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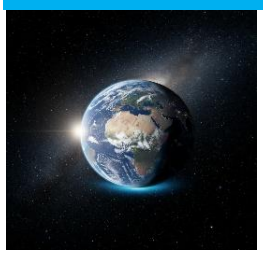

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Use of myo-inositol in treatment of subclinical hypothyroidism

Kacper Szada-Borzyszkowski
ORCID: https://orcid.org/0009-0006-4967-215X
Lower Silesian Center of Oncology, Pulmonology and Hematology, plac Ludwika Hirszfelda 12, 53-413 Wroclaw, Poland
e-mail: kacperrrada@gmail.com

Konstancja Owczarenko
ORCID: https://orcid.org/0009-0009-2232-7753
Lower Silesian Centre of Oncology, Pulmonology and Hematology, plac Ludwika Hirszfelda 12, 53-413 Wroclaw, Poland
e-mail: konstancja.owczarenko@gmail.com

Corresponding author: Kacper Szada-Borzyszkowski, kacperrrada@gmail.com

Abstract

Introduction Myo-inositol is a widely researched compound that is prevalent in nature. Its properties have been thoroughly analyzed, and its role in transduction of hormonal signal in cells has been proven. It is an important substrate for the synthesis of phosphatidylinositol 4,5-biphosphate, which is then broken down by phospholipase C, resulting in the activation of various cellular cascades. Due to this fact, this substance has been found to have many clinical applications, such as PCOS, diabetes, fertility disorders and neurological disorders. The use of myo-inositol in the treatment of subclinical hypothyroidism has been proposed due to the fact that the TSH receptor activates the aforementioned cascade, resulting in numerous clinical studies investigating the applications of this molecule in this condition.

Aim. The aim of this study is to review the current knowledge regarding the impact of myo-inositol supplementation on subclinical hypothyroidism.

Materials and methods. A search of PubMed and Google Scholar was carried out. Only studies concerning the use of myo-inositol on subclinical hypothyroidism were included, while studies investigating only overt hypothyroidism, euthyroidism, or other illnesses without subclinical hypothyroidism were excluded.

Results. All of the studies discussed in this review show that supplementation with myo-inositol helps to reduce TSH levels, anti-thyroid peroxidase antibodies (TPOAb), anti-thyroglobulin antibodies (TgAb), and improves the overall health of patients, while being a relatively safe compound with only a few negligible side effects.

Conclusion. Myo-inositol is a safe and reliable compound that can be used in the treatment of subclinical hypothyroidism. In the future it may be used as a first line treatment for this disorder.

Keywords: subclinical hypothyroidism, myo-inositol, thyroid, TSH

Introduction

The thyroid gland is located anterior to the trachea and inferior to the larynx. It is divided into two lobes connected by an isthmus and has a follicular microstructure. This gland is responsible for the production of the only two iodine-containing hormones- triiodothyronine (T3) and thyroxine (T4), which regulate a wide variety of physiological processes and affect almost all cells in the human body. These hormones are produced by thyrocytes and stored in the colloid fluid inside the follicles, bound to thyroglobulin, and released when needed. The production and release of these hormones are regulated by thyrotropin (TSH) produced in the pituitary gland, whose release is controlled by the thyrotropin-releasing hormone (TRH). This system is regulated by a negative feedback loop, in which an excess of thyroid hormones downregulates TSH and TRH, thereby reducing further production of thyroid hormones [1]. When TSH binds to the TSH receptor (TSHR), two signalling pathways are activated. The first pathway occurs via Gαs signalling and is dependent on cyclic adenosine monophosphate (cAMP) produced by adenylate cyclase, while the second pathway is dependent on inositol triphosphate (IP3) produced by phospholipase C (PLC). These pathways are responsible for the production and release of the thyroid hormones [2], [3].

