

Supplementation in Autoimmune Thyroid Hashimoto's Disease. Vitamin D and Selenium

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Abstract This review aims to present the importance of nutrients for thyroid health in light of autoimmune Hashimoto's disease. Authors focus mainly on vitamin D and selenium function in the body, metabolism, serum concentration in patients, replenishment outcome after singular or combined the treatment and dose. Vitamin D is essential for immune regulation and yields inflammatory properties. Selenium plays an important role in thyroid metabolism by protecting it from oxidative damage during iodine metabolism and by taking part in thyroid hormone production. Hashimoto is a complex disease and cross-curricular therapies probably will find more interest than one-way therapy.

Keywords: *cholecalciferol, calcitriol, hypothyroidism, myo-inositol, antithyroid antibodies, selenomethionine*

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1. Introduction

Hashimoto's (HT) disease is one of the autoimmune thyroid diseases associated with thyroid hypofunction, lymphocytic infiltration and increased antithyroid antibodies titers especially thyroglobulin (TG-Ab) and thyroperoxidase (TPO-Ab) titers. HT is a lymphocyte T-mediated immune disorder with constant thyroid gland damage caused by the interaction of environmental factors with particular genes in susceptible patients. One of those factors are vitamin D (VD), iodine and selenium (Se) status [1]. This literature review is based on an electronic search in PubMed and Google Scholar database published from January 2011 to March 2019 regarding HT and use of over-mentioned compounds as individual supplements or in combination with other on HT patients in clinical trials. Both importance, functions of those nutrients and studies results are presented in the review. Any relevant papers to the subject were included either.

2. Vitamin D

VD is mostly produced in the skin through sun exposure initially as an inactive precursor. Then it is converted in the liver to cholecalciferol – 25(OH)D, and then in the kidney to its active form known as calcitriol – 1,25(OH)₂D. Serum cholecalciferol level is used as a marker of VD saturation. Despite the way

it is synthesised in the body, VD deficiency is a worldwide problem in all age groups [2]. Calcitriol by binding with vitamin D receptor (VDR) regulates many genes which processes includes immunological modulation. This interaction yields to an anti-inflammatory effect on both innate and regulatory and suppressive action on adaptive immunity [3]. Regulatory action of VD on T cells, subpopulation Th1, Th2 and Th17 [3,4] and dendritic and B cells, monocyte and macrophages activity and functions [3] may explain why lower levels of VD might contribute to HT and other autoimmune diseases [5].

2.1. Serum Vitamin D Concentration in Hashimoto Patients

Wang et al. meta-analysis showed, that VD was lower in HT patients compared with healthy controls and autoimmune thyroid disease development was more likely to develop on those with a low level of VD [4]. VD deficiency among HT patients were reported by others [1,6-17]. In a Turkish HT population severity of VD deficiency correlated with duration of the disease, thyroid volume and antibody levels [8]. Although there are still conflicting results regarding the association between VD level and HT [3,18,19]. The low VD levels might be a risk factor [10,15] as well as a consequence of disease like malabsorption [20]. Food is one source of VD but it scares [21]. Inadequate dietary intake of VD was reported in polish HT patients. This gives a point about the importance of nutritional assistance for HT patients [22].

2.2. Association between Serum VD Concentration and Hashimoto's Disease

Low VD level is associated with increased thyroid antibodies level in HT patients [6,8,12,13,15,23-26] and worsen thyroid functions [6,7,13]. Nutritional improvement attenuates thyroid functions and/or decreases antibodies levels in HT patients [1,8,12,17,25,27,28] and healthy people at higher risk of hypothyroidism [29]. However, Ma et al. reported in a cross-sectional case-control study that an increase of each 2 ng/mL VD concentration was associated with a 1.62-fold reduction in HT risk without the association of VD concentration with thyroid antibodies or thyroid hormones [27]. Immunoregulating functions of VD like regulation of inflammatory cytokine production may be responsible for these effects [30].

Among participants in Mirhosseini study (n=11,017), VD deficiency was found to existing in 80% (n=1946) of those considered to be at higher risk of developing autoimmune thyroid disease (n=2433). Serum level of VD ≥ 50 ng/mL was associated with a 30% and 32% reduced risk of elevated anti-thyroid antibodies and hypothyroidism. This result suggests that level ≥ 50 ng/mL might be necessary for optimal thyroid function in healthy person and protection from hypothyroidism [29]. In contrast, Effraimidis et al. in cross-sectional, longitudinal study did not find an association between low VD level and early stages of thyroid autoimmunity [18].

2.3. Vitamin D metabolism in Hashimoto Patients

In fact, vitamin status can be related to HT pathogenesis but does not have to. Hypothyroid patients may not absorb VD from the intestine properly [9]. Moreover, an association between VD binding protein (DBP), 1α -hydroxylases [31], particular VDR single-nucleotide polymorphisms (SNPs) and risk of autoimmune thyroid diseases development was found [11,16,32]. This leads to the belief that interaction between VD and VDR, and so the ability of VD to act on the immune system might be more important. Currently, the role of VD in HT is not completely known and more studies are needed. In fact achievement of appropriate VD concentration might be critical to achieve positive results in HT and it might be necessary to use the active form of VD – calcitriol instead of cholecalciferol in order to avoid VD conversion blockage by DBP in immune cells [30].

2.4. How Much Vitamin D Hashimoto Patients Need?

Categorization of VD status is usually defined as deficient for the level below 20 ng/mL (50 nmol/L) and insufficient for 20-29 ng/mL (50-72.5 nmol/L). Holick et al. points for results from epidemiological studies, that level above 30 ng/mL reduces the risk of autoimmune diseases [21]. Heaney concludes, that an adequate level of serum VD for the proper physiological function is 40-52 ng/mL (100-130 nmol/L) [33]. In light of Mirhosseini et al. study results, it seems reasonable to achieve a serum level of 50 ng/mL [29]. Nodehi et al. used 50,000 IU VD weekly (7143 IU daily) for 3 months in HT

patients what increased mean VD concentration from 25.9 to 42.3 ng/mL in the intervention group. Despite positive results of TH17/Tr1 ratio in HT patients indicating an improvement of disease control and immune regulatory effect of VD other immune measured factors was not changed. Authors conclude that it might be different when a higher dose of VD would be used [30] what might be true if achieved serum VD concentration would be higher than 50 ng/mL [29].

