UDC: 616.44-007/008(497.75)
Professional paper

MORPHOLOGICAL AND HORMONAL CHANGES OF THE THYROID GLAND IN THE POPULATION OF POLOG AND ITS SURROUNDINGS IN THE REPUBLIC OF NORTH MACEDONIA

Albulena BEADINI [1], Irfan AMETI [2], Sheqibe BEADINI [3], Adelina ELEZI [4], Albin BEADINI [5], Egzona ZIBERI [6] , Afet BAJRAMI [6]

1 Department of Biochemistry, Faculty of Medical Sciences, University of Tetovo, Republic of North Macedonia
2 Department of Endocrinology, Faculty of Medical Sciences, Saints Cyril and Methodius University, Skopje, Republic of North Macedonia
3 Department of Biochemistry, Faculty of Medical Sciences, University of Tetovo, Republic of North Macedonia
4 Department of Pathology, Faculty of Medical Sciences, University of Tetovo, Republic of North Macedonia
5 Department of Physiology, Faculty of Medical Sciences, University of Tetovo, Republic of North Macedonia
6 Scientific Laboratory of Medical Sciences, Faculty of Medical Sciences, University of Tetovo, Republic of North Macedonia
Corresponding author: sheqibe.beadini@unite.edu.mk

Abstract

Introduction: The thyroid gland is a vital endocrine (hormone-producing) gland. It plays an important role in the metabolism, growth and development of the human body. It helps regulate many body functions by continuously secreting a constant amount of thyroid hormones into the bloodstream. The size and shape of the thyroid gland can vary significantly with age, gender, physiological state, etc. but it can be larger in women than in men and can enlarge during menstruation and pregnancy.
Morphological disorders of the thyroid mainly include thyroid nodules. Thyroid nodules are a common occurrence and are detected in approximately 5% to 7% of the adult population by physical examination. The risk of thyroid nodules is higher with increasing age, female gender,in pregnancy, iodine deficiency, etc. The initial workup for a thyroid nodule should consist of obtaining a medical history, performing a physical exam, assessing thyroid-stimulating hormone (TSH) levels and conducting a thyroid ultrasound to evaluate the gland's structure.
Physiological hormonal disorders of the gland can result in excessive production of FT_3 and FT_4 along with a compensatory decrease in TSH. In addition, thyrotrophic adenoma can produce abnormally regulated TSH and can lead to increased production of FT_3 and FT_4. Under certain conditions, thyroid hormone is produced ectopically, resulting in elevated thyroid hormone levels and a compensatory reduction in TSH.
Aim of the Study: This study aims to analyze morphological and hormonal changes of the thyroid gland in the population of Polog and surrounding areas in North Macedonia, with focus on endogenous or exogenous factors, treatment, and potential thyroid endemism, especially in mountainous villages compared to urban and highway areas.
Material and Methods: The study includes 30 female patients divided into three age groups (20–40 age, 41–60 age, and over 61 age) and 10 control subjects. Blood serum levels of TSH, FT_4 and FT_3 will be analyzed using the automated fluorescent enzyme immunoassay method (Vidas – Biomerie, France).
Results and Conclusion: The findings will provide a clear overview of thyroid hormone levels in the Polog region and highlight the prevalence of thyroid disorders across different geographical zones. Thyroid hormones are essential for metabolism and physiological functions their imbalance can lead to conditions like hyperthyroidism and hypothyroidism. Understanding these mechanisms is key to effective diagnosis and personalized treatment in this population.

Keywords: Thyroid hormones, endogenous factors, exogenous factors, endemic, treatment, thyroid gland.

1. Introduction

Thyroid gland is the largest gland of the endocrine system, despite the fact that it weighs 15-20 g in an adult individual, the importance of this gland is extraordinary. The gland is responsible for mental and physical development both during the embryonic period and in other stages of life (Allen E, et al 2025).
The thyroid diverticulum begins to form at the end of the fourth week of development as a solid, proliferating cluster of endodermal cells at the foramen cecum, located on the developing

https://doi.org/10.62792/ut.amb.v10.i19-20.p3190

tongue. This endodermal mass then migrates downward through the forming neck along the thyroglossal duct, ultimately settling just below the cricoid cartilage. The foramen cecum at the base of the tongue is the only remnant of the thyroid's embryonic development. By this stage, the developing thyroid gland forms two distinct lobes connected by a narrow isthmus of tissue. It continues to descend through the neck and reaches its final position by the end of the seventh week of development (Coste AH et al., 2023).

The thyroid is a crucial, butterfly-shaped endocrine organ located in the lower neck, positioned anteriorly and laterally to the trachea, just below the larynx. It is key in controlling the basal metabolic rate, supports both physical and mental development and also contributes significantly to calcium homeostasis.

