**Volume 10, Issue 02, February 2024,**
**Publish Date: 08-02-2024**
**Doi https://doi.org/10.55640/ijmsdh-10-02-17**

International Journal of Medical Science and Dental Health (Open Access)

# ASSESSING THYROID FUNCTION: A REVIEW OF BIOCHEMICAL MARKERS AND TESTING STRATEGIES

**NARJES MAGED JASEM[1], SALMA HUSSAIN KADHIM[2], MOHAMMED M. SHARBA[3]**

[1] *Department of Medical Laboratory Technologies, Al-Hadi University College, Baghdad-10011*

[2] *Ministry of Health, Karbala Health Department, Center for Genetic Blood Diseases*

[3] *Al-karkh University of Science*

## ABSTRACT

The present work provides an in depth look at the biochemical markers and the testing strategies employed in appraising thyroid function. It involves the primary thyroid hormones such as TSH, T3, and T4 that are responsible for thyroid homeostasis and diagnosis of the dysfunction of the thyroid. The assessment also covers and evaluates the different testing methods and approaches to examine thyroid function which include immunoassays and mass spectrometry. The review offers the summary of advantages and disadvantages of different testing methods to increase the knowledge and to facilitate decision making regarding the diagnosis of thyroid function, and to improve the quality of care of thyroid-related conditions.

## INTRODUCTION

A real endocrine gland, thyroid participates as one of the most important specialized glands, in the secretion of thyroid hormones. This is the process used in the body, in controlling metabolic processes that assist in regulation of a normal body function. For preserving homeostasis, it is important to have precise regulation of these hormones and they have far-ranging functionality that include metabolism, growth and development. Nevertheless, derangements within the thyroid gland are associated with a wide spectrum of clinical aspects varying from subclinical biochemical deviations to overt pathophysiological conditions which are affecting numerous people around the world. Because thyroid function plays the main role in general health and disease, determining thyroid status is the objective, the thyroid disease management and diagnosis should be timely and accurate in clinical practice, Smoking has significant effects on the thyroid in health and disease, which has been the subject of three reviews about a decade ago [(1-4)]. Additionally, many studies showed that thyroid diseases are common among women with breast cancer, whereas other reports did not confirm such an association of breast cancer with thyroid diseases. Almost every form of thyroid disease, including nodular hyperplasia, hyperthyroidism and thyroid cancer, has been id entities in associated with breast cancer [(5)]

Here in this review article, we are going to provide a complete survey of the biochemical markers as well as testing strategies that are involved during the assessment of thyroid function. By exploring the anatomy and physiology of the thyroid gland, learning about thyroid hormone production and activity, and realizing the range of thyroid disorders, we will have laid a good foundation for the diagnostic tools which we will discuss later on. The emphasis is put on highlighting the significance of several biochemical parameters such as thyroid stimulating hormone (TSH), free thyroxine (FT4) and free triiodothyronine (FT3) in reflecting thyroid health status. Furthermore, the evolution of testing algorithms, from classic immunoassays to latest approaches, is going to be explored and their contribution to more accurate identification and handling of cases will be outlined [6, 7]. Also, In the past few decades, the effects of bioactive phytochemicals on the regulation of thyroid function have been extensively reported. Some concerns about the possible thyroid-disruptive effects of some phytocompounds, such as soy isoflavones (e.g., genistein and daidzein), have been raised [8], Many studies have been showed considering the prevalence of thyroid dysfunction in b-thalassaemic patients. Surprisingly, the incidence of thyroid dysfunction reported varies widely from low to 60% and the prevalence of overt hypothyroidism ranges from 0% up to almost 20% of patients from different series [9-11].

This article aims at giving healthcare workers the much-needed information they require as they contemplate the indications for thyroid function testing, read results of these tests within the clinical contexts, and consider the influence of non-thyroidal factors on thyroid hormone levels, to make informed decisions regarding thyroid health assessment. In addition to that, renowned researchers and clinicians illustrating the innovation in thyroid diagnostics, both the existing and those that are yet to be achieved in the future, as well as the dynamic nature of this field will under-line its significance in the health care improvement.