Generally, recommended an upper limit of serum VD concentration is 50 or 60 ng/mL (125-150 nmol/L) [34]. In HT patients it seems reasonable to keep it at a level higher than 50 ng/mL [29] what seems to be safe [34]. Daily supplementation with doses of 3000-5000 IU should let obtain and maintain such level. Although the dose of VD supplementation depends on age, weight, ethnicity and environment besides serum concentration [34] and individual response to VD supplementation may vary widely [35]. Obese adult patients should take 2.5-3 times more VD than the recommended dose for a normal weight person. As Pludowski et al. stated in guidelines VD dosage should be adjusted based on regional or national recommendations with the treatment duration of 1 to 3 months [34].

2.5. Vitamin D Supplementation, Thyroid and Immune Functions in Hashimoto Patients

Mazokopakis et al. found an inverse correlation between VD and TPO-Ab level. They showed that TPO-Ab level is significantly higher in VD deficient (<20 ng/mL) euthyroid HT patients compared with HT patients without deficiency. 186 of 218 patients (85%) had VD level below 20 ng/mL. After 4 months of VD supplementation (1200-4000 IU/d) in order to achieve serum VD level of 40 ng/mL, a decrease of 20.3% (from 361 to 290 IU/mL) TPO-Ab was observed [25]. In an Iranian population with overt or subclinical hypothyroidism, Mansournia et al. conducted a cross-sectional study in which found an inverse association between serum VD level and HT. Each 5 ng/mL increase were associated with a 19% decrease in the risk of HT [10]. During one month of 1000 IU/d of VD supplementation, Simsek et al. in prospective study on autoimmune thyroid diseases (AITDs) patients reported a significant increase in VD level from 10.9 to 21.4 ng/mL and decrease of thyroid antibodies. TPO-Ab and TG-Ab dropped significantly from 278.3 to 267.9 IU/mL (3.8%) and from 331.9 to 275.4 IU/mL (17.1%) respectively. There were no changes in thyroid functions in the intervention group. As VD level increased barely above 20 ng/mL it can be speculated that higher supplemental dose would give better results [36].

In an open-labelled randomized controlled trial (RCT) Chaudhary et al. found that TPO-Ab concentration in newly diagnosed patients with autoimmune thyroid disease (TPO-Ab >34 kIU/L and/or sonographic evidence of thyroiditis) were highest among those in the lowest VD quartile. 93% patients had abnormal in VD level (<30 ng/mL) and 74% were deficient (<20 ng/mL). Analysed at 3 months, after 8 weeks of 60,000 IU VD intake weekly with 500 mg calcium/d they reported 46.73% (from 739.1 to 387 kIU/L) decrease in TPO-Ab in the intervention

group (n=50) compared with 16.6% drop in the control group (n=50) receiving only calcium. Reduction of TPO-Ab greater than 25% was achieved by 68% and 44% patients in the interventional and control group [12]. Pan'kiv used a lower dose of VD for a longer time. He conducted a randomized study on 52 patients with newly diagnosed hypothyroidism on the background of autoimmune thyroid disease. As common, most patients were VD deficient (94.2%). In the interventional group, patients received VD 2000 IU/d with calcium 1000 mg/d for 12 weeks. Control group received only calcium 1000 mg/d in addition to levothyroxine. There was a significant negative correlation between VD concentration and TPO-Ab. The intervention group decreased significantly the level of TPO-Ab by 48.1% in which 73.1% of patients reduced it of at least 25% [37]. Aminian et al. in clinical trial divided 52 female patients with subclinical hypothyroidism and inappropriate VD status (100% of patients had VD level <30 ng/mL and 75% <20 ng/mL) into 2 groups: TPO-Ab positive (TPO-Ab >75 IU/mL, n=29) and TPO-Ab negative (<75 IU/mL, n=29). After 8 weeks of VD supplementation 50,000 IU/wk, they improved VD level from 14.32 to 52.72 ng/mL [28]. It seems to be appropriately achieved level based on literature [21,29,33]. As a result, they reported a significant decrease of TPO-Ab and TSH concentration only in TPO-Ab positive group from 755.57 to 535.37 IU/mL (29.15%) and from 7.96 to 7.51 mIU/L (5.66%) respectively [28].

VD supplementation improves thyroid function as well. Talaei et al. for 12-week in a randomized, double-blind, placebo-controlled trial gave 50,000 IU VD weekly to 102 hypothyroid patients on their stable levothyroxine dose and TSH level 0.5-5 mIU/L for more than one year. Serum VD concentration increased from 17.1 to 43.7 ng/mL and calcium by 0.4 mg/dL, TSH and parathormone level decreased by 0.4 mIU/L and 3.8 pg/mL respectively. There were no significant changes in T3, T4, alkaline phosphatase and albumin levels [17].

A recent meta-analysis including 6 RCT conducted by Wang et al. in patients with AITDs found that 6-months VD supplementation significantly decreased TPO-Ab (3 studies, standardized mean difference [SMD]: -1.11, 95% CI -1.52 to -0.70, P <0.01) and TG-Ab titers (SMD: -0.12, 95% CI: -0.69 to 0.44, P = 0.67) compared with controls [38].

Most studies have found an association between VD status and HT. However, there is still a gap in the intervention studies for VD and HT and more need to be done to establish the potential of VD supplementation in the treatment of HT. There is also a need for more studies of combined VD and levothyroxine treatment in HT patients as it seems to be beneficial even with normal VD status (>30 ng/mL) [39]. Current results support the need for those randomized and controlled studies. Usually, cholecalciferol is used in HT patients, although active form calcitriol might be more beneficial as DBP may block the conversion of inactive VD form and thus blocks its function on immune cells [30].

It is worth to mention, that elevated VD level increases serum calcium and phosphorus level and in a result may increase calcification of soft tissues (like kidneys and blood vessels). It is generally accepted, that VD concentration up to 100 ng/mL is safe for both children

and adults except those hypersensitive to VD (those with idiopathic infantile hypercalcemia, Williams-Beuren syndrome, granulomatous disorders and some lymphomas). Serum VD concentration should be measured after at least 8-12 weeks after initiation of treatment. Either serum calcium and phosphorus concentration, as well as kidney function should be measured if serum VD level exceeds toxic concentration >100 ng/mL while VD supplementation has to be stopped immediately [34].

