is a simple and safe treatment that is capable of restoring spontaneous ovarian activity and consequently fertility in most patients with PCOS. This therapy did not cause multiple pregnancy.

22. Bizzarri, Mariano, et al. An innovative approach to polycystic ovary syndrome: Vittorio Unfer and his pioneering research on inositols. *Journal of Obstetrics and Gynaecology* 42.4 (2022): 546-556.

Myo-inositol and D-chiro-inositol are insulin sensitizing agents. In the ovary, myo-inositol acts as second messenger of Follicle Stimulating Hormone (FSH). Both molecules were administered to Polycystic Ovary Syndrome (PCOS) women. The gynecologist Vittorio Unfer was the first to give specific value to myo-inositol for the treatment of PCOS: this important innovation opened new ways of research to identify efficient therapies based on myo-inositol alone or with low doses of D-chiro-inositol. Significant successes were also gained using myo-inositol in treating male and female infertility. Unfer's researches allowed to identify "the D-Chiro-Inositol Paradox in the Ovary" and the best myo-inositol/Dchiro- inositol ratio (40:1) for the treatment of PCOS. Furthermore, his studies allowed to improve the inositol's efficacy using alpha-lactalbumin.

23. Unfer, Vittorio. D-Chiro-inositol in PCOS: the myths and what we know about the reality. *International Journal of Food Sciences and Nutrition* 73.7 (2022): 989-991.

PCOS and AODM

24. Facchinetti, Fabio, et al. Experts' opinion on inositols in treating polycystic ovary syndrome and non-insulin dependent diabetes mellitus: A further help for human reproduction and beyond. *Expert Opinion on Drug Metabolism and Toxicology* 16.3 (2020): 255-274.

25. Merviel, Philippe, et al. Impact of myo-inositol treatment in women with polycystic ovary syndrome in assisted reproductive technologies. *Reproductive Health* 18.1 (2021): 1-8.

Panic and OCD, Depression

26. Benjamin, Jonathan, et al. Double-blind, placebo-controlled, crossover trial of inositol treatment for panic disorder. *American Journal of Psychiatry* 152.7 (1995): 1084-1086.

Because they found in an earlier study that inositol, an important intracellular second-messenger precursor, was effective against depression in open and double-blind trials, the authors studied its effectiveness against panic disorder.

Method: Twenty-one patients with panic disorder with or without agoraphobia completed a double-blind, placebo-controlled, 4-week, random-assignment crossover treatment trial of 12 g/day of inositol.

Results: The frequency and severity of panic attacks and the severity of agoraphobia declined significantly more after inositol than after placebo administration. Side effects were minimal.

Conclusions: The authors conclude that inositol's efficacy, the absence of significant side effects, and the fact that inositol is a natural component of the human diet make it a potentially attractive therapeutic for panic disorder.

27. Fux, Mendel, et al. Inositol treatment of obsessive-compulsive

disorder. *American Journal of Psychiatry* 153.9 (1996): 1219-1221.

Earlier studies reported that inositol, a simple polyol second messenger precursor, was effective in controlled trials for patients with depression and panic. In this study its effectiveness in obsessive-compulsive disorder was investigated.

Method: Thirteen patients with obsessive-compulsive disorder completed a double-blind, controlled crossover trial of 18 g/day of inositol or placebo for 6 weeks each.

Results: The subjects had significantly lower scores on the Yale-Brown Obsessive Compulsive Scale when taking inositol than when taking placebo.

Conclusions: The authors conclude that inositol is effective in depression, panic, and obsessive-compulsive disorder, a spectrum of disorders responsive to selective serotonin reuptake inhibitors.

12 g daily

28. Levine, Joseph. Controlled trials of inositol in psychiatry. *European Neuropsychopharmacology* 7.2 (1997): 147-155.

Inositol is a simple polyol precursor in a second messenger system important in the brain. Cerebrospinal fluid inositol has been reported as decreased in depression. A double-blind controlled trial of 12 g daily of inositol in 28 depressed patients for four weeks was performed. Significant overall benefit for inositol compared to placebo was found at week 4 on the Hamilton Depression Scale. No changes were noted in hematology, kidney or liver function. Since many antidepressants are effective in panic disorder, twenty-one patients with panic disorder with or without agoraphobia completed a double-blind, placebo-controlled, four week, random-assignment crossover treatment trial of inositol 12 g per day. Frequency and severity of panic attacks and severity of

agoraphobia declined significantly with inositol compared to placebo. Side-effects were minimal. Since serotonin reuptake inhibitors benefit obsessive compulsive disorder (OCD) and inositol is reported to reverse desensitization of serotonin receptors, thirteen patients with OCD completed a double-blind controlled crossover trial of 18 g inositol or placebo for six weeks each. Inositol significantly reduced scores of OCD symptoms compared with placebo. A controlled double-blind crossover trial of 12 g daily of inositol for a month in twelve anergic schizophrenic patients, did not show any beneficial effects. A double-blind controlled crossover trial of 6 g of inositol daily vs. glucose for one month each was carried out in eleven Alzheimer patients, with on clearly significant therapeutic effects. Antidepressant drugs have been reported to improve attention deficit disorder (ADDH) with hyperactivity symptomatology. We studied oral inositol in children with ADDH in a double-blind, crossover, placebo-controlled manner. Eleven children, mean age 8.9 +/- 3.6 years were enrolled in an eight week trial of inositol or placebo at a dose of 200 mg/kg body weight. Results show a trend for aggravation of the syndrome with myo-inositol as compared to placebo. Recent studies suggest that serotonin reuptake inhibitors are helpful in at least some symptoms of autism. However a controlled double-blind crossover trial of inositol 200 mg/kg per day showed no benefit in nine children with autism. Cholinergic agonists have been reported to ameliorate electroconvulsive therapy (ECT)-induced memory impairment. Inositol metabolism is involved in the second messenger system for several muscarinic cholinergic receptors. Inositol 6 g daily was given in a crossover-double-blind manner for five days before the fifth or sixth ECT to a series of twelve patients, without effect. These results suggest that inositol has therapeutic effects in the spectrum of illness responsive to serotonin selective reuptake inhibitors, including depression, panic and OCD, and is not beneficial in schizophrenia, Alzheimer’s ADDH, autism or ECT-induced cognitive impairment.

