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Effects of Combined Iodinated Casein and Selenomethionine Supplementation on Thyroid Function and Immune Regulation in Hypothyroid Rats

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Abstract: Hypothyroidism, characterized by insufficient thyroid hormone production, is frequently associated with iodine deficiency. Selenium is essential for thyroid hormone metabolism and immune regulation. This study examined the effects of iodinated casein and selenomethionine supplementation on thyroid function and immune-inflammatory markers in a rat model of hypothyroidism. Thirty-six male Wistar rats were divided into four groups: control, hypothyroid (induced by thyrozol), hypothyroid rats treated with iodinated casein and selenomethionine, and hypothyroid rats treated with iodinated casein only. After 10 days of supplementation, serum levels of thyroid-stimulating hormone (TSH), triiodothyronine (T3), thyroxine (T4), calcitonin, and cytokines (IL-6, TNF-α, IL-10, IFN-γ) were assessed. Compared to the controls, the hypothyroid group showed elevated TSH levels, decreased T3 and T4 levels, and a pro-inflammatory cytokine profile. Treatment with both iodinated casein and selenomethionine improved TSH levels, partially restored T3 and T4 levels, and normalized cytokine levels, whereas iodinated casein alone was less effective. Calcitonin levels remained unchanged after combined supplementation. These findings suggest that supplementation with both micronutrients is more effective than iodine alone in restoring thyroid hormone balance and modulating immune responses in individuals with hypothyroidism.

Keywords: Hypothyroidism; Iodinated Casein; Selenomethionine; Thyroid Hormones; Iodine Absorption; Levothyroxine

1. Introduction

Hypothyroidism is a chronic condition resulting from inadequate production or effectiveness of thyroid hormones, mainly triiodothyronine (T3) and thyroxine (T4), which regulate metabolism and physiological functions in human organs. The presence of thyroid hormone receptors accounts for the wide clinical manifestations of hypothyroidism, from metabolic issues to multi-organ dysfunction. Research has revealed various morphological and functional abnormalities caused by hypothyroidism, including changes in cardiovascular function, neurocognitive development, and lipid metabolism [1,2].

Iodine deficiency is a primary cause of endemic hypothyroidism. This micronutrient is essential for thyroid hormone production, and insufficient intake reduces T3 and T4 levels, leading to hypothyroidism and iodine deficiency disorder (IDD). The World Health Organization defines IDD as a clinical condition caused by iodine deficiency that can be prevented with adequate iodine nutrition [3,4].

Iodine deficiency remains a significant global public health concern, despite the implementation of universal salt iodization programs. One-third of the global population is affected, particularly in South Asia and sub-Saharan Africa, with pregnant women, newborns, and children at the highest risk [3,4]. Areas that previously had adequate iodine levels now exhibit mild deficiency due to changes in dietary patterns and reduced iodine fortification [3,4].

During pregnancy, insufficient iodine can severely impact fetal brain development due to inadequate thyroid hormones from the mother, leading to permanent neurodevelopmental issues and cretinism. Studies have shown that maternal hypothyroxinemia and fetal hypothyroidism due to inadequate iodine interfere with central nervous system development. The timing of iodine supplementation during pregnancy is vital, as delayed intake may not prevent neurodevelopmental harm [5,6].

Infants, particularly those with health issues such as congenital heart disease or those receiving long-term parenteral nutrition, face an increased risk of hypothyroidism due to iodine imbalance. Both iodine deficiency and excess (from antiseptics or contrast media) can trigger hypothyroidism, requiring close monitoring of iodine and thyroid function in these populations [7,8].

Hypothyroidism can result from pituitary dysfunction, causing thyroid-stimulating hormone (TSH) deficiency, which complicates diagnosis because TSH becomes unreliable. Clinical assessment, including free T4 measurements, is essential for diagnosis and treatment, highlighting the need for personalized treatment approaches [1,9].

Levothyroxine (L-T4) remains the main treatment for hypothyroidism. However, challenges persist in determining the optimal dosage, achieving euthyroidism, and monitoring treatment, particularly in subclinical cases, older adults, and patients with comorbidities. New approaches, such as combined T3/T4 therapy, require more evidence for widespread adoption [1,2].

The relationship between dietary selenium, serum selenium concentrations, and thyroid hormone-related diseases has been documented over the last 30 years. This has been observed in small-scale observational or interventional studies across regions, subpopulations, and groups with varying baseline selenium consumption [10,11].

Although extensive epidemiological or prospective studies are limited [12], experimental animal and *in vitro* research support the link between inadequate selenium levels and disease development, establishing clear cause-and-effect relationships. The biochemical and metabolic interactions between iodine and selenium, particularly in thyroid hormone metabolism, are of notable interest [13,14].

Endemic goiter and cretinism cannot be eradicated by adding iodine to diets in iodine-deficient areas due to selenium deficiency. This deficiency reduces the enzymes crucial for activating and regulating thyroid hormone levels; iodine supplementation alone does not address this issue. Studies on selenium deficiency have shown reduced conversion of T4 to T3, leading to hypothyroidism [15]. Despite knowing for over a century that sufficient iodine is necessary for thyroid function and hormone production, the global implementation of strategies to ensure adequate dietary iodine or prevent health and social issues linked to iodine deficiency remains unachieved [16].

The genetic, molecular, and biochemical traits of iodine absorption, utilization, and function have been unraveled in recent decades, advancing the diagnosis, treatment, and monitoring of IDDs [17,18]. While sufficient iodine and thyroid gland production are crucial for normal thyroid function during fetal development and throughout life, they are not the only factors involved in this process. Trace elements, such as selenium and iron, play a significant role in the synthesis of iodine-containing hormones and their systemic availability and efficacy [12,19].

Essential micronutrients, such as iodine and selenium, are crucial for thyroid hormone production, activation,

and gland health. Iodine forms thyroxine (T4) and triiodothyronine (T3) through tyrosine iodination in thyroglobulin. Selenium, in selenoproteins such as glutathione peroxidases and iodothyronine deiodinases, converts T4 to T3 and protects thyroid cells by neutralizing hydrogen peroxide during hormone synthesis [20,21]. These micronutrients also affect the balance of the immune system. Selenium deficiency disrupts T-cell responses and increases pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), worsening autoimmune thyroiditis. Selenium supports anti-inflammatory processes through cytokines such as interleukin-10 (IL-10), whereas interferon-gamma (IFN-γ) from Th1 cells influences thyroid inflammation [22,23].