2.6. Magnesium-dependent Vitamin D Metabolism

Inactive VD forms need to be converted to active calcitriol and these conversions are magnesium (Mg) dependent. It acts either as a cofactor for VD-binding protein. As VD metabolism depends on Mg bioavailability and action it was reported that adequate presence is necessary for VD action. It's deficiency results in decreased levels of calcitriol. As Mg supplementation let rickets patients reduce their resistance to VD treatment, same results can be expected in HT patients [40]. In a WOMED study done on patients with thyroid disease (hyper- and hypothyroidism) Mg deficiency was associated with thyroid functions what was attenuated after Mg supplementation [41]. Mg is necessary for iodine uptake by thyroid cells and its deficiency decreases it leading to hypothyroidism as well as an increase in TSH concentration [41,42]. Mg is rarely studied nutrient in HT patients while it seems it might be one of the critical factors in undernourished patients. Because of the relationship between Mg metabolism and thyroid hormones it seems to be true, that some disease symptoms related to thyroid function are in fact a result of Mg deficiency [41].

There is one study describing an association between Mg level and thyroid antibodies. In an observational cross-sectional study Wang et al. associated deficient serum Mg levels (<0.55 nmol/L) with an increased risk of TG-Ab positivity, mainly subclinical hypothyroidism and the prevalence of HT. However, no association was found between TPO-Ab and Mg level. Authors speculate that these phenomena suggests that Mg deficiency influence on inflammation and oxidative stress and may aggravate disease symptoms rather than be a cause of them [42].

3. Selenium

As VD regulates genes expression [3] Se is the main structure of selenoproteins affecting thyroid function as glutathione peroxidase (GPXs), thioredoxin reductases (TRs), and iodothyronine deiodinases (DIO). As a part of the antioxidant defence system, those enzymes protect the thyroid from oxidative stress because of hydrogen peroxide generated naturally from iodide oxidation during the production of thyroid hormones. Se is also an essential trace element for the synthesis of T3, rT3 and T2 by being a part of DIO. As a result of Se deficiency increased T4 [43], fT4 [44] and reduced T3 level are observed [43]. The thyroid gland contains the highest amount of Se per gram in the whole human body [45]. Its deficiency directly impacts thyroid metabolism and immune function and

leads to radical and autoimmune destruction of the gland [43] and formation of fibrotic tissue [46].

Despite the fact that Se sources are widely eaten there is still seen inadequate daily intake in Europe (about 40 µg per day) and other parts of the world. Scientific Committee on Food of the European Commission recommends a daily intake of 55 µg of Se daily [46].

3.1. Serum Selenium Concentration in HT Patients

Decreased plasma Se concentration is reported in HT patients what can be reversed by supplementation the treatment [41]. There are a few points that need to be addressed regarding HT patients. In literature there are conflicting results regards Se supplementation in thyroid parameters no matter if subjects are deficient of it [43]. Secondly, even if Se repletion in HT deficient patients demonstrates a significant increase in plasma Se concentration it doesn't have to lead to thyroid function improvement. Although standard serum Se level range is 60-120 µg/L what is related to dietary intake, it doesn't reflect tissue saturation. Currently, there is no reliable marker of thyroid gland Se saturation. Thus dose and duration the treatment still cannot be evaluated [45].

Despite the unclear relationship between serum Se level and intrathyroid repletion, some studies correlate its deficiency with increased thyroid cells damage and impairment of thyroid diseases [47]. As worth to note, in rare situations excess Se (selenosis) with its toxic effect was reported in literature mainly by acute poisoning or by prolonged exposure to high levels (200 µg/d) [46,48]. In one controlled trial Se intake of 200 µg/d in a long-term (~7.7 years) increased the relative risk of type 2 diabetes by 2.7 compared with placebo [45]. Wichman et al. in systemic review and meta-analysis reported an adverse effect of Se supplementation which was gastric discomfort, headache, hair loss and skin rash in some patients in the intervention groups [49]. Plasma Se concentration depends directly on its intake, especially bioavailability. Therefore, long-term supplementation treatment should be under control of repetitive measurement of serum Se concentration in order to avoid potential adverse effects of Se toxicity [45,48].

3.2. Association between Serum Selenium Concentration and Hashimoto's Disease

Se supplementation in autoimmune thyroid diseases seems to alleviate inflammatory processes and immune antioxidative defence [48,50]. Those properties probably let, at least at some point to reversed changes in the echostructure in HT patients after Se replenishment [51]. It is believed that enhance of plasma selenoproteins are responsible for those effects [43]. Organic Se compounds (selenomethionine and selenocysteine) have a better absorption rate than inorganic (selenite and selenate). It seems reasonable to use former compounds than the latter in HT the treatment [48]. Selenomethionine inhibits production of inflammatory cytokines IFN-γ, TNF-α and IL-2 especially when the treatment is accompanied by levothyroxine (LT4). With Se deficiency the oxidative

stress can occur which decreases suppressor T cells activity and consequently increased IL-2 production leads to activation of autoreactive T cells and finally to autoantibodies production [48, 50]. It is probable that non-significant results of selenite treatment used in clinical trials result from two-third absorption of selenomethionine and thus, might be dose-dependent [49].

Epidemiological results from studies done in China and Europe points for negative impact of Se deficiency for thyroid function, thyroid volume, risk of thyroid enlargement and multiple nodules development as well as prevalence of pathological thyroid conditions (hypothyroidism, subclinical hypothyroidism, autoimmune thyroiditis and enlarged thyroid gland) compared with regions with adequate Se status [52].

RCTs bring conflicting results [43] eg. in Esposito et al. study although, despite no change in TSH, TPO-Ab and CXCL10 there were a significant positive amelioration in fT3 and fT4 concentration in Se group [53]. Those already done RCTs puts the use of Se supplementation in the treatment of HT at the positive site. In an RCT done on newly diagnosed and previously untreated euthyroid HT women with adequate iodine intake (median urinary iodine concentration – 123 µg/L). 200 µg selenomethionine daily for 6 months significantly reduced inflammatory cytokine release by lymphocytes. When LT4 were supplemented, a different effector system was noticed such as suppression of monocyte inflammatory compounds and monocyte chemoattractant protein-1. When both of those agents were administered together, the decrease in cytokine release and plasma C-reactive protein were stronger [50]. Recently Kachouei et al. conducted RCT on subclinical hypothyroid patients with 3-months LT4 treatment. The intervention group was taking 200 µg sodium selenite daily and control group placebo. Plasma Se level increased only in the Se-treated group by from 86.5 to 123 µg/l (42.1%). Levothyroxine was administered in order to keep the TSH level in the lower range (0.3-2 mIU/L). After 3 months fT3 and fT4 dropped in both groups at the same level. In control group, there were no changes in antithyroid antibodies while Se group significantly decreased TPO-Ab concentration from 682.18 to 522.96 U/L (23.3%) and TG-Ab from 226.01 to 155.12 U/L (31.4%). Se may be helpful in decreasing antithyroid antibodies concentration with LT4 treatment [54].