When serum levels of T3 and T4 are below the reference range, a state of hypothyroidism can be diagnosed. Nevertheless some individuals may be in a state known as subclinical hypothyroidism, in which levels of T3 and T4 remain within the reference range, while TSH levels are elevated, indicating an insufficiency of thyroid hormone action. Although this insufficiency does not manifest in such a wide array of symptoms as overt hypothyroidism, it has been shown to cause long-term effects on multiple organs; therefore management by a physician is recommended [4]. The treatment of subclinical hypothyroidism remains a topic of debate, with several therapeutic approaches proposed [5]. One of the newly emerging treatments is supplementation with myo-inositol, which is part of the aforementioned TSH-TSHR signalling pathway. Inositol is a cyclic polyol, with myo-inositol being its most abundant form. Myo-inositol is a widely researched substance and has been applied in a broad range of conditions, such as polycystic ovary syndrome (PCOS), diabetes, gestational diabetes, and assisted reproductive technologies; however its applications appear to be much broader than

these indications alone [6], [7]. The aim of this review is to summarize the current knowledge regarding myo-inositol supplementation in subclinical hypothyroidism as a potential therapeutic approach.

Physiology of the thyroid gland

a) Hypothalamic - pituitary- thyroid axis

The most important factor regulating almost every step, from iodine uptake to the production and release of thyroid hormones is TSH. It is a glycoprotein produced in the pituitary gland, which is connected to the hypothalamus via a stalk called the infundibulum. Through this structure, signalling molecules, that can either stimulate or inhibit the release of pituitary hormones, are transported via blood vessels or nerve fibres [8]. The hypothalamic hormone responsible for the release of TSH is TRH, which is produced in the paraventricular nucleus and carried in the blood via the venous portal system to the anterior, where it binds to TRH receptors (TRHR1) on thyrotropes [9]. Subsequently, TSH is transported via the bloodstream and binds to the TSHR, stimulating thyroid follicular cells to produce and release T3 and T4, which in turn inhibit the release of TRH through a long feedback loop. In addition, TSH inhibits the release of TRH via a short feedback loop and its own release via an ultra-short feedback loop [8]. Moreover, the release of TSH can be inhibited by various other substances, such as cortisol, dopamine, somatostatin, inflammatory cytokines, as well as during fasting states [9].

b) Production of thyroid hormones

The thyroid gland is composed of functional units called follicles. These follicles resemble cysts, with an interior filled with colloid that consists mostly of thyroglobulin, and is surrounded by a single layer of specialized epithelial cells known as follicular cells, or thyrocytes. These cells are responsible for the production of T3 and T4, and therefore require iodide [10]. The recommended daily intake of iodide for a non-pregnant adult is 150 µg, while pregnant adults should increase the intake to 250 µg per day. A healthy adult typically contains approximately 15-20 mg of iodine in the body, with the most of it (70-80%) stored in the thyroid gland. The concentration of iodine in the gland exceeds that in plasma by approximately 30-fold and during

periods of active stimulation can reach levels of up to 250-fold [11], [12]. Iodide is actively transported into thyrocytes by the transmembrane Na^+/I^- symporter located on the basolateral part of the cells, which transports two sodium ions and iodide ion at a time. This process is dependent on the sodium gradient between extracellular and intracellular compartments, which is maintained by the Na^+/K^+ ATPase [13]. Subsequently, iodide is transported into the follicular lumen through a channel protein called pendrin, located on the apical membrane of the cell. Within the colloid, iodide is oxidized by the transmembrane hemoprotein thyroid peroxidase (TPO), forming molecular iodine (I_2). One of the substrates required for this reaction as an electron acceptor is hydrogen peroxide (H_2O_2), which is generated by dual oxidases 1 and 2 (DUOX1 and DUOX2 respectively). Activation of these enzymes occurs through two distinct pathways: DUOX1 is dependent on protein kinase A pathway (PKA), while DUOX2 is activated via phospholipase C (PLC) cascade. The production of H_2O_2 is dependent on calcium and NADPH [14], [15].