28B. Levine, Joseph, et al. Double-blind, controlled trial of inositol treatment of depression. *American Journal of Psychiatry* 152.5 (1995): 792-793.

Objective: CSF levels of inositol have been reported to be lower than normal in depressed subjects. The authors administered inositol to depressed patients in a double-blind, controlled trial.

Method: Under double-blind conditions, 12 g/day of inositol (N = 13) or placebo (N = 15) was administered to depressed patients for 4 weeks.

Results: The overall improvement in scores on the Hamilton Depression Rating Scale was significantly greater for inositol than for placebo at week 4. No changes were noted in hematology or in kidney or liver function.

Conclusions: This may be the first use of the precursor strategy for a second messenger rather than a neurotransmitter in treating depression. Although inositol had a significant antidepressant effect in this study, replication is crucial.

28C. Harvey, Brian H., et al. Defining the neuromolecular action of myo-inositol: application to obsessive-compulsive disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 26.1 (2002): 21-32.

29. Chiappelli, Joshua, et al. Evaluation of myo-inositol as a potential biomarker for depression in schizophrenia. *Neuropsychopharmacology* 40.9 (2015): 2157-2164.

AODM type 2 diabetes

30. Pintaudi, Basilio, Giacoma Di Vieste, and Matteo Bonomo. The effectiveness of myo-inositol and D-chiro inositol treatment in type 2

diabetes. *International Journal of Endocrinology* 2016 (2016).

31. Omoruyi, Felix O., et al. New frontiers for the use of IP6 and inositol combination in treating diabetes mellitus: A review. *Molecules* 25.7 (2020): 1720.

A daily oral dose of 18 g of inositol for three months has been reported to be safe and well-tolerated.[14] Others have suggested that myo-inositol is safe up to doses of 12 g per day.[15] Clements and Darnell[16] observed that the greatest amounts of myo-inositol were present in fruits, beans, grains, and nuts. Myo-inositol serves as the backbone and precursor of other inositol phosphates. It is produced in the human body from d-glucose and is present in all living cells as phosphatidylinositol and phytic acid.[17] It plays important physiological roles, which include mediation of osmoregulation, anticancer activity, and the enhancement of the anticancer effects of IP6 on various cancers.[18-20] It is also involved in the regulation of insulin release from the pancreatic beta-cells.[21-24]

Sanchis et al. reported that 3-month IP6 diet consumption significantly reduced the levels of circulating advanced glycation end products in patients with type 2 diabetes mellitus alongside a 3.8% decline in HbA1C, which they presumably attributed to reduced protein glycation.[52]

The combination of IP6 and inositol has been known to be effective in cancer treatment and is frequently reported today.[58]

PCOS

32. Greff, Dorina, et al. Inositol is an effective and safe treatment in polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled trials. *Reproductive Biology and Endocrinology* 21.1 (2023): 10.

32B.. Bevilacqua, Arturo, Simona Dinicola, and Mariano Bizzarri. Treating PCOS with inositols: Choosing the most appropriate myo-to d-

chiro-inositol ratio. *A Clinical Guide to Inositols*. Academic Press, 2023. 53-64

33. Haghollahi, Fedyeh, et al. Polycystic Ovary Syndrome in Adolescence: From the Cradle to the Grave. *Fertility, Gynecology and Andrology* 2.1 (2022).

34. Barbaro, Daniele, Beatrice Orrù, and Vittorio Unfer. Iodine and myo-inositol: a novel promising combination for iodine deficiency. *Frontiers in Endocrinology* 10 (2019): 457.

Myo-inositol, a carbocyclic polyol, regulates the generation of hydrogen peroxide (H2O2) in thyrocytes, crucial for iodine organification and thyroid hormone biosynthesis.

Either *in vitro* and *in vivo* iodide main roles are:

(1) decreasing the response of TSH;

(2) inhibiting its own oxidation (the Wolff-Chaikoff effect);

(3) reducing its trapping after a delay;

(4) at high levels, inhibiting thyroid hormone secretion.

The Wolff-Chaikoff effect is an autoregulatory phenomenon that prevents the thyroid gland from synthesizing and releasing large quantities of thyroid hormones[19,29] through the inhibition of organification when inorganic iodide levels in thyrocytes are too high.[30,31] The mechanism responsible for such effect is still unknown, but it may be ascribable to the inhibitory effect of iodide on TPO or other enzymes.[19] Indeed, iodide is able to block the cyclic adenosine monophosphate cascade and the Ca2+-phosphatidylinositol 4, 5-bisphosphate (PIP2) cascade in thyrocytes and to induce H2O2 generation.[28] H2O2 is crucial for the TPO-catalyzed thyroid hormone

formation.[32] In 1993, Chen at al. demonstrated *in vitro* that H2O2 specifically regulates iodide transport and organification in a dose-dependent manner.[33] High H2O2 concentrations inhibit these functions and can be detrimental to the thyroid, although protection mechanisms prevents damages to the thyrocytes under physiological conditions.[34] Intrathyroidal H2O2 generation, first reported about 50 years ago,[35] and iodination are both stimulated by TSH. H2O2 can regulate iodination either directly, as a substrate of TPO, or indirectly by regulating the activity of TPO when iodide and Tg concentrations are kept constant.