Singular RCT positive results of Se supplementation in HT patients found confirmation in Fan et al. and Wichman et al. meta-analysis [47, 49] but not in Cochrane collaboration [55] and recent meta-analysis by Winther et al. [56]. Fan et al. conducted meta-analysis in which nine RCTs were analysed finally. Efficacy of Se supplementation in different chemical forms was determined for the treatment of AITDs collectively. TPO-Ab titers decreased at 6 month (three studies: SMD: -1.516; 95% CI -2.823 to -0.210; P=0.023) and 12 months (two studies: SMD: -4.940; 95% CI -5.887 to -3.992; P <0.001) while TG-Ab only at 12 months (two studies: SMD: -2.210; 95% CI -2.956 to -1.464; P <0.001). The intervention group had a higher chance to improve mood [47]. Changes had a large effect in SMD (>0.8) [57]. There were no adverse effects of supplementation except mild gastric discomfort in few

patients and again, limitations of the study unable to define firm conclusions [47]. Although a year before in Cochrane systemic review authors assessed the effect of Se supplementation on HT with a conclusion that there is no evidence to support or refute the efficacy on Se treatment on HT patients because of incomplete data, unclear to high risk of bias and, therefore unclear clinical relevance [55].

Cochrane meta-analysis results [55] stands in contradiction with Wichman et al. meta-analysis. Results of controlled trials on patients with AITDs and Se supplementation versus placebo both with or no LT4 treatment were collected. After screening 11 controlled trials were included in quantitative synthesis. As a result Se groups with LT4 treatment reduced TPO-Ab concentration at 3 months (seven studies: WMD= -271 [CI: -366 to -175]; $p < 0.0001$), 6 months (three studies: WMD= -469 [CI -617 to -322]; $p < 0.001$) and 12 months (one study: WMD= -423 [CI: -450 to -396]; $p < 0.0001$) and in Se treated LT4 free population at 3 months (three studies: WMD= -512 [CI: -626 to -398]; $p < 0.0001$) but not at 6 and 12 months. Relative changes across studies following three months, TPO-Ab titers dropped significantly by 24% compared with 6% in control groups. In a subgroup meta-analysis the five of seven studies reported a positive results on TPO-Ab reduction after use of selenomethionine (200 µg/d) at 3 months (five studies: WMD= -267.99 [CI: -341.97 to -194.01]; $p < 0.0001$) while another two with use of sodium selenite (200 µg/d) did not reported significant changes. TG-Ab titers decreased at 12 months (one study: WMD= -176 [CI -199 to -153]; $p < 0.0001$) in Se-L4 treatment group and at 3 months (two studies: WMD= -215 [CI: -407 to -24]; $p = 0.027$) in Se-treated L4-naive group [49]. Se supplementation had stronger impact in combination with LT4 treatment.

A recent meta-analysis by Winther et al. concludes fairly that there were conflicting results regards Se supplementation used in the treatment of AITDs including HT [56]. Although Se deficiency is accompanied with benefits in deficient patients, exceeding serum concentration above normal range is associated with possible health risk, hypothyroidism exacerbation and other diseases development [58]. Thus, Winther et al. conclude that currently Se treatment use in HT patients with normal Se status should be discouraged [56].

3.3. Selenium and Myo-inositol

Se supplementation seems to have a better impact when administered together with myo-inositol. In Nordio et al. RCT 83 µg selenomethionine intake for 6 months decreased significantly TPO-Ab and TG-Ab from 905.6 to 522.6 mIU/mL (42%) and from 1080.8 to 670.1 (38%) in subclinical hypothyroidism patients. A stronger effect such as decrease from 913.9 to 516.1 (44%) and from 1019 to 533.9 mIU/mL (48%) was reported in myo-ino-Se treatment arm, where Myo-inositol (600 mg) were used concomitantly with Se. Se level in myo-ino-Se and Se group increased from ~128 to 225.4 and 223.5 µg/L, respectively. The TSH concentration decreased only in Myo-ino-Se group by 31% [59]. Those results stand in a line with another study done in HT patients with TSH

level 3-6 mIU/L, elevated TPO-Ab, TG-Ab and normal fT4 and fT3 level. After 6 months of 600 mg myo-inositol intake with 83 µg Se in the form of selenomethionine the TSH, TPO-Ab and TG-Ab level decreased by 28% (from 4.32 to 3.12 mIU/L), 16.3% (from 720.67 to 620.38 IU/mL) and 14% (from 344.96 to 288.84 IU/mL), respectively. There were slight but significant increase of fT3 and fT4 by 4.5% (from 2.67 to 2.79 pg/mL) and 13.8% (from 0.94 to 1.07 ng/mL), respectively. The myo-inositol role in increasing TSH sensitivity in HT patients and regulation of H₂O₂-mediated iodination explains seen results [60]. Phosphatidylinositol signal transduction pathway is important for thyroid function and myo-inositol takes a role in its function which activity is regulated by calcitriol [51]. Combination of selenomethionine supplementation with myo-inositol seems to be efficacious and safe for the treatment of HT patients [59,60]. The effectiveness of combined therapy was reported also in patients with AITDs [61]. It can be speculated that myo-ino-Se-VD treatment in patients with low VD status would benefit more from such the intervention.

3.4. Selenium and Iodine

A meta-analysis by O'Kane et al. based on observational and the interventional studies concluded that the status of Se is positively associated with iodine status. Iodine is an important compound for expression and function of proteins and enzymes necessary for the metabolism of thyroid hormones and biosynthesis. Besides iron and zinc, Se deficiency can diminish iodine metabolism and effectiveness of iodine supplementation in HT deficient patients [62,63]. Iodine deficiency needs to be corrected concomitantly with Se deficiency [62]. There is an importance of keeping iodine level within normal range as accordingly to U shape disease risk, deficiency and excess of iodine might exacerbate thyroid dysfunction and develop iodine-induced hypothyroidism [64]. As mentioned before, Mg is necessary for iodine uptake by thyroid and replenishment of it might increase iodine bioavailability for the gland [41].