Subsequently, iodine is incorporated by TPO into thyroglobulin (Tg) molecule. Tg is a 330 kDa protein consisting of 2750 amino acids and containing at least 66 tyrosine residues that can be iodinated. Initially, iodine is incorporated into tyrosine residues to form either 3-iodotyrosine (or monoiodotyrosine- MIT) or 3,5-diiodotyrosine (diiodotyrosine- DIT) in a process known as organification. These iodotyrosine molecules are then coupled to form thyroid hormones: coupling of two DIT residues results in the synthesis of T4, whereas coupling of a MIT donor with a DIT acceptor produces T3. Approximately 80% of the hormones produced are T4, while the remaining 20% are T3. Throughout this process, both T4 and T3 remain bound within the Tg molecule [1], [15], [16]. Iodinated Tg is stored in the colloid until hormonal release is required. Tg is then internalized into thyrocytes via endocytosis, followed by the fusion of endosomes with lysosomes, where proteolysis of the Tg occurs, releasing MIT, DIT, T3, and T4. MIT and DIT are deiodinated by deiodinases to allow iodine recycling, while biologically active T3 and T4 are transported into the bloodstream via the monocarboxylate transporter 8 (MCT8) [1], [16], [17].

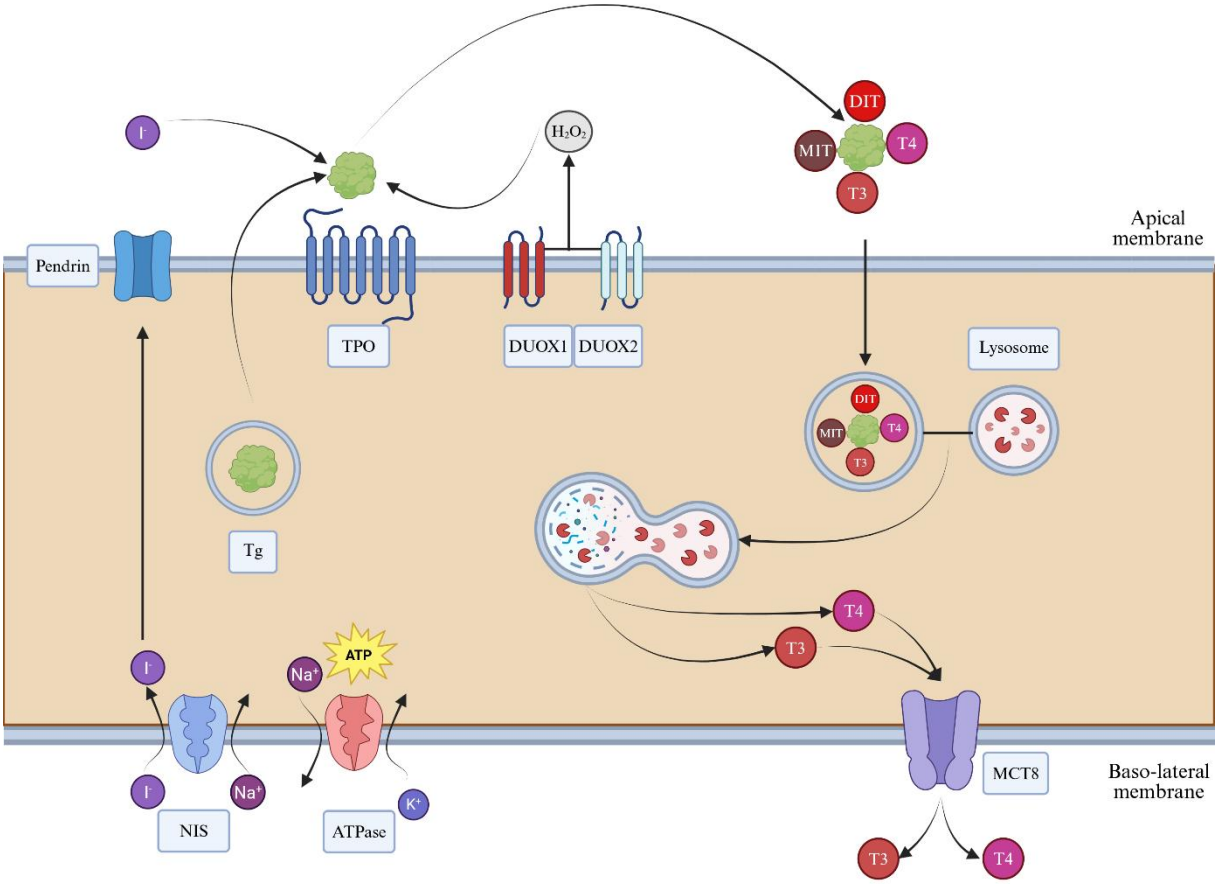

Fig. 1. Production of the thyroid hormones

NIS- Na^+/I^- symporter; ATPase- Na^+/K^+ ATPase; Tg- thyroglobulin; TPO- thyroid peroxidase; DUOX1- Dual oxidase 1; DUOX2- Dual oxidase 2; MCT8- monocarboxylate transporter 8

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c) TSH impact on the thyrocytes

TSH is the primary hormone regulating thyroid hormone production, from NIS gene expression, and Tg iodination to internalization of iodinated Tg and release of T3 and T4. It is a peptide hormone produced in the anterior pituitary gland and resembles other hormones such as luteinizing hormone (LH), follicle-stimulating hormone (FSH) and human chorionic gonadotropin (hCG) [1], [10], [13].