As a precursor also of the second messenger phosphoinositide, myo-inositol is involved in cell signaling and regulates the activities of hormones such as TSH, follicle-stimulating hormone (FSH) and insulin.[37-39]

It recently proved to be a very efficacious and safe treatment for subclinical hypothyroid patients with Autoimmune Thyroiditis.[40-46] In 2013, Nordio and Pajalich demonstrated that treatment with myo-inositol plus selenium for 6 months in patients with subclinical hypothyroidism reduced significantly TSH concentrations by 31% (4.4 ± 0.9 mIU/mL vs. 3.1 ± 0.6 mIU/mL), compared to the control group treated only with selenium.

Interestingly, myo-inositol helps thyroid-hormone-producing cells to become more efficient and faster at building T4.[32,41] This might be ascribable to a higher availability of iodine, whose organification is boosted by myo-inositol action. Indeed, myo-inositol is involved in one of the first steps of thyroid hormone production and modulates the H2O2-mediated iodination through the phospholipase C-dependent inositol phosphate Ca2+/diacylglycerol pathway, resulting in increased H2O2 generation (Figure 1).

Differently, the cAMP cascade, induced by the TSH activity (through the TSH receptor activation), is more involved in cell growth and differentiation, and in thyroid hormone secretion.

As myo-inositol plays a crucial role in the regulation of iodine organification, supplementation may promote faster recovery from ID. Indeed, H2O2 generated under the stimulus of myo-inositol is available for iodine incorporation inside the thyroid.[33,48] Such activity makes myo-inositol very appealing as a novel molecule to increase iodine availability.

To date, endocrinologists and gynecologists recommend taking myo-inositol for several benefits in different pathologies, from thyroid diseases to polycystic ovary syndrome and gestational diabetes. Due to its action in regulating iodine organification and thyroid hormone biosynthesis, myo-inositol supplementation along with iodine may improve thyroid functionality and possibly lead to a faster recovery from ID. …When iodine intake is insufficient, the T3:T4 ratio increases along with the decrease of T4 production,

Hashimotos

35. Fallahi, Poupak, et al. Myo-inositol in autoimmune thyroiditis, and hypothyroidism. *Reviews in Endocrine and Metabolic Disorders* 19.4 (2018): 349-354.

36. Ferrari, Silvia Martina, et al. Chemokines in hyperthyroidism. *Journal of Clinical and Translational Endocrinology* 16 (2019): 100196.

37)

38. Pace, Cinzia, et al. Role of selenium and myo-inositol supplementation on autoimmune thyroiditis progression. *Endocrine*

Journal 67.11 (2020): 1093-1098.

39. Pankiv, Ivan, et al. Efficacy of a combined administration of myo-inositol and vitamin D in patients with autoimmune thyroiditis. *Endocrine Abstracts*. Vol. 73. Bioscientifica, 2021.

Autoimmune thyroiditis (AIT) is one of the most common autoimmune diseases, affecting more than 10% of females and 2% of males in the overall population.

74 outpatients (mean age 42.39 ± 8.2 years) with AIT were enrolled in this prospective randomized controlled trial from May to September 2019. A total of 74 patients with AIT having TSH levels between 4.0 and 6.0 μIU/ml, elevated serum thyroid peroxidase antibodies (TPO-Ab) and thyroglobulin antibodies (Tg-Ab), normal free thyroxine (fT4) and free triiodothyronine (fT3) levels were randomized into 2 groups: one receiving MI-VD and the other one VD alone.

A significant decrease in serum TSH levels was noted in patients of group MI-VD compared prior and after treatment ($P < 0.05$), showing at baseline 5.18 ± 0.52 μIU/ml and 3.06 ± 0.48 μIU/ml over 6 months treatment.

The administration of MI-VD is significantly effective in decreasing TSH, TPO-Ab and Tg-Ab levels. Such treatment restored euthyroidism in patients diagnosed with AIT.

40. Ferrari, Silvia Martina, et al. Precision medicine in autoimmune thyroiditis and hypothyroidism. *Frontiers in Pharmacology* (2021): 3123.

Myoinositol has a crucial role in thyroid autoimmunity and function. Clinical studies reported a significant decline in TSH and antithyroid autoantibodies levels after treatment with myo-inositol + selenium in patients with subclinical hypothyroidism and autoimmune thyroiditis.

Moreover, myoinositol has a key role in thyroid autoimmunity and function. A significant decline in TSH and ATA levels has been reported in patients with subclinical hypothyroidism and AT after treatment with myoinositol + selenium, corroborating the immune-modulatory effect of myoinositol (Ferrari et al., 2017b).

41. Martina, Ferrari Silvia, et al. Autoimmune thyroiditis and hypothyroidism: a personalized medical approach. *Endocrine Abstracts*. Vol. 81. Bioscientifica, 2022.

42. Concerto, Carmen, et al. Neurobiology and Applications of Inositol in Psychiatry: A Narrative Review. *Current Issues in Molecular Biology* 45.2 (2023): 1762-1778.

43. Krysiak, Robert, Karolina Kowalcze, and Bogusław Okopień. The impact of vitamin D on thyroid autoimmunity and hypothalamic–pituitary–thyroid axis activity in myo-inositol-treated and myo-inositol-naïve women with autoimmune thyroiditis: A pilot study. *Journal of Clinical Pharmacy and Therapeutics* 47.11 (2022): 1759-1767.