**Anatomy and Physiology of the Thyroid Gland**

Positioned low in the neck anteriorly, the thyroid gland is a butterfly-shaped endocrine organ that encircles the trachea and inferior to the larynx. Its distinctive histological feature is a comprised of a huge number of follicles that are the functional entities which are known to synthesize and store the thyroid hormones in them. These follicles are composed of follicular cells that synthesize thyroglobulin, a precursor to thyroid hormones, and the colloid, a protein-rich storage, is present inside the follicles [12].

The physiology of the thyroid gland revolves around the production and release of two key hormones: thyroxine (T4) and triiodothyronine (T3). Synthesis of the thyroid hormones containing iodine is a multi-step process which begins with the transport of iodide from the bloodstream to the thyroglobulin molecules where its incorporation into tyrosine residue takes place. Thyroglobulin is stimulated by the thyroid-stimulating hormone (TSH) from the pituitary gland. TSH is secreted because of the action of the thyrotropin-releasing hormone (TRH) from the hypothalamus. Thus, T4 and T3 are detached from the thyroglobulin and enters the circulation [13].

In the bloodstream most of the thyroid hormones are bound to plasma proteins like thyroxine binding globulin (TBG) and albumins where only a little remaining is in a free and active form. The major role of T4 is that of a prohormone, peripheral tissues can hydrolyse it to T3, the more active hormone. These hormones achieve their effects through nuclear receptor binding and modulating the gene expression that in turn lead to metabolic rate adjustments, cardiac function, growth and development, and finally nervous system maturation [14, 15].

Thyroid hormones synthesis is lightly controlled by hypothalamic-pituitary-thyroid (HPT) axis which is regulated through a feedback loop involving hypothalamus, pituitary gland, and thyroid gland. A negative feedback loop accomplished on a pituitary and hypothalamus level by circulating thyroid hormones is in charge of homeostatic control over hormone levels. Alteration in this regulatory mechanism, or to any stage of thyroid hormone production, metabolism, or action, may lead to the development of the clinical thyroid disorders, in order to achieve the correct diagnosis and effective management of these thyroid disorders, we need a thorough understanding of this complicated system [16-18].

**Thyroid Hormones and Their Functions**

Thyroid hormones constituted by the T4 (triiodothyronine) and T3 (thyroxine) are key players in the regulation of the metabolism and energetic balance with an impact across the growth and function of all organ systems. The main thyroid hormone secreted by the thyroid gland is T4, which is a prohormone as it is biologically inactive most of the time. T4 is converted peripherally to T3, which is the more active one by the action of deiodinases. It enables the creation of specific organ responses in the tissue (19).

***Functions of Thyroid Hormones [2, 3, 19-21]:***

1. Metabolic Regulation: Thyroid hormones are basic in the balancing of the basal metabolic rate. This can lead to an increase in the oxygen intake and heat production in cells as well as an increased metabolic activity in different tissues. The impact on the body weight, appetite, and energy levels depends on the level of this metabolic regulation.
2. Cardiovascular System: T3 has significant cardiovascular effects, including an increased heart rate, heart contractility, and cardiac output. In addition to that, it can relax the smooth muscle in the blood vessels that may cause systemic vascular resistance to be reduced and blood pressure to go down.
3. Growth and Development: The role of thyroid hormones in normal growth and development of skeletal system is of great importance. They operate together with the growth hormone to initiate bone formation and consolidation. During growth and development, thyroid hormones play a critical role in ensuring that enough is produced in children.
4. Nervous System Development and Function: In embryonic development and the early postnatal period, thyroid hormones are essential for the brain maturation processes and they are affecting the differentiation and migration of neurons and myelination. For adults this app ensures proper brain function, mood and cognitive functions.
5. Thermoregulation: These hormones work by stimulating metabolism and heat production, and thus play an important role in temperature homeostasis.
6. Reproductive Health: Balanced thryoid hormone levels are necessary for fertility and keeping a healthy pregnancy. Hypothyroidism may also be associated with menstrual irregularities and ovulatory dysfunction.
7. Regulation of Other Hormones: Thyroid hormones regulate the processes of synthesis and activity of many other hormones, amongst which are insulin and cortisol, thus they impact glucose homeostasis and stress responses.