TSH acts on thyrocytes via the TSH receptor (TSHR), which belongs to the family of G-protein-coupled transmembrane receptors. It consists of seven transmembrane domains that share approximately 70% homology with LH, FSH and hCG receptors. However, this homology is much lower in the large (~ 400 amino acids) extracellular N-terminal region, which mediates TSH binding [18], [19]. Upon activation, TSHR initiates two G-protein mediated signaling cascades. The main Gαs pathway activates adenyl cyclase (AC), increasing cyclic adenosine monophosphate (cAMP) levels, which in turn activates protein kinase A (PKA), which activates cAMP response element-binding protein (CREB), as well as ELK1 (1-b-Raf-ERK-Ets-like transcription factor) cascade via MEK1/2 and Erk1/2 proteins
(fig. 2) [19], [20]. The Gαq pathway activates phospholipase C (PLC), which cleaves phosphatidylinositol 4,5-biphosphate into inositol 1,4,5-triphosphate (IP3) and diacylglycerol (DAG), which have multifaceted effects on the cell. First, the Akt (protein kinase B) pathway is activated, primary promoting cell proliferation and survival [20]. Additionally, this cascade induces Ca^{2+} release into the cytoplasm and activates transcription factors via the protein kinase C (PKC) pathway (fig. 2) [20], [21]. The Gαs pathway is primarily responsible for the expression of genes involved in the thyroid hormones production, such as NIS, Tg, and TPO, as well as for stimulating iodide uptake. Interestingly, the Gαq cascade appears to inhibit NIS transcription [13]. Conversely, the Gαq pathway and calcium influx stimulate DUOX1 and DUOX2, activation, increasing H_2O_2 production, and also promote Tg iodination via TPO. Both pathways are activated at different TSH concentrations: the AC / Gαs pathway requires approximately 100 times lower TSH concentrations than the PLC / Gαq pathway to reach EC50. This difference arises because TSHR has two binding sites with distinct TSH affinities, resulting in differential cascade activation. Nonetheless, both pathways are crucial for thyroid hormone production [21], [22].