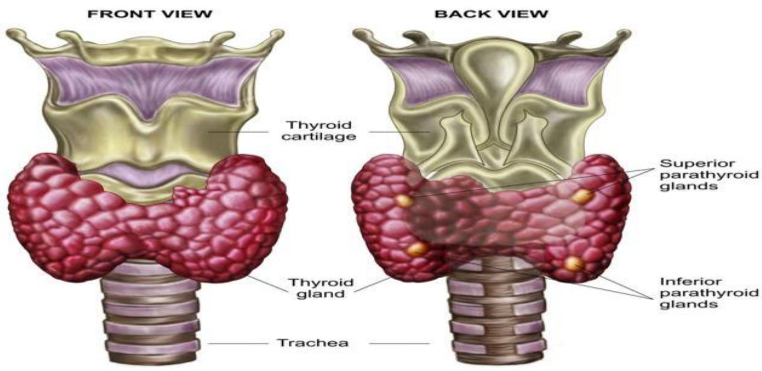


Figure 1. Thyroid gland anatomy (Regina Bailey, 2025)

The thyroid gland comprises two primary lobes right and left connected by a central structure known as the isthmus. Occasionally, a third lobe, referred to as the pyramidal lobe, may arise from the isthmus. A fibrous or fibromuscular band the **levator glandulae thyroideae**, stretches from the hyoid bone to the isthmus (Chaudhary P et al., 2013).

Each lobe typically measures about **5 x 2.5 x 2.5 cm** and weighs approximately **25 grams**. The gland spans from the **fifth cervical (C5)** to the **first thoracic (T1)** vertebra and extends vertically from the mid-thyroid cartilage down to the fifth tracheal ring. The isthmus itself is about **1.2 x 1.2 cm**, positioned across the second and third tracheal rings. Notably, the thyroid may increase in size in females during menstruation and pregnancy.

The lobes are **conical** in shape, featuring an **apex**, a **base**, **three surfaces** (lateral, medial, and posterolateral), and **two borders** (anterior and posterior). In contrast, the isthmus presents with **two surfaces** anterior and posterior and **two borders** superior and inferior. Anatomically, the lobes lie anteriorly in relation to the **skin**, **superficial and deep cervical fascia**, and the **platysma muscle**. Posteriorly, they are adjacent to the **thyroid cartilage laminae** and **tracheal rings**, while laterally, they are closely associated with the **external carotid artery** and **internal jugular vein** (Stocco AV et al.,2024).

The thyroid gland is highly vascularized, receiving its blood supply primarily from the **superior and inferior thyroid arteries**, with an occasional contribution from an additional vessel known as the **thyroidea ima artery** (Esen K et al., 2018).

Venous return is managed by the **superior, middle**, and **inferior thyroid veins**, although a fourth vein, termed the **vein of Kocher**, may sometimes be present. Neural innervation is predominantly derived from the **middle cervical ganglion**, with additional input from both the **superior and inferior cervical ganglia.** Structurally, the thyroid is enveloped by two distinct capsules. The **true capsule** is composed of **fibroelastic connective tissue**, while the **false capsule** originates from the **pretracheal layer of the deep cervical fascia**. A dense **capillary plexus** lies beneath the true capsule, making it essential to remove this plexus along with the

capsule during surgical procedures like thyroidectomy to minimize bleeding (*Gray's Anatomy*, 2020).
The thyroid gland's primary role is to produce the hormones T_4 and T_3, which are vital for controlling the body's metabolic activities. Just like in any factory, successful production requires three main components: an adequate supply of raw materials, efficient equipment, and effective regulation. Iodine is a crucial element for the thyroid gland, as it makes up about 65% of the weight of T_4. Once iodine is consumed, it is absorbed and transported in the bloodstream as iodide. The thyroid gland then actively takes up this iodide through the sodium,iodide symporter located on the basolateral membrane of thyrocytes. Inside the cells, iodide is moved into the lumen of the thyroid follicles. At the same time the endoplasmic reticulum within thyrocytes produces two important proteins: thyroid peroxidase (TPO) and thyroglobulin (Tg).

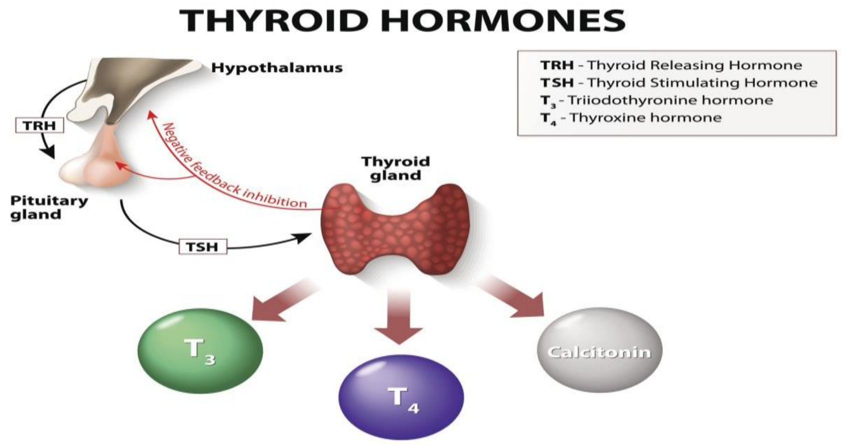


Figure 2. Thyroid gland hormones (Thyroid Hormones. ttsz/iStock/Getty Images Plus, 2025)

Thyroid-stimulating hormone (TSH) is the main regulator of thyroid hormone production and release, affecting almost every stage of the process. Initially, it triggers immediate activation of cellular and enzymatic systems, while long-term regulation involves changes in the expression of genes encoding essential proteins. An imbalance in iodine intake whether excessive or deficient can disrupt proper hormone synthesis. Antithyroid medications work by blocking the oxidation of iodide. Inherited defects in critical proteins such as NIS, TPO, Duox, or Tg can lead to goiter and hypothyroidism (Rousset B et al., 2015).