3.5. Selenium and Vitamin D

Krysiak et al. have conducted the first study with concomitant use of cholecalciferol (4000 IU/d) and selenomethionine (200 µg/d) in young (20-45 years old) euthyroid polish women with HT thyroiditis from Upper Silesia [65]. It is known that polish population intake of iodine is adequate thankfully to salt iodization and with low Se status. Serum Se level wasn't measured in the study. Although Kłapcińska et al. study made in the same area as Krysiak et al. proved that Se status was low especially in women (57.5 ± 18.9 µg/L) [66] who were the only gender included in the study [65]. Other, more recent studies done on polish population confirms Kłapcińska et al. results [67,68]. There were 47 subjects divided into 2 groups: Se-treated (n=23) who were supplementing selenomethionine for at least 12 months before the start of the study and throughout its duration and Se-naïve group. Both groups were treated with 4000 IU of VD every day. Serum VD level from mean 20-21 ng/mL increased to

43.2 and 41.1 ng/mL in Se-treated and Se-naïve group, respectively. At the end of the study (6 months) decrease of TPO-Ab by 38.5% (from 896 to 551 U/mL) and 21.5% (from 975 to 765 U/mL), TG-Ab by 33.8% (from 829 to 549 U/mL) and 22.6% (from 867 to 671 U/mL) and increase of SPINA-GT by 17.4% (from 2.59 to 3.04 pmol/s) and 11.1% (from 2.7 to 3.0 pmol/s) were reported in Se-treated and Se-naïve groups, respectively. The difference between Se-treated and Se-naïve group in TPO-Ab, Tg-Ab and SPINA-GT were 39.1%, 30% and 27.9%, respectively. SPINA-GT index indicates the secretory capacity of the thyroid gland. Changes were stronger in Se-treated than Se-naïve group. The difference in antithyroid antibodies titers level at the beginning of the study and at the end of it were significantly different between tertiles of VD status while higher tertile led to better treatment response. TPO-Ab concentration also correlated with SPINA-GT index. The Se-treated group at the beginning of the study had higher values of FT3:FT4 ratio and SPINA-GD index (indicating total activity of deiodinases which are selenoproteins) indicating the effectiveness of Se treatment. Although no change at the end of the study of those markers indicates the immunological effect of VD-Se combination therapy than the attained concentration of these nutrients. Differences between groups in SPINA-GD index indicates that Se intake enhanced VD action and decrease resistance to VD treatment. Authors propose possible mechanisms responsible for seen effects which are Se and VD effect on redox and inflammatory processes regulating enzymes as well as their role on inflammatory cells. Another possible mechanism is increased 1α -hydroxylation of VD to its active form calcitriol by organoselenium resin and increased Se uptake by self-reactive T cells mediated by calcitriol observed in independent studies. In conclusion, Se potentiates the effect of VD on thyroid autoimmunity [65].

In another study, Krysiak et al. compared the intervention of selenomethionine to VD in men. 37 young drug-free euthyroid men (20-50 years) with untreated autoimmune thyroiditis, recently diagnosed were treated for 6 months with either VD (group A, n=20, 4000 IU/d) or selenomethionine (group B, n=17, 200 µg/d). The baseline VD level changed from 25 and 26 to 42 and 27 ng/mL in group A and B in which 50% and 53% patients were VD deficient (<30 ng/mL), respectively. TPO-Ab decreased by 26.4% (from 846 to 638 U/mL) and 26.1% (from 878 to 649 U/mL) and TG-Ab by 25.7% (from 756 to 562 U/mL) and 27.2% (from 783 to 570 U/mL), SPINA-GT increased by 11.1% (from 2.07 to 2.38 pmol/s) and 10.2% (from 2.15 to 2.37 pmol/s) consecutively in both groups. As in another Krysiak et al. study [65], the greatest benefits were achieved by subjects with very high antithyroid titers in both treatment arms and with low VD status compared with normal in VD treatment arm. Worth to mention is that selenomethionine decreased TPO-Ab and TG-Ab independently of subjects VD status. Predictably, SPINA-GD increased in Se-treated group only by 11.7% (from 20.69 to 23.12 nmol/s). Reported changes indicate increased thyroid secretory capacity by inhibition its autoimmunity by applied the interventions and peripheral deiodinases in Se-group [51].

3.6. Supplement Dose of Selenium in HT Patients

It is worth to note that non-rare Se deficiency seen in HT patients' needs to be replenished in a caution of potentially toxic effects of plasma Se excess level >140 µg/L. Because some adverse health effects were observed in studies using generally accepted as sage 200 µg of Se daily (alopecia, dermatitis, squamous cell carcinoma, type II diabetes) in non-deficient Se patients the therapeutic dose should be addressed individually. Se supplementation should be discarded if plasma Se level is adequate (~125 µg/L) as there is a U-shaped relationship between Se concentration and disease risk. In an RCT of UK elderly patients, a dose of 100 µg/d increased plasma Se concentration from 91.3 µg/L to ~140 µg/L which is well enough for selenoproteins synthesis [58]. We believe that the dosage of 200 µg/d of Se in deficient patients is safe. Although, it is prudent to check Se status before initiating any the treatment with it uses.

4. Conclusion

VD plays an important role in immune regulation by the influence of genes expression. Its deficiency increases the risk of HT development and correlates negatively with severity of disease and prognosis in ill patients. The interventional treatment by oral VD supplementation seems to alleviate disease symptom. This effect is stronger when accompanied by levothyroxine, Mg or Se. Mg is important for VD conversion to its active form while the latter has anti-inflammatory and antioxidant properties as well as is necessary for thyroid hormone metabolism. Se, especially in the form of selenomethionine decreases antithyroid titers concentration and improves thyroid function. Those effects are stronger in combined therapy with levothyroxine, iodine in deficient patients or myo-inositol. At patients with excess iodine intake, Se replenishment decreases thyroid gland destruction by iodine toxicity. Exceeding serum Se concentration higher than 140 µg may increase risk of other diseases development in a time of years. Its concentration should be measured, especially in a long-time treatment (more than 12 months). There is still a big gap in the literature regarding all of those compounds and HT. More well-designed, large-sample, double-blinded, placebo-controlled randomized trials with long-term follow-up and studies with combined therapies are needed. Reporting compounds status and disease stage would help in an assessment of the efficacy of the treatment.

Conflict of Interests

The authors declares that there is no conflict of interests.

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The heading of the Acknowledgment section and the References section must not be numbered.