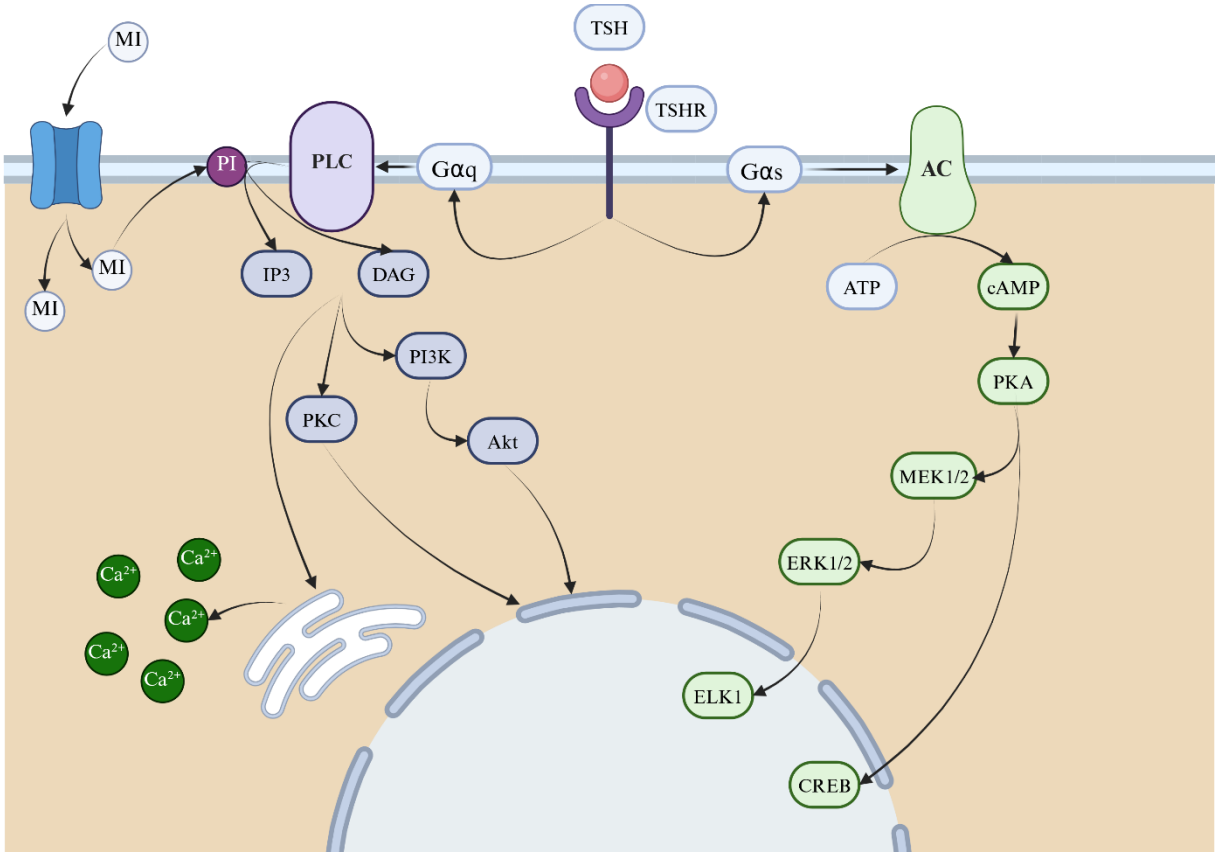

Fig. 2. TSHR-dependent pathways in the thyrocyte cell

TSH- thyrotropin; TSHR- thyrotropin receptor; AC- adenyl cyclase; PKA- Protein kinase A; MEK1/2- mitogen activated protein kinase kinase 1/2; ERK1/2- extracellular signal-regulated kinase 1/2; ELK1- 1-b-Raf-ERK-Ets-like transcription factor; CREB- cAMP response element-binding protein; PLC- phospholipase C; PI- phosphatidylinositol 4,5-biphosphate; IP3- inositol 1,4,5-triphosphate; DAG- diacylglycerol; PKC- protein kinase C; PI3K- phosphoinositide 3-kinase; Akt- protein kinase B; MI- myo-inositol;

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Subclinical hypothyroidism

Hypothyroidism can be classified into various types, such as overt and subclinical. Overt hypothyroidism is characterized by an increase in TSH levels and a decrease in T3/T4 (unless it is central hypothyroidism, in which case both hormone levels are decreased), whereas subclinical hypothyroidism is defined by elevated serum TSH levels with T3 and T4 within the normal range [4], [5], [23], [24]. The prevalence of subclinical hypothyroidism varies between

populations, affecting approximately 2,5- 15 % of adults. It occurs more commonly in older adults, women and those with suboptimal iodine intake, with particularly high prevalence among the women older than 60-70 years (15-18%) [4], [23], [24], [25].