2. Material and methods

The research will include a total of 30 female patients divided by age group into 3 categories and 10 patients as control group. The first group will include patients aged: 20-40 years, the second group patients from 41-60 years and the third group over 61 years.
Blood samples (serum) will be taken for thyroid hormones TSH, FT_4, FT_3. Hormones will be analyzed by serum with the modern automatic fluorescent enzyme immunoassay method (Vidas - Biomerie).
All patients underwent thyroid gland ultrasonography conducted by a specialist in endocrinology, during which morphological alterations of the thyroid and associated disorders present in the study cohort were identified.

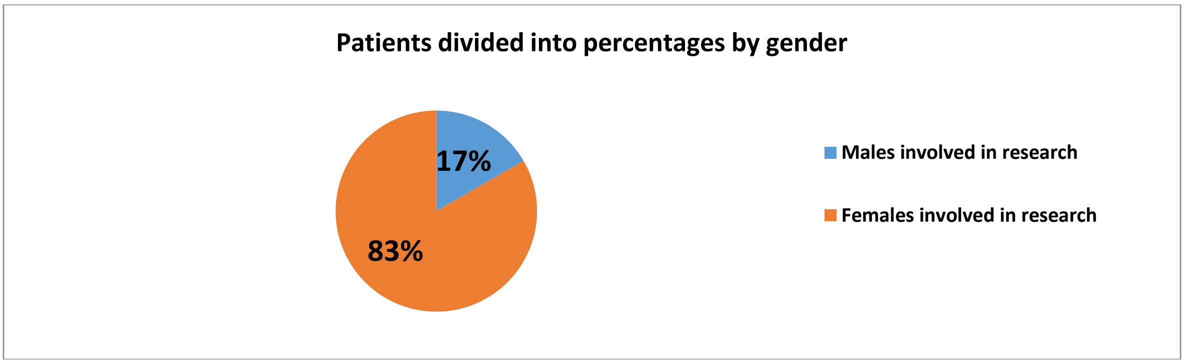
Figure 3. Ultrasonography of thyroid gland conducted by a specialist endocrinolog (Dr.Spec.Irfan Ahmeti-Albimedica, 2025)

Figure 4. The patients' hormone analyses were performed at the Albimedica laboratory with the Mini VIDAS apparatus (Albimedica laboratory, 2025)

All analyses, including comprehensive laboratory testing and thyroid gland echography, were conducted at Polyclinic Albimedica, ensuring high-quality, standardized data that significantly enhance the scientific rigor and reliability of the study.

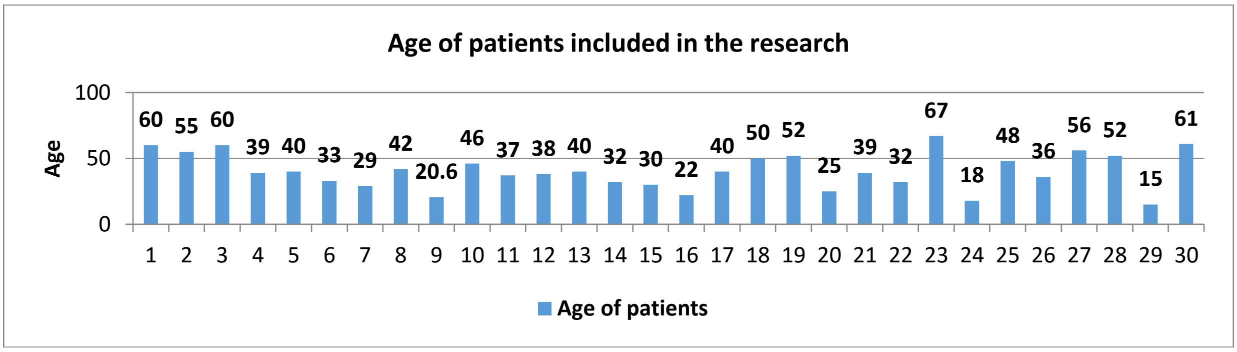
3. Results

In the results section, we will present the data obtained from patients using clear and informative graphics to facilitate interpretation and highlight key findings.