In hypothyroidism, altered cytokine levels indicate an immune imbalance that may worsen thyroid issues. Elevated IL-6 and TNF-α levels are associated with thyroid inflammation, whereas changes in IL-10 and IFN-γ levels indicate immune regulation disturbances [22]. During pregnancy, iodine deficiency reduces maternal thyroid hormones, which are essential for fetal neurodevelopment, as the fetus depends on maternal free T4 for cerebral T3 production. Maternal hypothyroxinemia due to inadequate iodine is associated with poor neurodevelopmental outcomes, necessitating increased iodine intake during pregnancy to prevent conditions such as cretinism [3,5,6]. Selenium's immunomodulatory role reduces thyroid autoimmune activity postpartum, with studies showing that selenium supplementation decreases thyroid peroxidase antibodies and postpartum thyroid dysfunction [22,23].

Excess iodine can lead to hypothyroidism, particularly in full-term infants with congenital heart disease who are exposed to iodinated contrast agents [7]. In central hypothyroidism due to TSH deficiency, treatment monitoring requires free T4 levels and clinical evaluation rather than TSH levels [1, 9]. While levothyroxine is the primary treatment, optimizing outcomes requires consideration of comorbidities, age, and disease etiology [1].

Iodinated casein and selenomethionine address different thyroid functions: iodine serves as a hormone substrate, whereas selenium aids T4 to T3 conversion and supports redox regulation. Thomson et al. showed that adults receiving L-selenomethionine (100 μg/day), iodine (80 μg/day), both, or placebo for 12 weeks showed selenium increased glutathione peroxidase activity and iodine decreased thyroglobulin levels (indicating iodine deficiency), showing how each nutrient addresses separate thyroid challenges, although no combined effects on TSH/T3/T4 were noted in this euthyroid group [24].

Despite extensive iodization initiatives, hypothyroidism remains a significant health issue worldwide, especially in areas where selenium deficiency exists. Iodine and selenium are crucial micronutrients for thyroid hormone synthesis, metabolism, and immune system regulation. Iodine deficiency affects the production of T3 and T4 hormones, whereas selenium is vital for converting T4 into active T3 and protecting the thyroid tissue from oxidative damage. Evidence suggests that iodine supplementation alone may be inadequate and potentially detrimental if selenium deficiency is not addressed in the same treatment. The immunological aspects of hypothyroidism, particularly inflammatory cytokine profiles, remain understudied in the context of combined trace element supplementation. It is important to explore whether the co-administration of iodinated casein and selenomethionine can more effectively restore thyroid hormone balance and maintain immune homeostasis in individuals with hypothyroidism.

This study assessed the therapeutic effects of iodinated casein and selenomethionine supplementation on thyroid hormone levels and immune modulation in a rat model of hypothyroidism. The study aimed to (1) evaluate serum levels of T3, T4, TSH, and calcitonin; (2) examine the effects on pro-inflammatory cytokines (IL-6, TNF-α, IFN-γ) and anti-inflammatory cytokine (IL-10); and (3) explore the relationship between endocrine recovery and immune regulation after combined therapy compared to iodine alone. This study aimed to determine whether adding selenium to iodine treatments enhances the effectiveness and safety of managing hypothyroidism.

2. Materials and Methods

Thirty-six male Wistar rats (Rattus norvegicus) weighing 200–300 grams were kept in standard laboratory conditions. The environment was maintained at a 12-hour light/dark cycle, a temperature of 22 ± 2 °C, and a humidity of 55 ± 10%. The rats had free access to a balanced diet and to water. All procedures were approved by the Institutional Animal Ethics Committee of I.K. Akhunbaev Kyrgyz State Medical Academy (protocol no. 22, February 10, 2024).

The basal Laboratory Rodent Diet (LabDiet 5001; Purina Mills, St. Louis, MO, USA) contained 1,000 μg iodine/kg diet and 300 μg selenium/kg diet, as indicated by the manufacturer's data. These levels were consistent across the groups, with additional micronutrient intake occurring through experimental supplementation. Animals

were assigned to treatment groups using computer-generated randomization to reduce allocation bias in the study. For biochemical and cytokine analyses, serum samples were labeled with anonymized identification numbers by external personnel. The laboratory staff performing ELISA and hormone measurements remained blinded to the group assignments. Data decoding was performed only after all assays and statistical analyses were completed.

To induce hypothyroidism, thyrozol (an antithyroid agent also known as thiamazole) was administered at 5,000 μg (5 mg) per 200–250 g body weight in the diet for 21 days. After this phase, thyrozol was halted, and micronutrient treatment was initiated on day 22.

After acclimatization, the animals were divided into four groups of 9 subjects each. Group 1 (Control) comprised healthy rats fed a standard diet without any treatment. Group 2 (Hypothyroid) included rats that developed hypothyroidism after thyrozol treatment. Group 3 (Combination Therapy) consisted of hypothyroid rats administered daily oral doses of iodinated casein at 25,000 μg/kg/day (25 mg/kg/day) and selenomethionine at 250 μg/kg/day (0.25 mg/kg/day) for 10 days. Group 4 (Iodine Monotherapy) included hypothyroid rats treated with iodinated casein at 5,000 μg/kg/day (5 mg/kg/day) for 10 days. Iodinated casein and selenomethionine were prepared in microencapsulated granulated forms and mixed with standard feed for consistent administration.

Blood samples were collected after the treatment period, not immediately after thyrozol administration. The rats received thyrozol for 21 days, after which they received supplementation (Groups 3 and 4) or did not (Group 2) for 10 days. Twenty-four hours after the last supplementation day, which was 10 days after thyrozol cessation, the animals were euthanized by decapitation under light anesthesia. Blood was promptly collected in serum-separator tubes. The serum was extracted through centrifugation and stored at −20 °C for later examination. All procedures adhered to the guidelines for animal welfare. This timing minimized acute fluctuations after dosing and ensured that hormone and cytokine levels represented the post-induction, early recovery phase rather than immediate withdrawal effects.