Subclinical hypothyroidism can be divided into two grades of severity: grade 1 with TSH levels up to 9,9 mU/L, and grade 2 with levels ≥10 mU/L [24]. Although subclinical hypothyroidism has sometimes been considered a benign clinical finding, many studies indicate otherwise. Patients are often asymptomatic, but higher TSH levels correlate with the presence of overt hypothyroidism symptoms, especially in grade 2 cases. Moreover, there is a 2- 4% annual risk of progression to overt hypothyroidism among patients with subclinical disease, whereas up to 60% of individuals with grade 1 revert to euthyroidism within 5 years, depending on TPOAb status and serum TSH levels [4], [26].

The most common cause of subclinical hypothyroidism is chronic lymphocytic thyroiditis (Hashimoto's thyroiditis), accounting for approximately 60- 80% of cases. Some patients treated for overt hypothyroidism may develop a subclinical due to insufficient drug intake. Other causes include iatrogenic factors (partial thyroidectomy, neck radiotherapy, medications such as lithium, radioactive iodine, amiodarone, and radiographic contrast), infiltrative diseases (sarcoidosis, amyloidosis), obesity, impaired renal function and individual variations in TSH biological activity [26]. TSH elevation can also be temporary, as in de Quervain's thyroiditis or during recovery from non-thyroidal illness. Rarely, it may be caused by a pituitary adenoma, in which case symptoms usually resemble hyperthyroidism rather than hypothyroidism. In practice, blood TSH and T4 measurements should be repeated after 2-3 months to confirm the diagnosis of subclinical hypothyroidism [24].

Common symptoms include impaired cognitive function and memory, depressive mood, anxiety, and overall reduced quality of life. These symptoms are generally more prevalent among these patients than in the general population, although some studies report contrary findings. Symptoms tend to be more apparent in younger and middle-aged adults than among the elderly (over 65 years) [24], [26], [27]. The long-term impact of subclinical hypothyroidism appears to be more clinically significant. Several studies have reported a notable increase in cardiovascular risk, particularly in fatal and nonfatal coronary heart disease and congestive heart failure, especially in patients with TSH levels above 7 mU/L [28], [29]. Slightly increased stroke risk has also been proven [30]. Moreover, a meta-analysis by Liu XL et al. demonstrated significant increases in total cholesterol, LDL-C, and total triglyceride levels in patients with

subclinical hypothyroidism, which may contribute to elevated cardiovascular risk [31]. Additionally, women with subclinical hypothyroidism and coexisting thyroid autoimmunity have higher risks of infertility, spontaneous abortion, preeclampsia, gestational hypertension, and other pregnancy complications [24]. Furthermore, the approach to managing subclinical hypothyroidism remains a widely discussed topic among researchers.

Treatment relies mostly on levothyroxine and indications include pregnancy (either planned or current), TSH levels above 10 mU/L, coexisting conditions, and overall reduction of cardiovascular risk [4], [24]. Nevertheless, each case should be managed individually, to avoid overtreatment and polypharmacy.