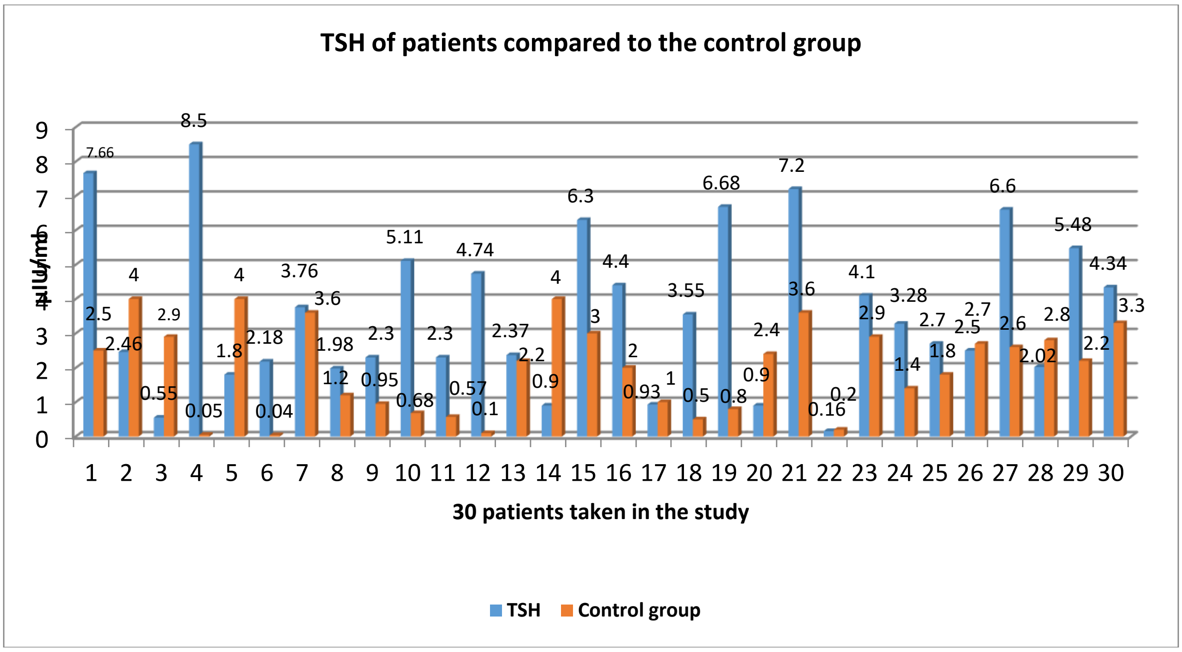
Graph.1: Patients divided into percentages by gender:

This graphic clearly illustrates the gender distribution among patients, showing that 17% are male and 83% are female. This notable imbalance may indicate trends in healthcare-seeking behavior, access, or underlying health conditions. Understanding such disparities is crucial for ensuring equitable healthcare planning and delivery.



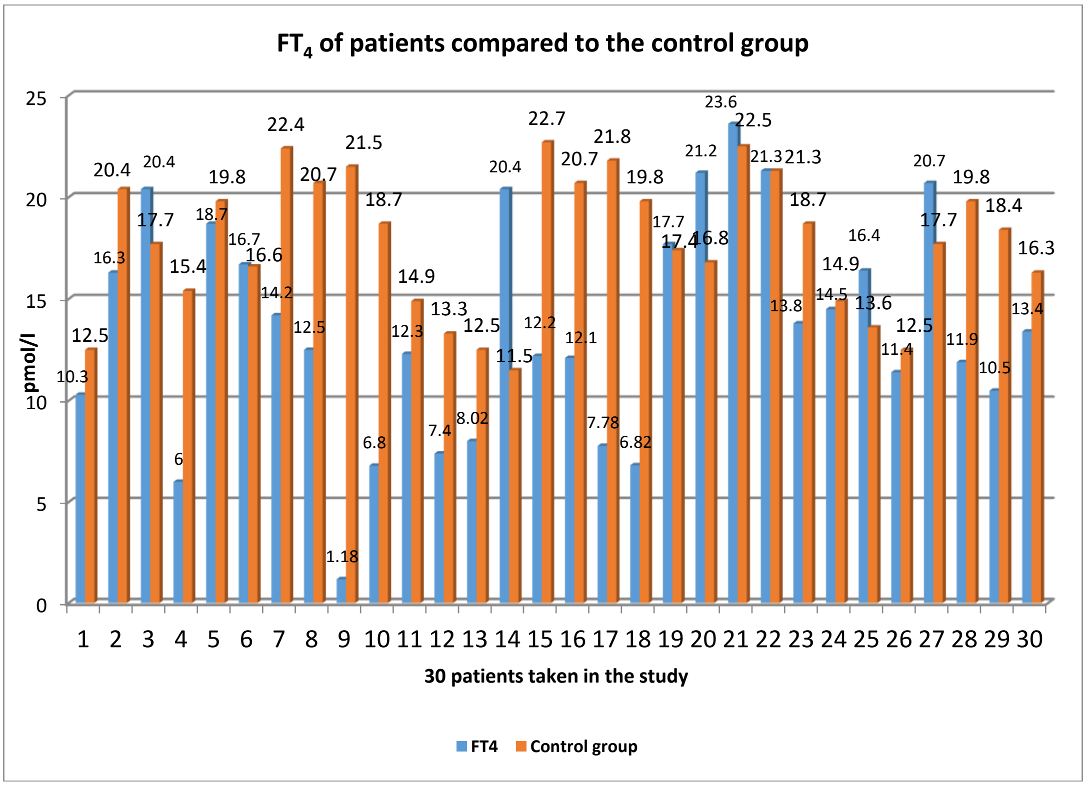
Graph.2: Age of patients included in the research:

This graphic illustrates the age distribution of patients included in the research on thyroid gland diseases. Understanding how thyroid conditions are spread across different age groups is essential, as age can significantly influence the onset, progression, and management of both hyperthyroidism and hypothyroidism. The data can help identify age-related trends and guide more targeted screening and treatment strategies.