The impact of vitamin D on thyroid autoimmunity and hypothalamic-pituitary-thyroid axis activity in subjects with autoimmune thyroiditis is more pronounced if they receive myo-inositol.

44. Martina, Ferrari Silvia, et al. Autoimmune thyroiditis and hypothyroidism: a personalized medical approach. *Endocrine Abstracts*. Vol. 81. Bioscientifica, 2022.

Furthermore, the administration of myoinositol and seleno-methionine in patients with subclinical hypothyroidism and AT showed promising effect; with a significant decline in TSH and antithyroid autoantibodies levels. Actually, myoinositol, which is the precursor of phosphoinositides and takes part into various cellular processes, has also a key role in thyroid autoimmunity and function.

45. Payer, Juraj, et al. Supplementation with myo-inositol and Selenium improves the clinical conditions and biochemical features of women with or at risk for subclinical hypothyroidism. *Frontiers in Endocrinology* 13 (2022).

In the molecular network underpinning thyroid activity, myo-Inositol (myo-Ins) covers a pivotal role.[1,15] Particularly myo-Ins besides the recognized activity of insulin-sensitizer in diabetic scenarios,[16,17] increases the sensitivity of the thyrocytes to TSH, thus contributing to maintain thyroid physiology.[18] Data retrieved from metabolic investigations described a higher demand of myo-Ins in subjects exhibiting hypothyroidism with respect to healthy individuals[19] and suggest that in hypothyroid patients the administration of exogenous myo-Ins might exert a positive activity on the thyroid functioning.[20]

Growing evidence indicates the use of myo-Ins as an effective approach to treat AITDs [autoimmune thyroid disease] and SCH [Subclinical hypothyroidism] conditions, especially when its administration is associated with the Selenium (Se).[27-29] Indeed, Se is an essential micronutrient in the selenoprotein biosynthesis, and is crucial in metabolism, homeostasis, and regulation of thyroid hormones.[30,31] The presence of Se improves the efficacy of myo-Ins treatment in patients affected by AITDs, thanks to its recognized antioxidant and anti-inflammatory activity.[32,33] Even if the beneficial role of Se is well described and recognized in literature, the administration of Se in association with myo-Ins seems more effective in reducing the TSH levels in hypothyroid patients than the administration of the only Se.[29,34-36] The combined administration of myo-Ins plus Se seems effective to reduce the TSH and auto-antibody levels, thus enhancing thyroid wellbeing, and therefore restoring euthyroidism in patients diagnosed with AITD.[37]

In detail, 38 patients were positive to TPO-Ab (TPO-Ab > 34 IU/ml) and 48 patients were positive to Tg-Ab (Tg-Ab > 115 IU/ml). After 6 months of treatment, the titer of TPO-Ab significantly decreased at T6 in more than 60% of patients, with a median value of the variation of -21 IU/L ($p<0.001$). The treatment had no effect on the remainder of patients.

The treatment significantly improved also the Tg-Ab titer at T6 with respect to T0 in more than 57% of the patients, with a median value of the variation of -46 IU/L ($p<0.001$). The treatment had no effect in the remainder of patients.

A significant improvement of the menstrual cycle was observed after 3 months of treatment ($p<0.001$), with the percentage of women with regular cycle that increased from 71.8% to 84.6%, and the percentage of women with absent/irregular menstrual cycles that decreased from 28.2% to 15.4%. The improvement of the menstrual cycle remained significant also after 6 months of treatment ($p<0.05$) (Figure 2A), without significant differences between T3 and T6.

46. Barbaro, Daniele, Giuseppina Porcaro, and Salvatore Benvenga. Myo-inositol for subclinical hypothyroidism and potential prevention of thyroid tumors. *A Clinical Guide to Inositols*. Academic Press, 2023. 213-231.

Myo-inositol when administered with selenium in patients affected by autoimmune thyroiditis contributes to restore the euthyroid status, to reduce the titer of the autoantibodies, and to prevent the progression of SCH to overt hypothyroidism. This positive activity of myo-inositol is further demonstrated in cases of hypothyroidism during pregnancy. Moreover, preliminary evidence on the role of myo-inositol on thyroid cancer has also been investigated, and the data on thyroid nodules appear promising. Also, animal studies suggest a protective effect of

myo-inositol against proliferation of cancer cells and indirectly by inhibition of secretion of chemokines.

Serum Negative Hashimotos

47. Lenti, Marco Vincenzo, et al. Seronegative autoimmune diseases: A challenging diagnosis. *Autoimmunity Reviews* (2022): 103143.

48. Croce, L., et al. Compared with classic Hashimoto's thyroiditis, chronic autoimmune serum-negative thyroiditis requires a lower substitution dose of L-thyroxine to correct hypothyroidism. *Journal of Endocrinological Investigation* 43 (2020): 1631-1636.

Purpose: Serum-negative-chronic-autoimmune-thyroiditis (SN-CAT) is considered a milder variant of classic Hashimoto's thyroiditis (CHT). However, its prevalence remains unknown and it is still unclear whether SN-CAT behaves differently in terms of L-thyroxine (LT4) substitution treatment of hypothyroidism. Aims of this study were to estimate the prevalence of SN-CAT in a large series of hypothyroid patients and to compare LT4 requirements in hypothyroid patients with SN-CAT and CHT.

Methods: Five-hundred-eighty-one consecutive patients with primary-autoimmune-hypothyroidism were enrolled in a cross-sectional study. LT4 requirements and thyroid-volume changes were longitudinally evaluated in 49 hypothyroid patients with SN-CAT and in 98 sex and age-matched hypothyroid patients with CHT.