Myo-inositol and its application in hypothyroidism

Inositol is a cyclic polyol, containing a cyclohexane ring and six hydroxyl groups, one for each carbon atom. It has nine possible stereoisomers, determined by the specific conformation of these groups. The most abundant form in nature is myo-inositol, or cis-1,2,3,5-trans-4,6-cyclohexanehexol, accounting for 99% of isomers found in living organisms. Myo-inositol was once regarded as a B-group vitamin, but since humans can synthesize this molecule, it is no longer considered one [32]. In a three-step reaction, D-glucose can be converted into myo-inositol: phosphate is first added to glucose by hexokinase; then it is isomerized by inositol-3-phosphate synthase 1 to form myo-inositol-1-phosphate; finally the product is dephosphorylated by inositol- monophosphatase. Nevertheless, this reaction has limited effectiveness and most of the myo-inositol comes from dietary sources, in the form of myo-inositol, inositol phospholipids, and phytic acid. The most abundant sources include citrus fruits, artichokes, legumes such as beans, peas and lentils, oilseeds such as sunflower kernels, sesame seeds and soybeans, as well as nuts (almonds, walnuts, Brazil nuts), the latter containing the highest amount of phytic acid of them all [7], [33]. Nevertheless, daily intake of myo-inositol fluctuates greatly, depending on the individual diet. In a study conducted by Clements et al. content of myo-inositol in a 1800 calories diet ranged between 225 to 1500 mg [34]. It is absorbed in the duodenum and jejunum through an active Na^+-involving transport, via SMIT1 and SMIT2 proteins. This transport varies greatly, depending on age, intake of medicine, or caffeine consumption [6], [35], [36]. Moreover, myo-inositol supplementation is relatively safe, with an LD_{50} of 10 g/kg in mice. A study by Lam et al. showed that a dose of or up to 18 grams

for 3 months was tolerated by the subjects, with mild side effects such as diarrhea, or nausea [37].

Myo-inositol plays a crucial role in the biosynthesis of substrates required for signal transduction across the cellular membrane via G protein-coupled signaling. The most important substrate located in the inner layer of the phospholipid bilayer is phosphatidylinositol, which is broken down by the phospholipase C activated by the Gαq protein. The produced IP3 and DAG are crucial in activation of various pathways and releasing of calcium into the cytoplasm [7]. The hormones associated with the IP3-related pathway include LH, FSH, insulin, and TSH. Therefore, myo-inositol supplementation has been extensively studied in diseases such as polycystic ovary syndrome, diabetes, gestational diabetes, and metabolic syndrome, as well as in its applications in assisted reproductive technology [6], [7]. Recently, due to metabolic similarities, the applications of myo-inositol have been investigated in subclinical hypothyroidism.

In a study conducted in 2013, Nordio M. and Pajalich R. enrolled 48 women with TSH levels between 4,01 mIU/L to 9,99 mIU/L who were positive for TPOAb or TgAb. The participants were randomly divided into two equivalent groups; one group received only selenium (83 µg daily), while the other received selenium (83 µg daily) plus myo-inositol (600 mg). A significantly greater improvement in subjective well-being was reported in the selenium + myo-inositol group, with 18 patients showing improvement compared to 8 in the selenium-only group ($p<0,05$). Moreover, TSH levels decreased only in the group receiving myo-inositol by 31% ($4,4 \pm 0,9$ vs $3,1 \pm 0,6$ mIU/L, $p<0,01$). In addition to this, both TPOAb and TgAb levels showed significant decreases in both groups [38].

In another study conducted by Payer J. et al., a larger cohort of 148 women was included. These women were either at risk of subclinical hypothyroidism (TSH 2,5 - 5,0 mIU/L; positive for TPOAb or TgAb) or had subclinical hypothyroidism (TSH 5-10 mIU/L; positive or negative for both TPOAb and TgAb). Similarly, these patients received myo-inositol (600 mg daily) and selenium (83 µg daily). In this case the patients with subclinical hypothyroidism also showed a significant reduction in TSH levels (median 5,9 to 4,6 mIU/L, $p<0,001$) and in antibody titers in antibody-positive patients (median TPOAb -21 IU/L, TgAb -46 IU/L; $p<0,001$ for both). Moreover, other symptoms, such as chronic fatigue, irregular menstrual cycles, tolerance to cold and heat improved significantly [39]. Another cohort of 87 patients (79 women and 8 men) with subclinical hypothyroidism due to Hashimoto's disease, as reported by Nordio M. and