Serum levels of TSH, T3, T4, and calcitonin were assessed using rat-specific immunoassay kits on a BS-240 VET Clinical Chemistry Analyzer (Mindray, Shenzhen, China). The assays included a rat TSH ELISA kit (Cusabio Biotech Co., Ltd., Cat No. CSB-E05115r), a Rat T3 ELISA Kit (MyBioSource, Cat No. MBS261285), a rat T4 ELISA kit (Elabscience, Cat No. E-EL-0100), and a rat calcitonin ELISA kit (Cloud-Clone Corp., Cat No. CEA472Ra). Cytokine concentrations were measured using rat-specific enzyme-linked immunosorbent assays. IL-6 was quantified using a rat IL-6 ELISA kit (R&D Systems, Cat No. R6000B), TNF-α with a rat TNF-α ELISA kit (Invitrogen/Thermo Fisher, Cat No. KRC3011), and IL-10 with a rat IL-10 ELISA kit (Invitrogen/Thermo Fisher, Cat No. BMS629) and IFN-γ using a rat IFN-γ ELISA kit (RayBiotech, Catalog No. ELR-IFNg-1). The intra-assay coefficients of variation of the assays were below 8–10%, while the inter-assay coefficients of variation were under 10–12%, ensuring reliable reproducibility of the measurements.

Experimental data, animal studies, and clinical observations have established connections between iodine and selenium compounds [25–27]. In mild iodine deficiency, the effects are less severe when accompanied by mild selenium deficiency due to reduced thyroid hormone metabolism through the deiodinase system. When organic iodine intake increases in cases of mild deficiency, latent selenium deficiency becomes apparent. Efforts to enhance dietary iodine intake should be paired with increased dietary selenium (and iron ions) to maintain thyroid function and reduce the negative effects (oxidative damage, inflammation, and fibrosis) caused by high iodine availability to angiofollicular units. Discrepancies in micronutrient supply, iodine use, and thyroid hormone synthesis and secretion occur in conditions such as congenital hypothyroidism, autoimmune thyroid disorders, and thyroid cancer, both in humans and in experimental animal models that replicate these diseases [28].

Data analysis was performed using IBM SPSS Statistics software, version 22.0 (IBM Corp., Armonk, NY, USA). The findings are presented as mean ± standard deviation. Student's t-test was used to compare continuous variables between groups. Categorical variables were assessed using the chi-square test. A $p < 0.05$ was considered statistically significant, with further significance levels set at $p < 0.01$ and $p < 0.001$, when relevant. Pearson's correlation coefficient was used to perform correlation analyses to examine the relationships between thyroid hormone levels and cytokine concentrations. We conducted a priori sample size calculation using G*Power (version 3.1.9.7). With an effect size of 1.5 (large), $\alpha = 0.05$, and power $(1-\beta) = 0.80$, eight rats per group were required to identify significant differences in thyroid hormone levels between groups. Our final sample size of nine rats per group satisfied this requirement, ensuring sufficient statistical power to detect biologically relevant differences.

3. Results

This study involved 36 male Wistar rats divided into four groups to investigate the effects of iodinated casein and selenomethionine on thyroid hormone levels and immune-inflammatory markers in experimentally induced hypothyroidism. Hypothyroidism was induced using thyrozol, and model success was verified by reduced serum T3 and T4 levels compared to the controls. To evaluate the effects of iodine, selenium, and their combined supplementation, biochemical, hormonal, and cytokine profiles were measured. The findings detail variations in thyroid hormones, TSH, calcitonin, and immunological markers (IL-6, IL-10, TNF-α, and IFN-γ) among the groups. All treatments began after 21 days of hypothyroidism induction using thyrozol. This approach ensured uniform severity of hypothyroidism across the groups before supplementation.

Table 1 shows the serum concentrations of thyroid hormones and calcitonin in the four experimental groups. Group 2 exhibited increased TSH levels (5.0 ± 1.2 mIU/L) compared to the controls (0.5 ± 0.1 mIU/L; $p < 0.001$), confirming the presence of hypothyroidism. Serum T3 and T4 levels decreased in group 2 (1.71 ± 0.04 nmol/L and 26.2 ± 0.77 nmol/L, respectively; $p < 0.001$). Group 3 had reduced TSH (2.0 ± 0.5 mIU/L; $p < 0.01$) and partially restored T3 (1.98 ± 0.07 nmol/L; $p < 0.01$) and T4 (50.5 ± 3.54 nmol/L; $p < 0.01$) levels. Group 4 showed improved hormone levels, with TSH at 3.0 ± 0.6 mIU/L ($p < 0.05$), T3 at 2.44 ± 0.08 nmol/L ($p < 0.05$), and T4 at 41.9 ± 4.59 nmol/L ($p < 0.05$). Calcitonin levels remained stable across groups, except for an increase in group 4 (0.63 ± 0.07 pg/mL; $p < 0.05$), suggesting a thyroid parafollicular cell response to iodine. These findings demonstrate the effectiveness of combined micronutrient therapy in restoring thyroid hormone balance.

Table 1. Parameters of thyroid hormones in the blood serum of the compared to different groups.

Parameters	Group 1 (n = 9)	Group 2 (n = 9)	Group 3 (n = 9)	Group 4 (n = 9)
TSH (mIU/L)	0.5 ± 0.1	5.0 ± 1.2***	2.0 ± 0.5**	3.0 ± 0.6*
T3 (nmol/L)	2.4 ± 0.15	1.71 ± 0.04 ***	1.98 ± 0.07**	2.44 ± 0.08*
T4 (nmol/L)	76.6 ± 3.75	26.2 ± 0.77 ***	50.5 ± 3.54**	41.9 ± 4.59*
Calcitonin (pg/mL)	0.48 ± 0.05	0.47 ± 0.04	0.49 ± 0.06	0.63 ± 0.07†

Note: Data presented as mean ± standard deviation. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ compared with Group 2, †Significantly increased compared to other groups ($p < 0.05$). T3 = Triiodothyronine, T4 = Thyroxine, TSH = Thyroid stimulating hormone.

Serum TSH levels differed among the four groups of rats. Group 2 showed increased TSH (5.0 ± 1.2 mIU/L) compared to Group 1 (0.5 ± 0.1 mIU/L; $p < 0.001$), confirming the induction of hypothyroidism. Supplementation decreased TSH levels in both treated groups, with Group 3 (2.0 ± 0.5 mIU/L; $p < 0.01$ vs. Group 2) showing a greater reduction than Group 4 (3.0 ± 0.6 mIU/L; $p < 0.05$ vs. Group 2). These results suggest that selenium enhances iodine's ability to suppress TSH elevation (**Figure 1**).