Results: In our series the prevalence of SN-CAT was 20.8%. At diagnosis, patients in the CHT and SN-CAT groups had similar male/female ratio, age and BMI, while serum TSH and thyroid-volume were significantly greater in the CHT group. In the longitudinal study, during a follow-up of 8.9 ± 4.6 years, 8 out of 49 (16.3%) SN-CAT patients developed positive tests for circulating TPO-Ab and/or Tg-Ab.

Thyroid-volume significantly decreased in CHT patients, but not in those with SN-CAT. The maximum daily substitution dose of LT4 was smaller in SN-CAT patients as compared with the CHT ones. Multivariate analysis showed that age, BMI, basal TSH and thyroid antibody status independently and significantly predicted the maximum daily substitution dose of LT4.

Conclusions: SN-CAT accounts for a significant proportion of patients with autoimmune hypothyroidism. Compared with hypothyroid patients diagnosed with CHT, the SN-CAT ones require smaller doses of LT4 to correct their hypothyroidism.

48B. Jeong, Sun Hye, Hyun Sook Hong, and Ji Ye Lee. The association between thyroid echogenicity and thyroid function in pediatric and adolescent Hashimoto's thyroiditis. *Medicine* 98.14 (2019).

48C. Raber, Wolfgang, et al. Thyroid ultrasound versus antithyroid peroxidase antibody determination: a cohort study of four hundred fifty-one subjects. *Thyroid* 12.8 (2002): 725-731.

49. Barbaro, Daniele, Giuseppina Porcaro, and Salvatore Benvenga. Myo-inositol for subclinical hypothyroidism and potential prevention of thyroid tumors. *A Clinical Guide to Inositols*. Academic Press, 2023. 213-231.

Inositol as Anticancer Agent

50. Vucenik, Ivana, Ana Druzijanic, and Nikica Druzijanic. Inositol hexaphosphate (IP6) and colon cancer: From concepts and first experiments to clinical application. *Molecules* 25.24 (2020): 5931.

51. Chen, Qian, Liangfang Shen, and Shan Li. Emerging role of inositol monophosphatase in cancer. *Biomedicine and Pharmacotherapy* 161 (2023): 114442.

52. Vucenik, Ivana. Anticancer properties of inositol hexaphosphate and inositol: An overview. *Journal of Nutritional Science and Vitaminology* 65.Supplement (2019): S18-S22.

53. Bizzarri, Mariano, et al. Broad spectrum anticancer activity of myo-inositol and inositol hexakisphosphate. *International Journal of Endocrinology* 2016 (2016).

54. Barbaro, Daniele, Giuseppina Porcaro, and Salvatore Benvenga. Myo-inositol for subclinical hypothyroidism and potential prevention of thyroid tumors. *A Clinical Guide to Inositols*. Academic Press, 2023. 213-231.

55. Barbaro, Daniele, Beatrice Orrù, and Vittorio Unfer. Iodine and myo-inositol: a novel promising combination for iodine deficiency. *Frontiers in Endocrinology* 10 (2019): 457.

56. Nordio, M., S. Basciani, and E. Camajani. The 40: 1 myo-inositol/D-chiro-inositol plasma ratio is able to restore ovulation in PCOS patients: comparison with other ratios. *Eur Rev Med Pharmacol Sci* 23.12 (2019): 5512-5521.

57. Benvenga, Salvatore, et al. Protective effects of myo-inositol and selenium on cadmium-induced thyroid toxicity in mice. *Nutrients* 12.5 (2020): 1222.

58. Benvenga, Salvatore, et al. The association of myo-inositol and selenium contrasts cadmium-induced thyroid C cell hyperplasia and hypertrophy in mice. *Frontiers in Endocrinology* 12 (2021): 608697.

59. Welker, Mary Jo, and Diane Orlov. Thyroid nodules. *American Family Physician* 67.3 (2003): 559-566.

60. Clark, Orlo H. TSH suppression in the management of thyroid

nodules and thyroid cancer. *World Journal of Surgery* 5.1 (1981): 39-46.

61. Wémeau, Jean-Louis, et al. Effects of thyroid-stimulating hormone suppression with levothyroxine in reducing the volume of solitary thyroid nodules and improving extranodular nonpalpable changes: a randomized, double-blind, placebo-controlled trial by the French Thyroid Research Group. *The Journal of Clinical Endocrinology and Metabolism* 87.11 (2002): 4928-4934.

62. Castro, M. Regina, Pedro J. Caraballo, and John C. Morris. Effectiveness of thyroid hormone suppressive therapy in benign solitary thyroid nodules: a meta-analysis. *The Journal of Clinical Endocrinology and Metabolism* 87.9 (2002): 4154-4159.

63. Gambioli, R., et al. The use of D-chiro-Inositol in clinical practice. *Eur. Rev. Med. Pharmacol.* Sci 25.1 (2021): 438-446.

D-chiro-Inositol has been widely used in clinical practice to induce ovulation in women with polycystic ovary syndrome. Only recent evidence established that this molecule acts through two different mechanisms, with potentially different outcomes. On the one hand, under a metabolic perspective, D-chiro-Inositol improves insulin signaling, thus restoring physiological insulin levels in resistant subjects. On the other hand, at a cellular level, it downregulates the expression of steroidogenic enzyme aromatase, which is responsible for the conversion of androgens to estrogens.

D-Chiro-Ins Treatment in Men Increase of Androgens Hypogonadotropic hypogonadism

Thus, dchiro-Ins could be a suitable treatment in hypogonadal hypogonadotropic patients, inhibiting aromatase expression and naturally restoring physiological androgen levels.