Basciani S., were treated similarly to the previous studies, showing comparable results: significant improvement of TSH, TPOAb, TgAb, as well as symptoms after 6 months. Interestingly, one patient with hyperthyroidism was enrolled in this study, and TSH levels in this patient also improved [40]. In a study conducted by Pasyechko N.V. et al., 148 women with autoimmune thyroiditis who were in a euthyroid state, subclinically hypothyroid, or overtly hypothyroid, were divided into two groups: the first group received cholecalciferol at a dose of 2000 IU, 100 µg of selenium, and 2000 mg of myo-inositol daily, while the second group received only cholecalciferol and selenium in the same doses. The patients with subclinical hypothyroidism (forming a subgroup of 49 patients divided into cohorts of 25 and 24) showed greater improvement in TSH, T4, T3, TPOAb, and TgAb levels in the group that recieved myo-inositol [41].

Nordio M. and Basciani S. analyzed the impact of this treatment on thyroid nodule characteristics. They found that after treatment, the number, size, and elasticity of nodules improved significantly; however the small number of participants and the lack of in vitro or in vivo studies limit the generalizability of these findings [42]. Other groups were analyzed for dynamics of the effectiveness of myo-inositol with selenium. In the first group, TSH levels improved after 3 months; however it was concluded that at least 6 months of treatment is adequate for patients [43]. The second study was the only one that lasted longer than 6 months, following the patients for one year. It showed that the effects of selenium and myo-inositol can help maintain the euthyroid state in the long term [44].

Another study showed that 600 mg of myo-inositol with 83 µg of selenium daily could potentially be used to prevent subclinical hypothyroidism in pregnant women, as patients taking these substances showed stabilized TSH, T3, and T4 levels [45]. In an interesting study conducted on 151 patients with PCOS, the possible impact of myo-inositol on insulin resistance and TSH levels in the subclinical hypothyroid state was investigated. The patients who took metformin with myo-inositol showed a significant improvement in TSH levels compared to those who took only metformin [46].

Another effect of myo-inositol was found to be immunomodulatory, especially in Hashimoto's disease. The chemokine CXCL10 is an important factor in this pathology. It is released from thyrocytes under the influence of INF-ɣ and TNF-α, which are induced by Th1 lymphocytes, thereby perpetuating inflammation. Myo-inositol was found to decrease levels of CXCL10, as well as other cytokines involved in the autoimmune process, such as TNF-α,

IL-6, IL-10, IL-17, and IL-23, which may explain the observed decrease in TPOAb and TgAb levels [41], [47].

Conclusion

Subclinical hypothyroidism is a condition in which thyroid hormones remain within the normal range, while TSH levels are elevated. The management of this condition remains highly debated, with various proposed treatment approaches. One potential approach is supplementation with myo-inositol, which plays a key role signal transduction in thyrocytes, and in the immunomodulatory processes associated with Hashimoto's disease. Several studies confirm that it can be safely used in patients, but further research is needed in larger cohorts and with longer follow-up periods. Moreover, no study has investigated the use of myo-inositol alone in this condition, making it difficult to assess its impact. Nevertheless, myo-inositol shows great potential and appears to be a promising alternative to the early introduction of levothyroxine therapy.

Disclosure

Author's contribution

Conceptualization - Konstancja Owczarenko
Methodology - Konstancja Owczarenko
Software - Kacper Szada-Borzyszkowski
Check - Konstancja Owczarenko
Formal analysis - Kacper Szada-Borzyszkowski
Investigation - Konstancja Owczarenko
Resources - Kacper Szada-Borzyszkowski
Data curation - Konstancja Owczarenko, Kacper Szada-Borzyszkowski
Writing - rough preparation - Konstancja Owczarenko, Kacper Szada-Borzyszkowski
Writing - review and editing - Kacper Szada-Borzyszkowski, Konstancja Owczarenko
Visualization - Kacper Szada-Borzyszkowski
Graphics - Kacper Szada-Borzyszkowski
Supervision - Konstancja Owczarenko

All authors have read and agreed with the published version of the manuscript

Supplementary materials

All graphics used in this article were made using BioRender under individual academic license.

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Conflict of Interest Statement

Authors declare no conflict of interest.

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