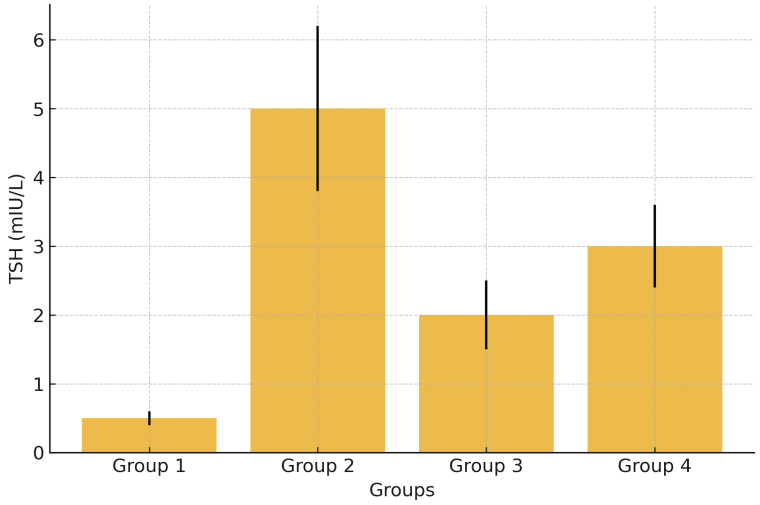

Figure 1. Dynamics of TSH levels in the blood serum of experimental rats.

Note: Values are presented as the mean ± standard deviation. TSH levels were higher in group 2 than in group 1, whereas group 3 and group 4 had reduced TSH levels.

Group 2 showed a significant decrease in T3 levels (1.71 ± 0.04 nmol/L) compared to Group 1 (2.4 ± 0.15 nmol/L; $p < 0.001$). Treatment improved T3 levels, with Group 3 showing partial recovery to 1.98 ± 0.07 nmol/L ($p < 0.01$ vs. Group 2), while Group 4 reached 2.44 ± 0.08 nmol/L ($p < 0.05$ vs. Group 2). While iodine alone better normalized T3 levels, combined treatment provided a balanced enhancement of T3 and TSH, indicating a more regulated thyroid response (**Figure 2**).

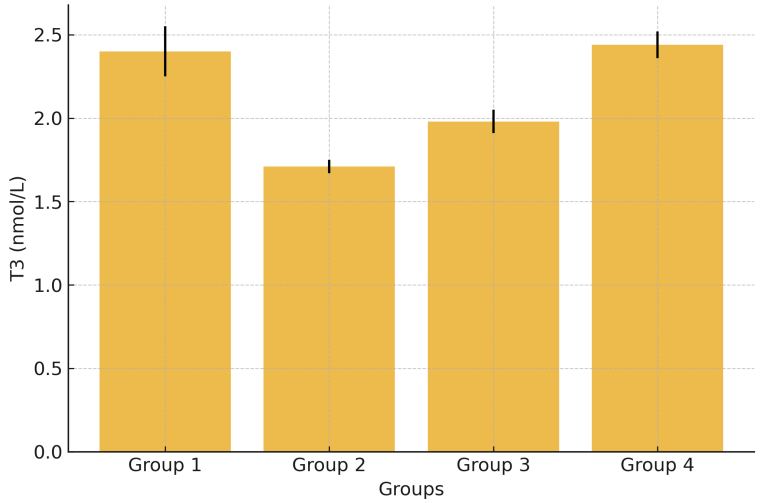

Figure 2. Dynamics of T3 levels in the blood serum of experimental rats.

Note: Values are presented as the mean ± standard deviation. In Group 2, hypothyroidism decreased T3 levels, whereas supplementation partially restored these levels, with Groups 3 and 4 showing notable improvements.

T4 levels were lower in Group 2 (26.2 ± 0.77 nmol/L) than in Group 1 (76.6 ± 3.75 nmol/L; $p < 0.001$). After supplementation, T4 levels increased in both groups, with Group 3 showing a higher increase (50.5 ± 3.54 nmol/L; $p < 0.01$ vs. Group 2) than Group 4 (41.9 ± 4.59 nmol/L; $p < 0.05$ vs. Group 2). These findings demonstrate the role of selenium in T4 recovery and indicate improved iodine utilization when selenium is administered alongside (**Figure 3**).

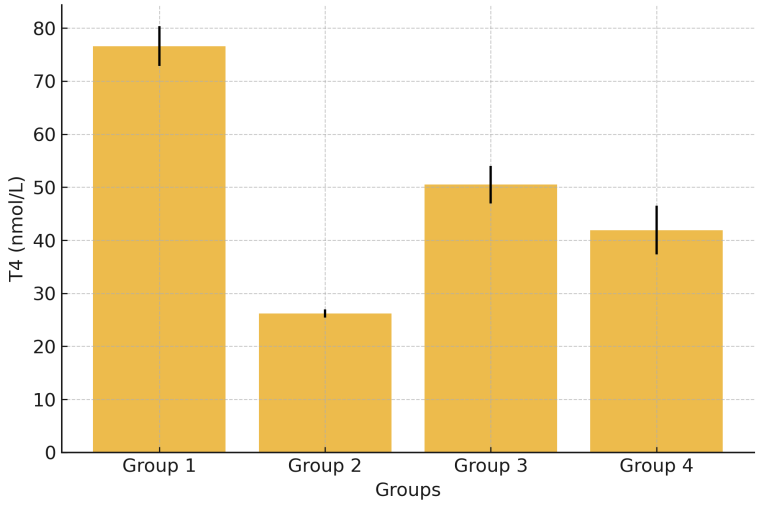

Figure 3. Dynamics of T4 levels in the blood serum of experimental rats.

Note: Values are presented as the mean ± standard deviation. T4 levels were significantly lower in Group 2 than in Group 1, but Groups 3 and 4 showed notable improvement in these levels.

Calcitonin levels remained consistent in group 1 (0.48 ± 0.05 pg/mL), 2 (0.47 ± 0.04 pg/mL), and 3 (0.49 ± 0.06 pg/mL). Group 4 showed a notable increase (0.63 ± 0.07; $p < 0.05$ compared to all other groups). This increase

suggests that group 4 may enhance parafollicular (C-cell) activity, while group 3 appears to stabilize calcitonin secretion, indicating a protective effect on thyroid C-cell function (**Figure 4**).