On the other hand, like aromatase inhibitors, dchiro-Ins must be avoided in primary hypogonadal males, where it could worsen the already overburdened gonadotropin signaling. Our preliminary unpublished data support the use of dchiro-Ins in hypogonadotropic hypogonadal males, showing that short-term administration of high dosages may improve hormonal parameters in these patients. We investigated the effects of 1200 mg/die dchiro-Ins for 30 days in elderly hypogonadal male subjects. In patients currently enrolled, testosterone increased by approximately 20% after 30 days of dchiro-Ins administration (Table I).

Male Breast Cancer (MBC) is an important estrogen-sensitive cancer, representing about 1% of total breast cancers. Despite MBC is known to respond to estrogens, current studies on aromatase expression remain controversial. Feminizing Adrenocortical Tumors are other important male cancerous formations that usually produce massive amounts of estrogens and androgens, which are later aromatized in other tissues. The resulting steroidal unbalance causes hyperestrogenism and related diseases, such as gynecomastia27. In these clinical pictures, dchiro-Ins adjuvant treatment could be very useful to reduce aromatase expression and thus estrogen production, restoring the physiological ratio between estrogens and androgens.

64. Korkmaz, Serol, S. A. İ. T. Ahmet, and Ayşen Gargili. The Potential Antiviral Activity of Inositol (Vitamin B8) as a Dietary Supplement in Human and Animal Nutrition. *Journal of Health Sciences and Management* 2.3 (2022): 68-72.

Gestational Diabetes

65. Motuhifonua, Soana K., et al. Antenatal dietary supplementation with myo-inositol for preventing gestational diabetes. *Cochrane Database of Systematic Reviews* 2 (2023).

66. Facchinetti, Fabio, Rosario D'Anna, and Moshe Hod. Inositol supplementation for preventing gestational diabetes mellitus. *A Clinical Guide to Inositols*. Academic Press, 2023. 123-150.

Psychiatry

67. Cantelmi, Tonino, and Cherubino Di Lorenzo. Myo-inositol could restore peripheral inositol depletion induced by treatments for psychiatric and neurological conditions. *A Clinical Guide to Inositols*. Academic Press, 2023. 73-85.

Neurological and psychiatric conditions, like bipolar disorder (BD), include the excessive activation of neuronal phosphoinositide signaling pathway among the pathogenetic mechanisms. The pharmacological management relies on the use of mood stabilizers like lithium (Li+), valproic acid (VA), and carbamazepine (CBZ) with the aim to reduce the firing and the severity of the manic phases, which are typical of BD. One of their mechanisms of action consists in reducing levels of inositol in the brain, whose high levels in the central nervous system (CNS) correlate with the firing of the manic phases. However, the use of such drugs exposes patients to various side effects that share an altered metabolism of inositols. Indeed, the inositol depletion occurring in CNS as a therapeutic outcome involves also peripheral tissues thus determining the occurrence of pathological conditions like hypothyroidism, polycystic ovary syndrome (PCOS), weight gain, cardiac and renal alterations, dermatological problems. To date, clinicians have no tools to counteract such side effects; therefore, inositol administration represents a step forward in the management of patients with BD bridging the therapeutic gap in clinical practice.

Obesity

68. Tutunchi, Helda, Sara Arefhosseini, and Mehrangiz Ebrahimi-Mameghani. Clinical Effectiveness of α-Lipoic Acid, Myo-Inositol and

Propolis Supplementation on Metabolic Profiles and Liver Function in Obese Patients with NAFLD: A Randomized Controlled Clinical Trial. *Clinical Nutrition ESPEN* (2023).

69. Arefhosseini, Sara, et al. Myo-inositol supplementation improves cardiometabolic factors, anthropometric measures, and liver function in obese patients with non-alcoholic fatty liver disease. *Frontiers in Nutrition* 10 (2023).

70. Diamanti-Kandarakis, Evanthia, Olga Papalou, and Christophe O. Soulage. Effectiveness of Myo-and d-chiro-inositol in the treatment of metabolic disorders. *A Clinical Guide to Inositols*. Academic Press, 2023. 31-51.

71. Kamenov, Zdravko, and Mario Montanino Oliva. Overcoming inositol resistance. *A Clinical Guide to Inositols*. Academic Press, 2023. 65-72.

72. Pkhaladze, Lali, Vittorio Unfer, and Didier Dewailly. Use of myo-inositol in the treatment of PCOS symptoms in adolescents. *A Clinical Guide to Inositols*. Academic Press, 2023. 151-165.

73. DiNicolantonio, James J., and James H. O'Keefe. Myo-inositol for insulin resistance, metabolic syndrome, polycystic ovary syndrome and gestational diabetes. *Open Heart* 9.1 (2022): e001989.

74. Amabile, Maria Ida, et al. Effects of Inositol Hexaphosphate and Myo-Inositol Administration in Breast Cancer Patients during Adjuvant Chemotherapy. *Journal of Personalized Medicine* 11.8 (2021).

75. Unfer, Vittorio, Simona Dinicola, and Michele Russo. A PCOS Paradox: Does Inositol Therapy Find a Rationale in All the Different Phenotypes?. *International Journal of Molecular Sciences* 24.7 (2023): 6213.