Graph.3: TSH of patients compared to the control group:

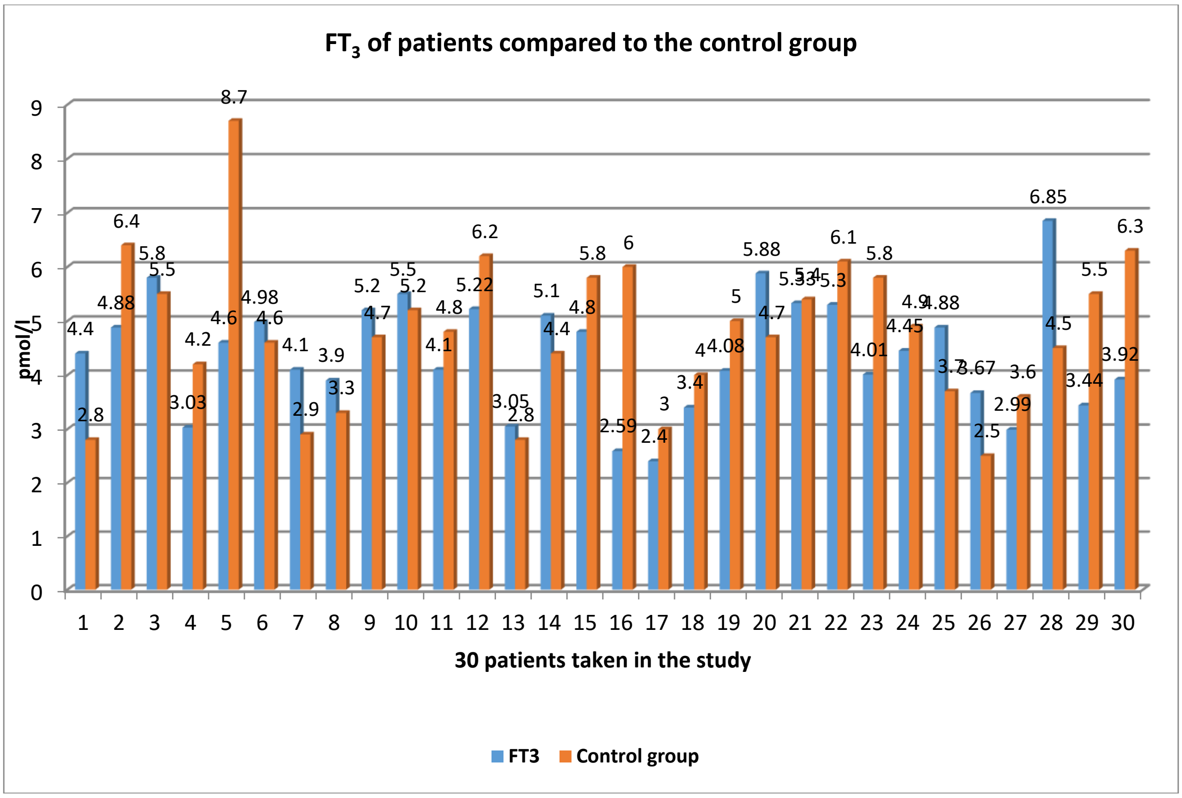
This graphic compares the TSH (thyroid-stimulating hormone) levels of patients with those of the control group. The differences observed may reflect variations in thyroid function, helping to distinguish between individuals with normal thyroid activity and those with conditions such as hypothyroidism or hyperthyroidism. This comparison is valuable for assessing the diagnostic relevance of TSH levels in thyroid-related disorders.



Graph.4: FT_4 of patients compared to the control group:

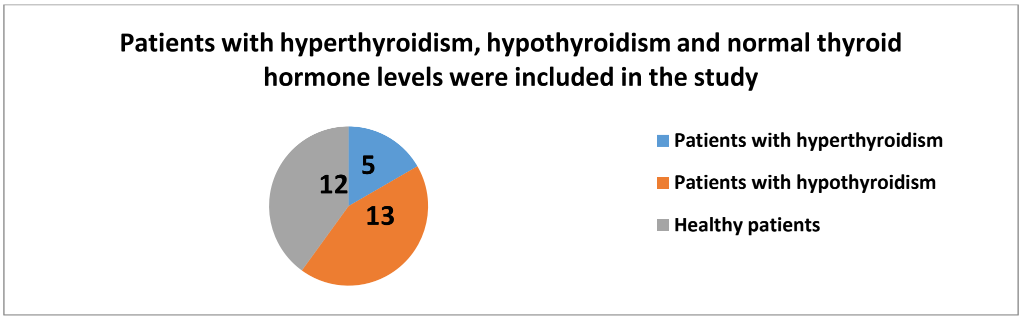
This graphic presents a comparison of FT4 (free thyroxine) levels between patients and the control group. The differences in FT4 concentrations help illustrate variations in thyroid function, supporting the diagnosis of conditions like hyperthyroidism or hypothyroidism.

Comparing these levels with those of healthy individuals provides important insight into the extent of thyroid hormone imbalance in affected patients.



Graph.5: FT$_3$ of patients compared to the control group:

This graphic compares FT3 (free triiodothyronine) levels between patients and the control group. Variations in FT3 levels can provide critical insight into thyroid gland activity, especially in diagnosing and monitoring hyperthyroidism. The comparison highlights how FT$_3$ levels differ in individuals with thyroid dysfunction compared to those with normal thyroid function, aiding in a more comprehensive understanding of thyroid hormone imbalance.



Graph.6: Patients with hyperthyroidism, hypothyroidism and normal thyroid hormone levels were included in the study:

This graphic presents patients based on thyroid hormone levels included in the study: 5 with hyperthyroidism, 13 with hypothyroidism, and 12 with normal thyroid function. The fairly balanced representation allows for meaningful comparisons across different thyroid conditions and helps in assessing the impact of thyroid status on the study's outcomes.