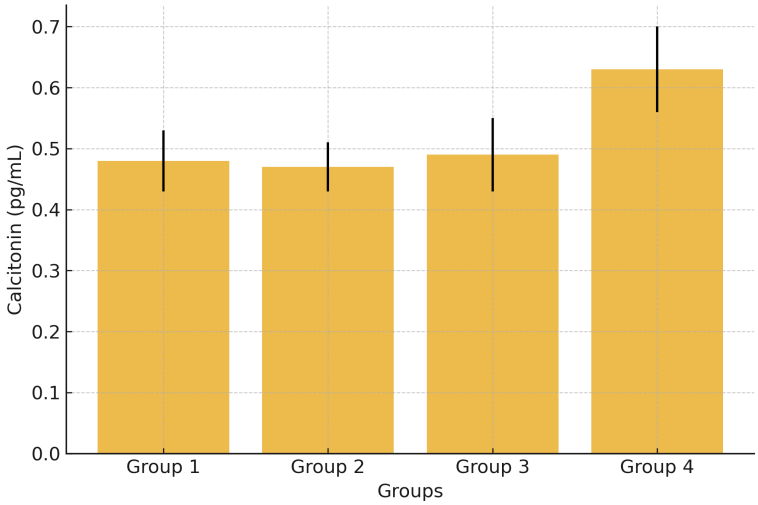

Figure 4. Dynamics of Calcitonin levels in the blood serum of experimental rats.

Note: Values are presented as the mean ± standard deviation. Calcitonin levels remained consistent in Groups 1–3, with an increase detected in Group 4.

Variations were detected in the serum cytokine levels, particularly those associated with thyroid autoimmunity and inflammation. In hypothyroid rats, IL-6 concentrations were higher (Group 2: 44.2 ± 5.3 pg/mL) than those in controls (Group 1: 21.7 ± 3.8 pg/mL, $p < 0.001$). Combined selenium and iodine (Group 3) decreased IL-6 levels to 27.5 ± 4.6 pg/mL ($p < 0.01$), whereas iodine alone (Group 4) had a lesser effect (35.1 ± 5.1 pg/mL).

TNF-α levels were elevated in the hypothyroid group (Group 2: 38.9 ± 4.7 pg/mL vs. Group 1: 19.5 ± 2.9 pg/mL, $p < 0.001$). Combined supplementation reduced TNF-α levels (Group 3: 22.1 ± 3.3 pg/mL, $p < 0.01$), surpassing those of the iodine-only treatment (Group 4: 30.6 ± 4.2 pg/mL).

IL-10 levels were lower in Group 2 (13.2 ± 2.1 pg/mL) than in the controls (24.8 ± 3.7 pg/mL, $p < 0.001$). Selenium and iodine raised IL-10 to 21.6 ± 2.9 pg/mL ($p < 0.01$), while iodine alone showed a modest increase (17.5 ± 2.8 pg/mL).

IFN-γ levels were elevated in hypothyroid rats (Group 2:42.3 ± 5.8 pg/mL vs. Group 1:25.1 ± 4.2 pg/mL, $p < 0.001$). Combined treatment brought IFN-γ levels near control values (Group 3: 26.7 ± 4.6 pg/mL), while iodine-only treatment showed intermediate results (Group 4: 34.5 ± 5.0 pg/mL).

Group 1 comprised control rats, Group 2 included hypothyroid rats induced by thyrozol, Group 3 contained hypothyroid rats treated with iodinated casein and selenomethionine, and Group 4 included hypothyroid rats treated with iodinated casein alone. Compared to the controls, hypothyroid rats (Group 2) exhibited increased levels of IL-6, TNF-α, and IFN-γ, accompanied by decreased levels of IL-10, indicating inflammation and immune dysregulation. Combined iodinated casein and selenomethionine treatment (Group 3) normalized the cytokine levels, whereas iodinated casein alone (Group 4) showed partial improvement. These findings indicate the crucial role of selenomethionine in restoring immune equilibrium in hypothyroidism (**Figure 5**).

In Group 3, thyroid hormone levels showed a strong negative correlation with decreased IL-6 and TNF-α levels (Pearson's $r = -0.71$ and -0.68, respectively; $p < 0.01$) and a positive correlation with increased IL-10 ($r = +0.62$, $p < 0.01$). These results suggest that selenium enhances deiodinase activity in hormone activation, while also reducing inflammation and immune imbalance related to the thyroid. Evidence suggests that combined supplementation provides dual benefits: restoring endocrine function and reversing the inflammatory immune profiles associated with hypothyroidism.

In hypothyroid rats, supplementation with combined iodinated casein and selenomethionine restored thyroid hormone levels and altered their immune profile. Compared to the hypothyroid group (Group 2), Group 3 exhibited increased T3 and T4 levels, accompanied by a decrease in pro-inflammatory cytokines (IL-6, TNF-α, and IFN-γ) and a restoration of the anti-inflammatory cytokine IL-10. These results highlight the role of selenium in enhancing

iodine metabolism and reestablishing immune balance. Although iodine-only supplementation (Group 4) improved T3 and T4 levels, it was less effective in correcting cytokine imbalances, suggesting incomplete immune modulation in the absence of selenium.

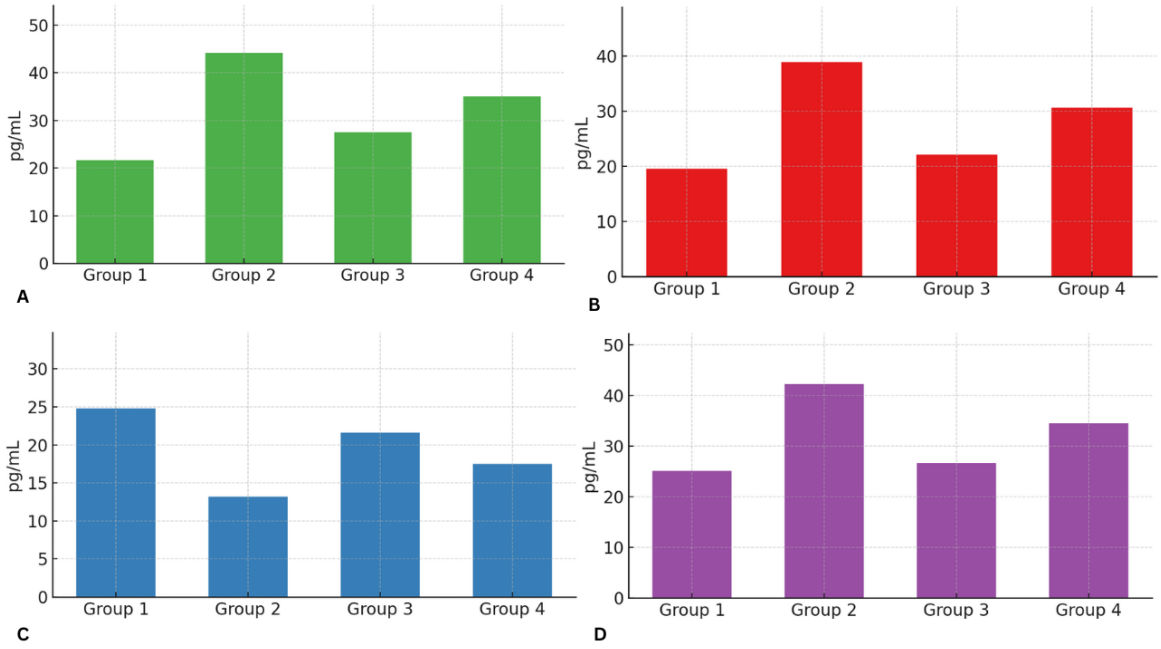

Figure 5. Dynamics of cytokine levels in blood serum of experimental rats: (**A**) Interleukin-6; (**B**) tumor necrosis factor-alpha; (**C**) Interleukin-10; and (**D**) interferon-gamma.