The efficacy of inositol supplementation in PCOS scenarios has been endorsed worldwide for more than 20 years,[53] but interestingly, therapy

with inositols is not appropriate for patients exhibiting phenotype D PCOS, since they are not affected by hyperandrogenism and do not always experience dysmetabolism.[16]

The Rotterdam criteria include oligo-anovulation (OA) (cycles greater than 35-day intervals or 8 cycles or less per year), hyperandrogenism (HA), and polycystic ovary morphology (PCOM) (ovarian volume of 10 ml and/or an antral follicle count [AFC] of more than 12 cysts of 2–9 mm in diameter, any two being enough for the diagnosis of PCOS) [7]. Based on Rotterdam criteria, four main phenotypes were described:

phenotype A, composed of OA, HA, and PCOM;

phenotype B (OA and HA);

phenotype C (HA and PCO); and

phenotype D (OA and PCO)[8] oligo-anovulation (OA) (cycles greater than 35-day intervals or 8 cycles or less per year), NO HA

Diabetes and Metabolic Syndrome

76. DiNicolantonio, James J., and James H. O'Keefe. Myo-inositol for insulin resistance, metabolic syndrome, polycystic ovary syndrome and gestational diabetes. *Open Heart* 9.1 (2022): e001989.
Myo-inositol should be considered in patients with insulin resistance, metabolic syndrome, type 1 diabetes, type 2 diabetes, PCOS and those with or at risk of gestational diabetes. Elevated levels of glucose reduce myo-inositol levels in tissues and increase its breakdown and elimination via the kidneys. Myo-inositol has been used safely for decades in many studies in those with insulin resistance and PCOS.

77. Wang, Yiguo, et al. Inositol-1, 4, 5-trisphosphate receptor regulates hepatic gluconeogenesis in fasting and diabetes. *Nature* 485.7396

(2012): 128-132.

78. Omoruyi, Felix O., et al. New frontiers for the use of IP6 and inositol combination in treating diabetes mellitus: A review. *Molecules* 25.7 (2020): 1720.

We demonstrated that an IP6 and inositol combination supplement may regulate insulin secretion, modulate serum leptin concentrations, food intake, and associated weight gain, which may be beneficial in both prediabetic and diabetic states.

79. Özturan, Ayçıl, et al. Effect of inositol and its derivatives on diabetes: a systematic review. *Critical Reviews in Food Science and Nutrition* 59.7 (2019): 1124-1136.

80. Pintaudi, Basilio, Giacoma Di Vieste, and Matteo Bonomo. The effectiveness of myo-inositol and D-chiro inositol treatment in type 2 diabetes. *International Journal of Endocrinology* 2016 (2016).

Inositol has been used as a supplement in treating several pathologies such as PCOS, metabolic syndrome, and gestational diabetes. Both myo-inositol and its isomer d-chiro-inositol showed insulin mimetic effects in conditions of insulin resistance. Type 2 diabetes (T2DM) is a condition typically caused by insulin resistance. There is a lack of evidence of inositol use in T2DM. We evaluated the effectiveness and safety of myo-inositol and d-chiro-inositol treatment in T2DM. This was a pilot study involving a consecutive sample of patients with T2DM with suboptimal glycemic control (HbA1c 7.0–10.0%) already treated with glucose-lowering agents.

Patients (23.1% males, mean age of 60.8 ± 11.7 years) took for three months a combination of myo-inositol (550 mg) and d-chiro-inositol (13.8 mg) orally twice a day as add-on supplement to their glucose-lowering drugs. Possible occurrence of side effects was investigated.

After three months of treatment fasting blood glucose (192.6 ± 60.2 versus 160.9 ± 36.4; p = 0.02) and HbA1c levels (8.6 ± 0.9 versus 7.7 ± 0.9; p = 0.02) significantly decreased compared to baseline.

There was no significant difference in blood pressure, lipid profile, and BMI levels. None of the participants reported side effects. In conclusion, a supplementation with a combination of myo- and d-chiro-inositol is an effective and safe strategy for improving glycemic control in T2DM.

81. Santamaria, A., et al. One-year effects of myo-inositol supplementation in postmenopausal women with metabolic syndrome. (2012): 490-495.

Objective: To evaluate the 12-month effect of myo-inositol treatment on some biochemical parameters of women affected by metabolic syndrome.

Methods: Eighty outpatient postmenopausal women, affected by metabolic syndrome, were enrolled in a 12-month study. All women were treated with a low-energy diet, and then they were randomly assigned to myo-inositol 2 g b.i.d. (n = 40) or placebo (n = 40). All the women were evaluated for serum glucose, insulin, HOMA-IR (Homeostasis Model Assessment-Insulin Resistance), triglycerides, total and high density lipoprotein cholesterol, body mass index (BMI), waist circumference and blood pressure at baseline and after 12 months of treatment.

Results: With the exception of BMI and waist circumference, after 12 months of treatment, all the parameters studied showed a significant improvement in the myo-inositol group compared to the control group. At the end of the study, in the myo-inositol group, the number of women without metabolic syndrome was eight (20%) whereas, in the control

group, only one woman no longer had the metabolic syndrome after 12 months of diet.

Conclusions: Myo-inositol might be considered one of the insulin-sensitizing substances in the treatment of metabolic syndrome.

82) Mancini, Mario, et al. Myoinositol and D-Chiro Inositol in Improving Insulin Resistance in Obese Male Children: Preliminary Data. *International Journal of Endocrinology* 2016 (2016): 8720342.

The effectiveness of inositol in lowering plasma glucose concentration and postprandial blood glucose levels has been reported in several cases of mellitus diabetes in rats, monkeys, and humans. These studies showed that this effect was related to insulin-sensitizing activity.[15-18] D-Pinitol exerted an acute and chronic insulin-like antihyperglycemic effect on glucose transport in STZ-diabetic mice, but acute administration of D-pinitol did not significantly alter plasma glucose or insulin concentration over 6 hours in severely insulin-resistant ob/ob mice.[19] When administered to insulin-resistant and diabetic monkeys, D-chiro inositol accelerated glucose disposal and activated glycogen synthase in muscle biopsies beyond that of maximal insulin stimulation.[20] Pinitol was administered to humans with type II diabetes for 13 weeks and it significantly decreased mean fasting plasma glucose and insulin and improved lipid profile,

82. D'anna, R., et al. Myo-inositol may prevent gestational diabetes in PCOS women. *Gynecological Endocrinology* 28.6 (2012): 440-442.