List of Abbreviation

Autoimmune thyroid diseases	AITDs
Iodothyronine deiodinases	DIO
free triiodothyronine	ft3
free thyroxine	ft4
Glutathione peroxidase	GPXs
Hashimoto's disease	HT
Magnesium	Mg
Randomized controlled trial	RCT
Selenium	Se
Standardized mean difference	SMD
Single-nucleotide polymorphisms	SNPs
Thyroglobulin	TG-Ab
Thyropoxidase	TPO-Ab
Thioredoxin reductases	TRs
Thyroid-stimulating hormone	TSH
Weighted mean	WMD
Vitamin D Binding Protein	DBP
Vitamin D receptor	VDR

References

- Liontiris, M.I. and Mazokopakis, E.E., "A concise review of hashimoto thyroiditis (HT) and the importance of iodine, selenium, vitamin D and gluten on the autoimmunity and dietary management of HT patients. Points that need more investigation", *Hell J Nucl Med*, 20 (1). 51-6. 2017.
- Van Schoor, N. and Lips, P., "Chapter 59. Worldwide Vitamin D Status". In: Feldman, D., Wesley Pike, J., Bouillon, R., Giovannucci, E., Goltzman, D. and Hewison, M., (editors), *Vitamin D, 4th edition*, Academic Press 2018, 15-40.
- Kim, D., "The Role of Vitamin D in Thyroid Diseases", *Int J Mol Sci*, 18 (9). 1949. 2017.
- Wang, J., Lv, S., Chen, G., Gao, C., He, J., Zhong, H. and Xu, Y., "Meta-analysis of the association between vitamin D and autoimmune thyroid disease", *Nutrients*, 7 (4). 2485-98. 2015.
- Agmon-Levin, N., Theodor, E., Segal, R.M. and Shoenfeld, Y., "Vitamin D in systemic and organ-specific autoimmune diseases", *Clin Rev Allergy Immunol*, 45 (2). 256-66. 2013.
- Kivity, S., Agmon-Levin, N., Zisappl, M., Shapira, Y., Nagy, E.V., Dankó, K., Szekanez, Z., Langevitz, P. and Shoenfeld, Y., "Vitamin D and autoimmune thyroid diseases", *Cell Mol Immunol*, 8 (3). 243-7. 2011.
- Tamer, G., Arik, S., Tamer, I., Coksert, D., "Relative vitamin D insufficiency in Hashimoto's thyroiditis", *Thyroid*, 21 (8). 891-6. 2011.
- Bozkurt, N.C., Karbek, B., Ucan, B., Sahin, M., Cakal, E., Ozbek, M. and Delibasi, T., "The association between severity of vitamin D deficiency and Hashimoto's thyroiditis", *Endocr Pract*, 19 (3). 479-84. 2013.
- Mackawy, A.M., Al-Ayed, B.M. and Al-Rashidi, B.M., "Vitamin D deficiency and its association with thyroid disease", *Int J Health Sci (Qassim)*, 7 (3). 267-75. 2013.
- Mansournia, N., Mansournia, M.A., Saeedi, S. and Dehghan, J., "The association between serum 25OHD levels and hypothyroid Hashimoto's thyroiditis", *J Endocrinol Invest*, 37 (5). 473-6. 2014.
- Lizis-Kolus, K., *Ocena wpływu niedoboru witaminy D na przebieg choroby Hashimoto u chorych w województwie świętokrzyskim*, PhD, Uniwersytet Jagielloński, Kraków, 2015.
- Chaudhary, S., Dutta, D., Kumar, M., Saha, S., Mondal, S.A., Kumar, A. and Mukhopadhyay, S., "Vitamin D supplementation reduces thyroid peroxidase antibody levels in patients with autoimmune thyroid disease: An open-labeled randomized controlled trial", *Indian J Endocrinol Metab*, 20 (3). 391-8. 2016.
- Muscogiuri, G., Mari, D., Prolo, S., Fatti, L.M., Cantone, M.C., Garagnani, P., Arosio, B., Di Somma, C. and Vitale, G., "25 Hydroxyvitamin D Deficiency and Its Relationship to Autoimmune Thyroid Disease in the Elderly", *Int J Environ Res Public Health*, 13 (9). pii: E850. 2016.
- Sönmezgöz, E., Ozer, S., Yilmaz, R., Önder, Y., Büttün, I. and Bilge, S., "Hypovitaminosis D in children with Hashimoto thyroiditis", *Rev Med Chil*, 144. 611-6. 2016.
- Giovinazzo, S., Vicchio, T.M., Certo, R., Alibrandi, A., Palmieri, O., Campenni, A., Cannavò, S., Trimarchi, F. and Ruggeri, R.M., "Vitamin D receptor gene polymorphisms/haplotypes and serum 25(OH)D3 levels in Hashimoto's thyroiditis", *Endocrine*, 55 (2). 599-606. 2017.
- Faghfour, A.H., Bagheri, M., Mehdizadeh, A., Ayremlou, P. and Zarrin, R., "Vitamin D Level and Vitamin D Receptor Gene Polymorphisms in Iranian Azeri Turkish Patients With Autoimmune Thyroid Diseases", *Acta Med Iran*, 56 (8). 508-15. 2018.
- Talaei, A., Ghorbani, F. and Asemi, Z., "The Effects of Vitamin D Supplementation on Thyroid Function in Hypothyroid Patients: A Randomized, Double-blind, Placebo-controlled Trial", *Indian J Endocrinol Metab*, 22 (5). 584-88. 2018.
- Effraimidis, G., Badenhoop, K., Tijssen, J.G. and Wiersinga, W.M., "Vitamin D deficiency is not associated with early stages of thyroid autoimmunity", *Eur J Endocrinol*, 167 (1). 43-8. 2012.
- D'Aurizio, F., Villalta, D., Metus, P., Doretto, P. and Tozzoli, R., "Is vitamin D a player or not in the pathophysiology of autoimmune thyroid diseases?", *Autoimmun Rev*, 14 (5). 363-9. 2015.
- Virili, C., Fallahi, P., Antonelli, A., Benvenega, S. and Centanni, M., "Gut microbiota and Hashimoto's thyroiditis", *Rev Endocr Metab Disord*, 19 (4). 293-300. 2018.
- Holick, M.F., Binkley, N.C., Bischoff-Ferrari, H.A., Gordon, C.M., Hanley, D.A., Heaney, R.P., Murad, M.H., Weaver, C.M. and Endocrine Society, "Evaluation, the treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline", *J Clin Endocrinol Metab*, 96 (7). 1911-30. 2011.
- Markiewicz-Żukowska, R., Naliwajko, S.K., Bartosiuk, E., Sawicka, E., Omeljaniuk, W.J. and Borawska, M.H., "The content of vitamins in diets of patients with Hashimoto disease", *Bromat Chem Toksykol*, XLIV (3). 539-43. 2011.
- Shin, D.Y., Kim, K.J., Kim, D., Hwang, S. and Lee, E.J., "Low serum vitamin D is associated with anti-thyroid peroxidase antibody in autoimmune thyroiditis", *Yonsei Med J*, 55 (2). 476-81. 2014.
- Unal, A.D., Tarcin, O., Parildar, H., Cigerli, O., Eroglu, H. and Demirag, N.G., "Vitamin D deficiency is related to thyroid antibodies in autoimmune thyroiditis. *Cent Eur J Immunol* 39 (4). 493-7. 2014.
- Mazokopakis, E.E., Papadomanolaki, M.G., Tsekouras, K.C., Evangelopoulos, A.D., Kotsiris, D.A. and Tzortzinis, A.A., "Is vitamin D related to pathogenesis and the treatment of Hashimoto's thyroiditis?", *Hell J Nucl Med*, 18 (3). 222-7. 2015.
- Kim, D., "Low vitamin D status is associated with hypothyroid Hashimoto's thyroiditis", *Hormones (Athens)*, 15 (3). 385-93. 2016.
- Ma, J., Wu, D., Li, C., Fan, C., Chao, N., Liu, J., Li, Y., Wang, R., Miao, W., Guan, H., Shan, Z. and Teng, W., "Lower Serum 25-Hydroxyvitamin D Level is Associated With 3 Types of Autoimmune Thyroid Diseases", *Medicine (Baltimore)*, 94 (39). e1639. 2015.
- Aminian, K., Bahrami, A., Najafipour, M. and Najafipour, F., "Effect of Vitamin D Replacement on Serum TSH in Women with Anti-TPO Positive Sub-clinical Hypothyroidism", *J Clin Diagn Res*, 3 (1). OC01-OC03. 2019.
- Mirhosseini, N., Brunel, L., Muscogiuri, G. and Kimball, S., "Physiological serum 25-hydroxyvitamin D concentrations are associated with improved thyroid function-observations from a community-based program", *Endocrine*, 58 (3). 563-73. 2017.
- Nodehi, M., Ajami, A., Izad, M., Asgarian Omran, H., Chahardoli, R., Amouzegar, A., Yekaninejad, S., Hemmatbadi, M., Azizi, F., Esfahanian, F., Mansouri, F., Mazaheri Nezhad Fard, R. and Saboor-Yaraghi, A.A., "Effects of vitamin D supplements on frequency of CD4+ T-cell subsets in women with Hashimoto's thyroiditis: a double-blind placebo-controlled study", *Eur J Clin Nutr*. January 2019. [online]. Available: 28.05.19
- Mazokopakis, E.E. and Kotsiris, D.A., "Hashimoto's autoimmune thyroiditis and vitamin D deficiency. Current aspects", *Hell J Nucl Med*, 17 (1). 37-40. 2014.
- Gao, X.R. and Yu, Y.G., "Meta-Analysis of the Association between Vitamin D Receptor Polymorphisms and the Risk of Autoimmune Thyroid Disease", *Int J Endocrinol*, 2018. 2846943. 2018.