Biochemical and immunological findings indicate that selenium facilitates the conversion of T4 to T3 through deiodinases, while also contributing to reduced inflammation and enhanced immune tolerance. The negative correlations between thyroid hormones and IL-6/TNF-α, with a positive correlation with IL-10, emphasize the dual role of selenomethionine in endocrine and immune modulation. These findings underscore the potential of combined treatment of hypothyroidism and immune dysfunction, highlighting the need for personalized multimicronutrient strategies to restore thyroid and systemic homeostasis.

4. Discussion

This study investigated the effects of iodinated casein and selenomethionine supplementation on thyroid hormone levels in a rat model of hypothyroidism. The findings showed that the simultaneous administration of these micronutrients significantly enhanced T3 and T4 levels, partially restoring thyroid function. This highlights the complementary roles of iodine and selenium in the metabolism and regulation of thyroid hormones.

Hypothyroidism was induced using thyrozol, which was indicated by decreased T3 and T4 levels in the second group. However, TSH and calcitonin levels did not change, likely due to feedback dysregulation and the limited sensitivity of the TSH assay in the early or central hypothyroidism models. These results align with those of studies demonstrating the limited diagnostic value of TSH alone in certain cases of hypothyroidism, particularly when the hypothalamic-pituitary axis is involved [29].

The group receiving iodinated casein and selenomethionine supplements (Group 3) showed a greater recovery in T4 levels (50.5 ± 3.54 nmol/l) than the iodine-only group (Group 4; 41.9 ± 4.59 nmol/l), indicating that selenium may enhance iodine metabolism. Selenium is essential for iodothyronine deiodinases, which convert T4 into the active form of T3 [30, 31]. Selenium deficiency impairs this enzymatic function, leading to the accumulation of inactive T4 and T3 deficiency, even with normal or near-normal iodine levels [32].

These results align with prior experimental and epidemiological research, suggesting that selenium deficiency can worsen IDDs and reduce the effectiveness of iodine supplementation [33,34]. In selenium-deficient populations,

providing iodine without addressing selenium deficiency may increase thyroid autoimmunity and oxidative damage to thyrocytes [35].

Our findings align with those of Kohrle et al. [27], who found that selenium deficiency in rats disrupts antioxidant defenses in thyroid follicles, making thyrocytes more susceptible to hydrogen peroxide damage during hormone production.

While the combination of iodinated casein and selenomethionine yielded better results by boosting T4 recovery and balancing cytokine levels, iodine alone also led to notable endocrine changes. Group 4 showed higher serum T3 levels (2.44 ± 0.08 nmol/L) than the combined treatment group (1.98 ± 0.07 nmol/L), indicating the effectiveness of iodine in triiodothyronine recovery. Iodine alone partially restored T4 levels and decreased TSH elevation; however, the lack of selenium limited the correction of cytokine balance. These results indicate that while iodine effectively restores T3 and T4 levels, its benefits are maximized when combined with selenium, which enhances hormone utilization and provides immunomodulatory effects. The superiority of combination therapy lies in its ability to complement iodine's function, thereby achieving both endocrine and immune recovery.

In this study, we observed that serum calcitonin levels remained relatively stable in the combined iodinated casein and selenomethionine treatment group compared to hypothyroid controls. While this finding may suggest a protective effect on parafollicular C-cells, it is important to emphasize that without direct histological examination of thyroid gland morphology and C-cell integrity, this interpretation remains speculative. We therefore propose this as a hypothesis that merits further investigation through detailed histopathological analyses to determine whether combined micronutrient supplementation confers structural protection to thyroid C-cells.

This mechanism might explain why calcitonin levels remained stable in our group receiving combined treatment, suggesting the protective effect of selenium against parafollicular C-cell dysfunction. Notably, animals in Group 4, which received only iodine, showed higher T3 levels than those in the combined treatment group (2.44 ± 0.08 vs. 1.98 ± 0.07 nmol/l). Although seemingly contradictory, this may indicate a temporary increase in hormone production due to iodine without improved conversion efficiency or cellular protection by selenium. Such iodine imbalance may increase thyroid hormone levels without proper peripheral activation or use, possibly leading to thyroid stress or inflammation over time [36].

Selenium's role in modulating immunity justifies its inclusion in strategies for maintaining thyroid health. It affects cytokine expression by decreasing pro-inflammatory agents, such as IL-6 and TNF-α, while boosting anti-inflammatory cytokines, such as IL-10 [37,38]. These actions are significant in autoimmune thyroiditis, postpartum thyroid issues, and groups experiencing chronic inflammation due to environmental or dietary factors [39]. Our research supports the notion that replenishing both iodine and selenium offers a more physiologically appropriate method for addressing thyroid dysfunction. It also shows that single micronutrient supplementation may be inadequate or counterproductive, especially when multiple trace element deficiencies exist. Given the interactions between iodine, selenium, and iron in thyroid hormone synthesis and regulation, future interventions should focus on multimicronutrient formulations tailored to regional nutritional profiles.

In Group 2 rats, hypothyroidism induced by thyrozol caused significant decreases in T3 and T4 levels, reflecting the characteristics of clinical hypothyroidism. These endocrine findings alone do not fully explain the pathophysiology of hypothyroidism, which involves immune dysregulation. Assessment of circulating cytokines revealed increased levels of IL-6, TNF-α, and IFN-γ accompanied by decreased levels of IL-10, in hypothyroid animals. These changes align with studies linking hypothyroidism to systemic inflammation and modified T cell function [12,19]. Such cytokine patterns indicate activation of innate immunity and Th1-dominated responses involved in the development of autoimmune thyroiditis [40].