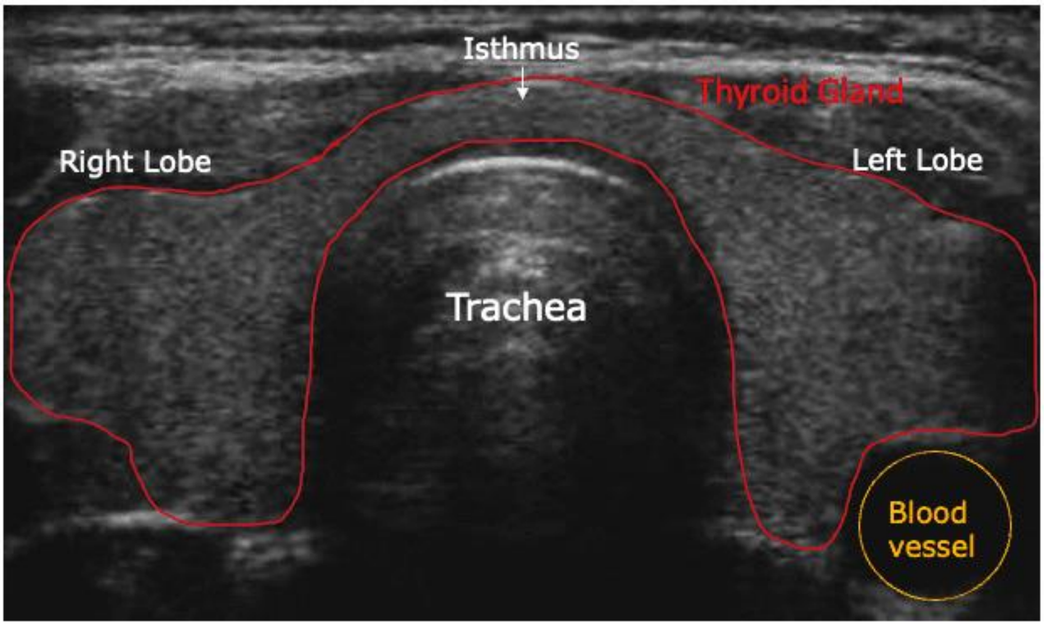


Figure 5. Ultrasonography of a healthy normal thyroid gland (STARmed America, 2025)

The ultrasound image depicts a healthy thyroid gland with normal size, smooth contours, and a homogeneous echotexture. The parenchyma appears isoechoic with no evidence of nodules, cysts, or increased vascularity. These findings are consistent with a structurally and functionally normal thyroid gland.

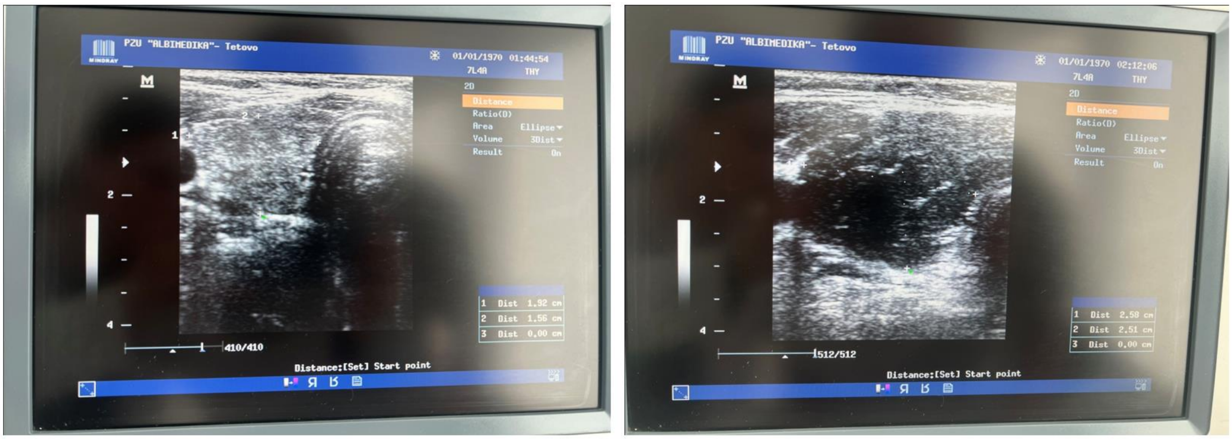


Figure 6. Ultrasonography of thyroid gland conducted by a specialist endocrinolog (Dr.Spec.Irfan Ahmeti-Albimedica, 2025)

Ultrasound in Patients with Hypothyroidism: The presented ultrasound images reveal a thyroid gland with a heterogeneous and hypoechoic parenchymal structure, findings typically observed in patients with hypothyroidism. Such sonographic characteristics are suggestive of chronic autoimmune thyroiditis, most commonly Hashimoto's thyroiditis, which leads to progressive destruction of thyroid tissue. The reduced echogenicity reflects lymphocytic infiltration and fibrosis, correlating with impaired hormone production and overall diminished glandular function. These findings support the clinical and biochemical diagnosis of hypothyroidism.