- [33] Heaney, R.P., "Toward a physiological referent for the vitamin D requirement", *J Endocrinol Invest*, 37 (11), 1127-30. 2014.
- [34] Pludowski, P., Holick, M.F., Grant, W.B., Konstantynowicz, J., Mascarenhas, M.R., Haq, A., Povorznyuk, V., Balaska, N., Barbosa, A.P., Karonova, T., Rudenka, E., Misiorowski, W., Zakharova, I., Rudenka, A., Łukaszkiewicz, J., Marciniowska-Suchowierska, E., Łaszcz, N., Abramowicz, P., Bhattoa, H.P. and Wimalawansa, S.J., "Vitamin D supplementation guidelines", *J Steroid Biochem Mol Biol*, 175: 125-135. 2018.
- [35] Heaney, R.P. and Armas L.A., "Quantifying the vitamin D economy", *Nutr Rev*, 73 (1), 51-67. 2015.
- [36] Simsek, Y., Cakir, I., Yetmis, M., Dizdar, O.S., Baspinar, O. and Gokay F., "Effects of Vitamin D treatment on thyroid autoimmunity", *J Res Med Sci*, 21, 85. 2016.
- [37] Pan'kiv, I.V., "Impact of vitamin D supplementation on the level of thyroid peroxidase antibodies in patients with autoimmune hypothyroidism", *Mižnarodnij Endokrinologičnij Žurnal* 5 (77), 78-82. 2016.
- [38] Wang, S., Wu, Y., Zuo, Z., Zhao, Y. and Wang K., "The effect of vitamin D supplementation on thyroid autoantibody levels in the treatment of autoimmune thyroiditis: a systematic review and a meta-analysis", *Endocrine*, 59 (3), 499-505. 2018.
- [39] Krysiak, R., Szkróbka, W. and Okopień, B., "The Effect of Vitamin D on Thyroid Autoimmunity in Levothyroxine-Treated Women with Hashimoto's Thyroiditis and Normal Vitamin D Status", *Exp Clin Endocrinol Diabetes*, 125 (4), 229-33. 2017.
- [40] Uwitonze, A.M. and Razzaque, M.S., "Role of Magnesium in Vitamin D Activation and Function", *J Am Osteopath Assoc*, 18 (3), 181-89. 2018.
- [41] Moncayo, R. and Moncayo, H., "The WOMED model of benign thyroid disease: Acquired magnesium deficiency due to physical and psychological stressors relates to dysfunction of oxidative phosphorylation", *BBA Clin*, 3, 44-64. 2014.
- [42] Wang, K., Wei, H., Zhang, W., Li, Z., Ding, L., Yu, T., Tan, L., Liu, Y., Liu, T., Wang, H., Fan, Y., Zhang, P., Shan, Z. and Zhu, M., "Severely low serum magnesium is associated with increased risks of positive anti-thyroglobulin antibody and hypothyroidism: A cross-sectional study", *Sci Rep*, 8 (1), 9904. 2018.
- [43] Santos, L.R., Neves, C., Melo, M. and Soares, P., "Selenium and Selenoproteins in Immune Mediated Thyroid Disorders", *Diagnostics (Basel)*, 8 (4), pii:E70. 2018.
- [44] Kawai, M., Shoji, Y., Onuma, S., Etani, Y. and Ida, S., "Thyroid hormone status in patients with severe selenium deficiency", *Clin Pediatr Endocrinol*, 27 (2), 67-74. 2018.
- [45] Drutel, A., Archambeaud, F. and Caron, P., "Selenium and the thyroid gland: more good news for clinicians", *Clin Endocrinol (Oxf)*, 78 (2), 155-64. 2013.
- [46] Duntas, L.H. and Benavenga, S., "Selenium: an element for life", *Endocrine*, 48 (3), 756-75. 2015.
- [47] Fan, Y., Xu, S., Zhang, H., Cao, W., Wang, K., Chen, G., Di H., Cao M. and Liu C., "Selenium supplementation for autoimmune thyroiditis: a systematic review and meta-analysis", *Int J Endocrinol*, 2014, 904573. 2014.
- [48] Ventura, M., Melo, M. and Carrilho, F., "Selenium and Thyroid Disease: From Pathophysiology to treatment", *Int J Endocrinol*, 2017, 1297658. 2017.
- [49] Wichman, J., Winther, K.H., Bonnema, S.J. and Hegedüs, L., "Selenium Supplementation Significantly Reduces Thyroid Autoantibody Levels in Patients with Chronic Autoimmune Thyroiditis: A Systematic Review and Meta-Analysis", *Thyroid*, 26 (12), 1681-92. 2016.
- [50] Krysiak, R. and Okopien B., "The effect of levothyroxine and selenomethionine on lymphocyte and monocyte cytokine release in women with Hashimoto's thyroiditis", *J Clin Endocrinol Metab*, 96 (7), 2206-15. 2011.
- [51] Krysiak, R., Szkróbka, W. and Okopień, B., "The effect of vitamin D and selenomethionine on thyroid antibody titers, hypothalamic-pituitary-thyroid axis activity and thyroid function tests in men with Hashimoto's thyroiditis: A pilot study", *Pharmacol Rep*, 71 (2), 243-47. 2018.