In Group 3, treatment with iodinated casein and selenomethionine enhanced T3 and T4 levels while normalizing cytokine expression. IL-6 and TNF-α levels decreased significantly, whereas IL-10 returned to control levels. Selenium's immunomodulatory effects, mediated by selenoproteins, reduce oxidative stress and inflammatory signaling [10,13,26]. Decreased IFN-γ levels suggest reduced pro-autoimmune Th1 responses, highlighting the role of selenium in immune tolerance [22]. Iodine-only treatment (Group 4) increased serum T3 more than selenium-iodine, but was less effective in lowering pro-inflammatory cytokines, indicating disrupted T4 to T3 conversion due to insufficient redox control [14,15]. Elevated calcitonin levels suggest C-cell stress due to iodine excess without antioxidant protection [25].

The altered cytokine profiles following combined iodinated casein and selenomethionine supplementation un-

derscore the role of selenium as an immunomodulator in thyroid health. By reducing pro-inflammatory agents IL-6 and TNF-α and restoring IL-10 levels, selenium helps re-establish immune tolerance and mitigates Th1-driven autoimmune reactions. These changes align with the therapeutic objectives of immunomodulatory approaches for autoimmune thyroiditis, suggesting that micronutrient supplementation is a low-risk complement for stabilizing immune responses. Rather than a standalone "immunotherapy," the benefits of selenium should be viewed as enhancing iodine metabolism while reducing inflammatory signaling, connecting endocrine recovery with immune equilibrium.

Supplementation with iodinated casein and selenomethionine enhanced thyroid hormone levels and balanced cytokine profiles by reducing pro-inflammatory signals and restoring IL-10 levels. These findings suggest that selenium aids endocrine recovery through deiodinase activity and stabilizes immunity via selenoprotein-driven antioxidant processes. Treatment with iodine alone improved T3 and T4 levels but was less effective in addressing cytokine imbalances, highlighting the role of selenium in immune equilibrium. The results showed that hypothyroidism promotes inflammation, which may hinder recovery. Selenium's role in enhancing iodine use and reducing inflammatory signaling explains the superior outcomes of combined therapy. While parallels exist with autoimmune thyroid disease, the data indicate immune dysregulation and systemic inflammation resulting from thyroid hormone deficiency.

In this study, elevated serum T3 levels in the iodine-only group were likely due to redox-driven and cytokine-mediated changes in thyroid hormone metabolism, which occured when selenium was insufficient. Iodide organification relies on H_2O_2, and limited seleno-antioxidant capacity can increase intrathyroidal H_2O_2 and inflammatory signaling, which suppresses iodothyronine deiodinase 1 (DIO1)/DIO2 while activating DIO3, resulting in higher circulating T3 but reduced tissue-level availability [41–43]. This pattern matches iodine-excess phenomena (acute Wolff–Chaikoff effect with escape, Jod-Basedow-like responses) and highlights the risks of isolated iodine supplementation [44]. The combined treatment of iodinated casein and selenomethionine can stabilize the redox balance and deiodinase activity, promoting balanced endocrine–immune recovery [41,45].

Future studies should evaluate hormones, cytokines, and other mechanistic endpoints, including markers of oxidative stress, assays for iodothyronine deiodinase 1, 2, and 3 (DIO1, DIO2, and DIO3), as well as histomorphology of the thyroid. These assessments would elucidate the redox-mediated effects of selenium on thyroid hormone metabolism and provide structural evidence for its protective function in thyroid follicular and parafollicular cells. Including these endpoints would enable a better understanding of endocrine–immune interactions in hypothyroidism and its management.

The elevated T3 levels in the iodine-only group may be attributed to changes in deiodinase activity due to selenium deficiency. Selenium-dependent enzymes DIO1 and DIO2 convert T4 to active T3, whereas DIO3 deactivates T4 to reverse T3. Without adequate selenium, increased iodide can temporarily raise T3 levels, leading to impaired regulation and decreased tissue utilization, as well as increased rT3 production. This imbalance suggests a compensatory response that may cause thyroid dysfunction. Future studies measuring rT3 and deiodinase activity will help to validate this mechanism.

Overall, these results highlight the importance of a dual-nutrient approach to managing hypothyroidism, especially in areas where multiple micronutrient deficiencies are prevalent. The observed improvement in thyroid hormone levels and reduction in inflammatory cytokines following the combined supplementation of iodinated casein and selenomethionine strongly supports the use of integrative nutritional therapy.

Understanding that combined iodine and selenium supplementation can be beneficial, excessive consumption of either micronutrient poses risks to susceptible groups. An overabundance of iodine may lead to thyroid issues, such as the Wolff–Chaikoff effect or iodine-induced hyperthyroidism, particularly in newborns, pregnant women, and those with thyroid conditions. Selenium overconsumption can result in selenosis, causing gastrointestinal distress, brittle hair and nails, and neurotoxicity in severe cases. These dangers highlight the need to optimize and monitor dosages, especially in high-risk populations such as infants with congenital heart disease, pregnant and lactating women, and patients with autoimmune thyroiditis. The future clinical use of dual micronutrient supplementation should strike a balance between effectiveness and safety through individualized assessments of baseline nutritional status.

Although serum calcitonin stability in the combined treatment group suggests a protective effect on parafollicular cells, this remains hypothetical and lacks structural evidence to support it. Future studies should include thy-

roid histopathology to examine follicular morphology and parafollicular cell integrity, thereby confirming whether iodinated casein and selenomethionine provide histological protection.

5. Limitations

Although this study presents compelling findings, several limitations must be acknowledged.