Figure 7. Ultrasonography of thyroid gland conducted by a specialist endocrinolog (Dr.Spec.Irfan Ahmeti-Albimedica, 2025)

Ultrasound in Patients with Hyperthyroidism: The presented ultrasound images demonstrate a thyroid gland that is enlarged with a hypoechoic and heterogeneous parenchymal structure, accompanied by increased vascularization—a hallmark of hyperthyroidism. These sonographic features are commonly associated with autoimmune conditions such as Graves' disease, which is characterized by diffuse glandular hyperactivity. The enhanced blood flow, often described as a "thyroid inferno" on Doppler imaging, reflects the gland's elevated metabolic state and excessive hormone production. These imaging findings align with the clinical and biochemical profile of hyperthyroidism.

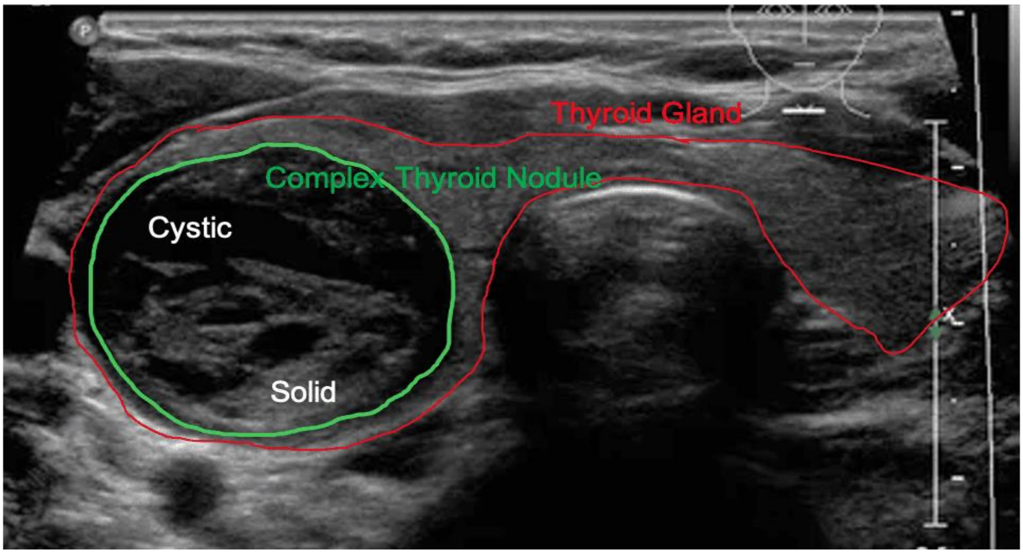


Figure 8. Ultrasonography of thyroid gland with cystic nodules (STARmed America, 2025)

The ultrasound image shows a thyroid gland containing cystic nodules, which appear as well-defined, anechoic or hypoechoic areas with posterior acoustic enhancement. These findings are typically benign and often represent colloid cysts or degenerative changes within pre-existing nodules. The absence of solid components, calcifications, or irregular margins reduces the likelihood of malignancy. However, further evaluation with fine-needle aspiration (FNA) may be warranted if there are suspicious features or clinical indications.

4. Discussion

The thyroid gland becomes hyperplastic and a goiter develops when there is severe nutritional iodine deficiency. This is the reverse of the usual meaning of toxic effects of a substance on an organ. In fact, the abnormality occurs when there is an insufficient amount rather than an excess of one of the important chemicals needed for that particular gland. Another aspect of toxicology of the thyroid is the fact that when the normal regulatory mechanisms with the usual feedback control of thyroxine secretion fail, very high levels of thyroxine develop with resultant hyperthyroidism or more appropriately for this conference, thyrotoxicosis (Edmund B. Flink, 1981).

An overactive thyroid makes too many hormones (hyperthyroidism). An underactive thyroid doesn't make enough hormones (hypothyroidism). Both of these imbalances can lead to many different symptoms. The gland may get bigger too. Sometimes the whole thyroid gland becomes enlarged (diffuse goiter), and sometimes individual lumps called nodules grow in the gland (nodular goiter). Various tests can be used to diagnose medical conditions affecting the thyroid (InformedHealth.org, 2006).

Thyroid disorders encompass both abnormal thyroid hormone levels and enlargement of the gland. An enlarged thyroid can manifest as benign conditions like nodules or goitre, or it may indicate malignancy in cases of thyroid cancer. Thyroid dysfunction can generally be categorized into two main types: conditions that lead to reduced thyroid gland activity (hypothyroidism) and those that cause excessive activity (thyrotoxicosis) (National Institute for Health and Care Excellence - NICE, 2019).

Thyroid-stimulating hormone (TSH) is a glycoprotein hormone secreted by specific basophils in the pituitary gland, which is a specific indicator for evaluating individual thyroid function. Clinically common thyroid diseases include hyperthyroidism, hypothyroidism, thyroiditis and so on (*Chan AO et al., 2011*).

Xing D et al., 2021 stated in their study that they comprehensively analysed the factors affecting the establishment of the TSH reference interval, including age, sex, iodine intake, sample size, region, assay methods and manufacturers and race. They suggest that TSH is significantly changed by age and sex, and our conclusions are as follows: the TSH reference interval in females was generally higher than that in males and TSH concentration increased with age in both males and females. The establishment of the TSH reference interval was also significantly influenced by sample size, region, assay methods and manufacturers. In the sample size, the effect of large sample size on TSH reference interval is more significant. In addition, the assay and reagents used in each laboratory were diverse manufacturers, and the test results will vary to different degrees. In different regions, the effect of other countries on TSH reference interval is more significant (Xing D et al., 2021).