- [52] Wu, Q., Rayman, M.P., Lv, H., Schomburg, L., Cui, B., Gao, C., Chen, P., Zhuang, G., Zhang, Z., Peng, X., Li, H., Zhao, Y., He, X., Zeng, G., Qin, F., Hou, P. and Shi, B., "Low Population Selenium Status Is Associated With Increased Prevalence of Thyroid Disease", *J Clin Endocrinol Metab*, 100 (11), 4037-47. 2015.
- [53] Esposito, D., Rotondi, M., Accardo, G., Vallone, G., Conzo, G., Docimo, G., Selvaggi, F., Cappelli, C., Chiovato, L., Giugliano, D. and Pasquali, D., "Influence of short-term selenium supplementation on the natural course of Hashimoto's thyroiditis: clinical results of a blinded placebo-controlled randomized prospective trial", *J Endocrinol Invest*, 40 (1), 83-9. 2017.
- [54] Kachouei, A., Rezvani, H., Amini, M., Aminorroaya, A. and Moradi, E., "The Effect of Levothyroxine and Selenium versus Levothyroxine Alone on Reducing the Level of Anti-thyroid Peroxidase Antibody in Autoimmune Hypothyroid Patients", *Adv Biomed Res*, 7, 1. 2018.
- [55] van Zuuren, E.J., Albusta, A.Y., Fedorowicz, Z., Carter, B. and Pijl, H., "Selenium Supplementation for Hashimoto's Thyroiditis: Summary of a Cochrane Systematic Review", *Eur Thyroid J*, 3 (1), 25-31. 2014.
- [56] Winther, K.H., Wichman, J.E., Bonnema, S.J. and Hegedüs, L., "Insufficient documentation for clinical efficacy of selenium supplementation in chronic autoimmune thyroiditis, based on a systematic review and meta-analysis", *Endocrine*, 55 (2), 376-385. 2017.
- [57] Faraone, S.V., "Interpreting estimates of the treatment effects: implications for managed care", *P T*, 33 (12), 700-11. 2008.
- [58] Rayman, M.P. and Duntas, L.H., "Selenium Deficiency and Thyroid Disease". In: Luster, M., Duntas, L. and Wartofsky, L. (editors), *The Thyroid and Its Diseases: A Comprehensive Guide for the Clinician*, Springer, 2019, 109-126.
- [59] Nordio, M. and Pajalich, R., "Combined treatment with Myo-inositol and selenium ensures euthyroidism in subclinical hypothyroidism patients with autoimmune thyroiditis", *J Thyroid Res*, 2013, 424163. 2013.
- [60] Nordio, M. and Basciani, S., "Treatment with Myo-Inositol and Selenium Ensures Euthyroidism in Patients with Autoimmune Thyroiditis", *Int J Endocrinol*, 2017: 2549491. 2017.
- [61] Ferrari, S.M., Fallahi, P., Di Bari, F., Vita, R., Benavenga, S. and Antonelli, A., "Myo-inositol and selenium reduce the risk of developing overt hypothyroidism in patients with autoimmune thyroiditis", *Eur Rev Med Pharmacol Sci*, 21 (2 Suppl), 36-42. 2017.
- [62] Gashu, D., Marquis, G.S., Bougma, K. and Stoecker, B.J., "Selenium inadequacy hampers thyroid response of young children after iodine repletion", *J Trace Elem Med Biol*, 50, 291-5. 2018.
- [63] O'Kane, S.M., Mulhern, M.S., Pourshahidi, L.K., Strain, J.J. and Yeates, A.J., "Micronutrients, iodine status and concentrations of thyroid hormones: a systematic review", *Nutr Rev*, 76 (6), 418-31. 2018.
- [64] Leung, A.M. and Braverman, L.E., "Iodine-induced thyroid dysfunction", *Curr Opin Endocrinol Diabetes Obes*, 19 (5), 414-9. 2012.
- [65] Krysiak, R., Kowalcze, K. and Okopien, B., "Selenomethionine potentiates the impact of vitamin D on thyroid autoimmunity in euthyroid women with Hashimoto's thyroiditis and low vitamin D status", *Pharmacol Rep*, 71 (2), 367-73. 2018.
- [66] Kłapcińska, B., Poprzecki, S., Danch, A., Sobczak, A. and Kempa, K., "Selenium levels in blood of upper Silesian population: evidence of suboptimal selenium status in a significant percentage of the population", *Biol Trace Elem Res*, 108 (1-3), 1-15. 2005.
- [67] Jablonska, E., Gromadzinska, J., Klos, A., Bertrandt, J., Skibniewska, K., Darago, A. and Wasowicz W., "Selenium, zinc and copper in the Polish diet", *J Food Compos Anal*, 31 (2), 259-65. 2013.
- [68] Ambroziak, U., Hybsier, S., Shahnazaryan, U., Krasnodębska-Kiljańska, M., Rijntjes, E., Bartoszewicz, Z., Bednarczuk, T. and Schomburg, L., "Severe selenium deficits in pregnant women irrespective of autoimmune thyroid disease in an area with marginal selenium intake", *J Trace Elem Med Biol*, 44, 186-91. 2017.