- This study had a relatively small sample size of nine participants per group. While power analysis suggested that this was adequate for the main endocrine outcomes, the small cohort may limit the detection of subtle immunological effects. Future research with larger samples would enhance the generalizability of the results.
- This study involved a small group of healthy laboratory rats, which may limit its applicability to humans. Although rodent thyroid physiology shares similarities with that of humans, notable differences exist in metabolic rate, hormone turnover, and immune response. However, these findings should be cautiously applied to clinical settings, especially in humans with comorbidities or autoimmune thyroid conditions.
- The treatment and follow-up lasted only 10 days, possibly not reflecting the long-term effects or negative outcomes of chronic supplementation with iodinated casein and selenomethionine. Additional studies are needed to evaluate the sustained effectiveness, toxicity, and thyroid gland histopathology over extended periods.
- While the study assessed key cytokines and thyroid hormones, it did not examine other markers, such as oxidative stress, antioxidant enzyme activity (e.g., glutathione peroxidase), and thyroid histomorphology, limiting the understanding of the role of selenium in redox modulation and immune balance. Furthermore, only one dosage level for each compound was tested, leaving the dose–response relationships undefined.
- The microencapsulated forms of iodinated casein and selenomethionine may not accurately represent the pharmacokinetics of naturally occurring or clinically used formulations for human supplementation.
- The interpretation of TSH is limited since sampling occurred only once, 10 days after stopping thyrozol and 24 hours after supplementation during HPT-axis recovery. Values were near the assay's lower detection limit without standardization for circadian or fasting control. We lacked orthogonal assay confirmation and mechanistic markers such as free T3/T4, reverse T3, DIO1, DIO2, and DIO3. Hypothyroidism was based on T3/T4 reductions and cytokine changes, with TSH as a supportive rather than conclusive indicator.
- This study used only male rats; therefore, the results may not apply to female rats. Future studies should include both male and female animals, as sex hormones affect thyroid function and immunity, with females being more prone to thyroid autoimmunity than males. Investigating sex-specific variations will enhance the translational significance of combined iodine and selenium supplementation.

6. Clinical Implications

This study has significant implications for the treatment of hypothyroidism, particularly in groups with both iodine and selenium deficiencies. Current treatment methods rely on levothyroxine (L-T4) alone or iodine supplementation alone. However, this study revealed that iodine supplementation alone may not be sufficient to restore thyroid balance and immune stability in the absence of selenium. The demonstrated benefit of combined iodinated casein and selenomethionine therapies suggests that a dual-nutrient approach could improve treatment effectiveness by stabilizing thyroid hormone levels and influencing immune-inflammatory responses.

Strong correlations between thyroid hormone recovery and decreased pro-inflammatory cytokines (IL-6, TNF-α, IFN-γ) suggest that a broader micronutrient evaluation is warranted in hypothyroid patients, particularly those with autoimmune thyroiditis or chronic inflammation. Selenium's ability to boost deiodinase activity and reduce immune activation highlights its potential as a supplement in cases where iodine-only or standard levothyroxine therapies are ineffective.

These findings support the evaluation of selenium levels in patients with hypothyroidism and suggest that selenium supplementation may be beneficial in areas with sufficient iodine but lacking selenium. Healthcare providers should consider the local micronutrient environment and patients' nutritional needs when formulating treatment strategies.

From a clinical perspective, iodine supplementation through salt iodization can significantly enhance thyroid hormone levels in individuals with hypothyroidism, supporting its role in reducing goiter globally. However, the results suggest that iodine alone may not sufficiently address the immune-inflammatory issues associated with hy-

pothyroidism. Selenium may fill this gap by enhancing the conversion of T4 to T3 and regulating inflammatory cytokines. Treatment plans should recognize the benefits of iodine, especially in populations with low intake. However, in areas with selenium deficiency and immune-related thyroid issues, combined supplementation may provide more comprehensive therapeutic benefits.

These findings show that hypothyroidism involves endocrine and systemic inflammatory disruptions. While iodine alone may not fully address immune imbalance, the combination of iodine and selenium supplementation appears to be more effective in restoring hormonal and inflammatory equilibrium. Although this rat model does not mimic autoimmune thyroiditis, its cytokine patterns resemble those observed in autoimmune conditions. Evaluating selenium levels could benefit areas with both deficiencies or patients with hypothyroidism, inflammation, or autoimmunity. Although our model represents an immune imbalance, its applications extend to both thyroid disorders. Future studies should examine whether dual supplementation improves outcomes in human hypothyroidism and affects inflammatory and autoimmune activities.

7. Conclusions

This study revealed that combined iodinated casein and selenomethionine supplementation enhanced thyroid hormone balance and immune regulation in hypothyroid rats. While iodine alone partially restored T3 and T4 levels, it failed to correct the cytokine imbalances. Selenium improves T4 to T3 conversion, decreases pro-inflammatory cytokines (IL-6, TNF-α, and IFN-γ), and increases the anti-inflammatory cytokine IL-10, thereby reestablishing endocrine and immune balance.

These results demonstrate the superiority of the dual-nutrient approach over iodine alone, emphasizing their complementary functions in thyroid physiology. Combined supplementation effectively addresses the complex pathophysiology of hypothyroidism through hormone metabolism and immune modulation.

Further research, including long-term clinical studies, is needed to confirm these findings in humans and to determine the optimal dosing strategies. Incorporating iodine and selenium supplementation can enhance the management of hypothyroidism and reduce immune-inflammatory effects.

8. Recommendations

- Assessing both iodine and selenium levels is crucial in managing hypothyroidism, particularly in areas prone to micronutrient deficiencies or among those with autoimmune thyroid conditions. Early identification of deficiencies can facilitate prompt treatment and prevent long-term issues affecting the endocrine and immune systems.
- Healthcare professionals should consider iodine and selenium supplementation for hypothyroidism, particularly in selenium-deficient regions. This combined approach has proven more effective in normalizing thyroid hormone levels and adjusting inflammatory cytokine profiles than iodine alone.
- Programs aimed at preventing IDDs should include selenium fortification, especially in regions where these deficiencies are prevalent. Policymakers should review and revise existing salt iodization methods to incorporate selenium-enriched options, as needed.
- Special attention should be paid to selenium monitoring in pregnant women, new mothers, infants receiving parenteral nutrition, and individuals with congenital heart disease or autoimmune thyroiditis, as they are susceptible to immune and endocrine imbalances.
- Longitudinal clinical trials are necessary to evaluate the long-term effectiveness of therapies that combine iodinated casein and selenomethionine. These investigations should focus on optimizing dosages, understanding pharmacokinetics, and identifying the side effects in diverse patient groups.
- Future studies should examine the immunomodulatory effects of selenium in thyroid disorders, particularly its influence on oxidative stress, T cell activation, and autoantibody modulation. Research on interactions with trace elements, such as iron and zinc, could enhance therapeutic strategies.
- Personalized multimicronutrient therapy, tailored to individual nutritional status, age, comorbidities, and genetic factors, should be considered to improve treatment outcomes in hypothyroid patients and reduce inflammation.

Author Contributions

Conceptualization, O.Z. and Z.T.; methodology, A.R.; software, T.T.; validation, M.T. and S.K.; formal analysis, T.T.; investigation, O.Z., Z.T., A.R., and M.T.; data curation, S.K.; writing—original draft preparation, M.T., S.K., and T.T.; writing—review and editing, T.T. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement

Not applicable.

Data Availability Statement

Data is available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare that there is no conflict of interest.

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