As TSH levels increase, FT_3/FT_4 ratios increase until age 40, but this differential increase does not occur in older age groups. This may reflect a decrease in thyroxine (T_4) to triiodothyronine (T_3) conversion with age, which may be part of the aging process (David Strich et al., 2016).

A large-scale study analyzing **27,940 serum samples** (after rigorous exclusion of unhealthy cases) tracked FT_3, FT_4, and TSH levels across ages and between sexes. **FT_3 levels were consistently higher in males than females throughout life** except in the very young and very old. **FT_3 declined with age**, more rapidly in females. **FT_4 also decreased modestly with age,** again more notably in women; among the very elderly, females had slightly higher FT_4 than males (Strich D et al., 2017).

5. Conclusions

The study of thyroid gland morphology and hormonal profiles in Pollog Valley patients reveals a high prevalence of hypothyroidism, marked by elevated TSH and reduced FT_4 and FT_3 levels. These hormonal imbalances often align with structural changes in the thyroid, such as enlargement or nodules, suggesting progressive dysfunction likely influenced by environmental and demographic factors.

Thyroid disorders in the region are endemic, likely due to iodine deficiency, poor dietary habits, and exposure to environmental goitrogens. Historically, endemic goiter was common in rural and mountainous parts of North Macedonia, including the Pollog Basin, where iodine levels in water and soil are low. Despite improvements, challenges persist, including pollution, inadequate screening, and limited public awareness. Women are disproportionately affected, consistent with global trends linked to hormonal and autoimmune factors. However, the pronounced gender gap in Pollog valley may also reflect cultural and environmental influences.

To address these issues, we recommend:

- **Public health campaigns** to raise awareness of thyroid disorders, especially among women
- **Routine thyroid screening** in primary care
- **Iodine supplementation and nutritional education**
- **Environmental assessments** to identify local risk factors
- **Improved access to endocrine and gynecological care**
- **Ongoing research and monitoring** to track disease trends and intervention outcomes

These actions are essential for reducing the burden of thyroid disease and improving long-term health outcomes in the region.

Reference

[1] Allen E, Fingeret A. Anatomy, Head and Neck, Thyroid. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470452/

[2] Coste AH, Lofgren DH, Shermetaro C. *Thyroid Gland Embryology.* StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK538338/

[3] Rousset B, Dupuy C, Miot F, et al. Chapter 2 Thyroid Hormone Synthesis And Secretion. [Updated 2015 Sep 2]. In: Feingold KR, Ahmed SF, Anawalt B, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/sites/books/NBK285550/

[4] Chaudhary P, Singh Z, Khullar M, Arora K. Levator glandulae thyroideae, a fibromusculoglandular band with absence of pyramidal lobe and its innervation: a case report. J Clin Diagn Res. 2013 Jul;7(7):1421-4. [PMC free article] [PubMed] [Reference list]

[5] Choudhry OJ, Ali K, Carty SE. Thyroid Gland Anatomy. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024. Available from: https://www.ncbi.nl m.nih.gov/books/NBK538337/

[6] Esen K, Ozgur A, Balci Y, Tok S, Kara E. Variations in the origins of the thyroid arteries on CT angiography. Jpn J Radiol. 2018 Feb;36(2):96-102. [PubMed] [Reference list]

[7] **Gray's Anatomy: The Anatomical Basis of Clinical Practice** Standring S, editor. *Gray's Anatomy.* 42nd ed. Elsevier; 2020.

[8] Edmund B. Flink*, Introductory Remarks: The Thyroid Gland Environmental Health Perspectives. Vol. 38, pp. 55-56, 1981. ISSN0091-6765

[9] InformedHealth.org [Internet]. Cologne, Germany: Institute for Quality and Efficiency in Health Care (IQWiG); 2006-. In brief: How does the thyroid gland work? [Updated 2024 May 28]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK279388/

[10] Thyroid disease: assessment and management. London: National Institute for Health and Care Excellence (NICE); 2019 Nov 20. (NICE Guideline, No. 145.) Available from: https://www.ncbi.nlm.nih.gov/books/NBK550859/

[11] *Chan AO, Iu YP, Shek CC. The reference interval of thyroid-stimulating hormone in Hong Kong Chinese. J Clin Pathol. 2011;64(5):433-436*

[12] Xing D, Liu D, Li R, Zhou Q, Xu J. Factors influencing the reference interval of thyroid-stimulating hormone in healthy adults: A systematic review and meta-analysis. *Clin Endocrinol (Oxf)*. 2021;95(3):378-389. doi:10.1111/cen.14454

[13] David Strich, Gilad Karavani, Shalom Edri, David Gillis, TSH enhancement of FT4 to FT3 conversion is age dependent, *European Journal of Endocrinology*, Volume 175, Issue 1, Jul 2016, Pages 49–54, https://doi.org/10.1530/EJE-16-0007

[14] Strich D, Karavani G, Edri S, Chay C, Gillis D. FT3 IS HIGHER IN MALES THAN IN FEMALES AND DECREASES OVER THE LIFESPAN. *Endocr Pract*. 2017;23(7):803-807. doi:10.4158/EP171776.OR