83. Mashayekh-Amiri, Sepideh, et al. Myo-inositol supplementation for prevention of gestational diabetes mellitus in overweight and obese pregnant women: a systematic review and meta-analysis. *Diabetology and Metabolic Syndrome* 14.1 (2022): 1-15.

84. Genazzani, Alessandro D., et al. Modulatory role of D-chiro-inositol (DCI) on LH and insulin secretion in obese PCOS patients. *Gynecological Endocrinology* 30.6 (2014): 438-443.

85. Chatree, Saimai, et al. Role of inositols and inositol phosphates in energy metabolism. *Molecules* 25.21 (2020): 5079.

86. Cabrera-Cruz, Heidy, et al. The insulin-sensitizing mechanism of myo-inositol is associated with AMPK activation and GLUT-4 expression in human endometrial cells exposed to a PCOS environment. *American Journal of Physiology-Endocrinology and Metabolism* 318.2 (2020): E237-E248.

Cancer

87. Vucenik, Ivana. Anticancer properties of inositol hexaphosphate and inositol: An overview. *Journal of Nutritional Science and Vitaminology* 65.Supplement (2019): S18-S22.

88. Yuan, Guixin, et al. Phosphatidyl inositol 3-kinase (PI3K)-mTOR inhibitor PKI-402 inhibits breast cancer induced osteolysis. *Cancer Letters* 443 (2019): 135-144.

89. Khurana, Sharad, Candice Baldeo, and Richard W. Joseph. Inositol hexaphosphate plus inositol induced complete remission in stage IV melanoma: A case report. *Melanoma Research* 29.3 (2019): 322-324.

Inositol hexaphosphate (IP6) also called phytic acid is a polyphosphorylated carbohydrate naturally found in cereals, nuts, grains, and high-fiber-containing foods. It has been shown to inhibit the growth of many different tumor cell lines both in vitro and in vivo like colon, pancreas, liver, prostate, and even melanoma. Vitamin B inositol is a precursor of IP6 and another naturally occurring compound with anticancer properties. We present a case report of a patient with metastatic melanoma who declined traditional therapy and opted to try

over the counter supplement IP6+inositol instead. To our surprise, the patient achieved a complete remission and remains in remission 3 years later. On the basis of this case and previous preclinical studies, we believe further research is indicated in exploring antiproliferative and potential immune stimulating effects of IP6+inositol in patients with metastatic melanoma.

90. Liu, Xiaohan, et al. Combination of inositol hexaphosphate and inositol inhibits liver metastasis of colorectal cancer in mice through the Wnt/β-catenin pathway. *OncoTargets and Therapy* (2020): 3223-3235.

IP6+INS Inositol hexaphosphate (IP6) and inositol (INS) was more effective in inhibiting liver metastasis of colorectal cancer than IP6 or INS alone. The better inhibition effect may be accomplished through regulating the mutation of Wnt/β-catenin signaling pathway by inhibiting Wnt10b, Tcf7, β-catenin, and c-Myc from abnormally high expression.

92. Shan, Kuizhong, et al. Inositol hexakisphosphate induces apoptosis, cell cycle arrest in non-Hodgkin's Burkitt lymphoma cells and mediates anti-angiogenic, antitumor effects in T-cell lymphoma bearing Swiss albino mice. *Arabian Journal of Chemistry* 15.5 (2022): 103760.

93. Li, Chunlei, et al. Inositol hexakisphosphate and inositol enhance the inhibition of colorectal cancer growth and liver metastasis by capecitabine in a mouse model. *Nutrition and Cancer* 73.11-12 (2021): 2306-2314.

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Effects of myo-inositol plus alpha-lactalbumin in myo-inositol-resistant PCOS women Mario Montanino Oliva 1 , Giovanna Buonomo 2 , Marco Calcagno 2 , Vittorio Unfer 3 Ovarian Res 2018 May 10;11(1):38.

Background: Myo-inositol (MI), successfully used in polycystic ovary syndrome (PCOS), was administered with α-LA to exploit its action of favoring the passage of other molecules through biological barriers, and also considering its anti-inflammatory effect.Methods: PCOS patients, according to the Rotterdam ESHRE-ASRM criteria, with anovulation and infertility > 1 year, were included in this open and prospective study. The preliminary phase was aimed at determining a set of MI-resistant

PCOS patients. This treatment involved 2 g MI, taken twice per day by oral route, for three months. The Homeostasis Model Assessment (HOMA) index and MI plasma levels were measured. In the main phase, previously selected MI-resistant patients received the same daily amount of MI plus 50 mg α-LA twice a day, for a further three months. Ovulation was assessed using ultrasound examination on days 12, 14 and 20 of the cycle. The HOMA index, lipid, hormone and MI plasma levels were detected at baseline and at the end of this phase.Results: Thirty-seven anovulatory PCOS subjects were included in the study. Following MI treatment, 23 of the 37 women (62%) ovulated, while 14 (38%) were resistant and did not ovulate. In the latter group, MI plasma levels did not increase. These MI-resistant patients underwent treatment in the main phase of the study, receiving MI and α-LA. After this combined treatment, 12 (86%) of them ovulated. Their MI plasma levels were found to be significantly higher than at baseline; also, a hormone and lipid profile improvement was recorded.

Conclusion: The combination of MI with α-LA allowed us to obtain significant progress in the treatment of PCOS MI-resistant patients. Therefore, this new formulation was able to re-establish ovulation, greatly increasing the chances of desired pregnancy.

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