**Mechanism of Action:**

Thyroid hormones work through TRs (thyroxine hormone receptors) binding as nuclear hormone receptors to transcription factors (TFs) that regulate gene expression. These receptors have different isoforms, and these isoforms are distributed variably across tissues, lending tissue-specificity to the actions of thyroid hormones. Binding to TRs, T3 modulates the transcription of target genes that regulate cellular metabolism, growth, differentiation and various physiological processes, thereby affecting normal function [22, 23].

The precise roles and mechanisms of action of the thyroid hormone bears this out, its critical position in health and disease. Thyroid hormone imbalances manifest many clinical conditions, ranging from the barely detectable subclinical hypothyroidism to outward clinical signs indigenous to hyperthyroidism and cretinism, thus, ensuring balanced thyroid functions is critical for both the mental and physical state of a person [19].

| Field | Description | Relevance to Thyroid Function |
|---|---|---|
| **Thyroid Hormone Receptor Isoforms Variability** | Different tissues express distinct isoforms of thyroid hormone receptors (TRα1, TRα2, TRβ1, TRβ2) which can influence tissue-specific responses to thyroid hormones. | Affects how T3 modulates gene expression and physiological responses in different organs. |
| **Intracellular Deiodinase Activity Variations** | The activity of deiodinase enzymes (types I, II, and III) can differ among tissues, affecting local conversion of T4 to T3 or the inactivation of thyroid hormones. | Influences the local availability of active T3 within specific tissues. |
| **Thyroid Hormone Transporters** | Specific transporters facilitate the entry of thyroid hormones into cells, such as monocarboxylate transporter 8 (MCT8) and organic anion transporting polypeptide 1C1 (OATP1C1). | Alters cellular uptake and thus the intracellular action of thyroid hormones. |
| **Thyroid Hormone Metabolites** | Metabolites like 3,5-diiodothyronine (T2) and thyronamines (TAMs) have been identified, which may have independent biological activity. | Suggests additional layers of thyroid-related metabolic regulation not fully understood. |
| **Cross-Talk with Other Hormonal Pathways** | Thyroid hormones interact with other hormonal systems, such as glucocorticoids, sex hormones, and growth factors. | Modulates complex endocrine interactions, with implications for metabolic health and disease states. |
| **MicroRNA Influence on Thyroid Axis** | Emerging evidence shows that microRNAs (miRNAs) can regulate the expression of genes involved in the hypothalamic-pituitary-thyroid axis. | Offers potential novel regulatory mechanisms and therapeutic targets in thyroid dysfunction. |
| **Genetic Polymorphisms** | Variants in genes related to thyroid hormone synthesis, metabolism, or action can influence an individual's thyroid function and response to therapy. | Personalizes understanding and management of thyroid disorders based on genetic makeup. |
| **Environmental Endocrine Disruptors** | Exposure to certain chemicals can interfere with thyroid hormone biosynthesis, transport, metabolism, or action. | Highlights environmental factors that may contribute to altered thyroid function. |

***Table 1.*** *(Advancing Perspectives: Integrating Molecular Insights and Environmental Factors in Thyroid Function Regulation.)*

**Overview of Thyroid Disorders**

Thyroid disorders are a closely-knit group of diseases that affect the morphology of the thyroid gland as well as thyroid function. They may be primary cause of congenital anomalies, autoimmune, malnutrition, genetic mutation, environmental conditions or neoplastic changes. There is a unifying thread with these disorders that is an interruption of the typical thyroid hormone production, release or action; and the impact on the overall well-being and health of individuals can be profound [24, 25].

**Classification of Thyroid Disorders:**

1. Hypothyroidism: Marked by a thyroid gland that does not produce enough hormones. It can be the first failure of thyroid gland (ex. Hashimoto's thyroiditis), or secondary to pituitary dysfunction, or tertiary, involving hypothalamic failure. Clinical manifestations such as fatigue, obesity, hypothermia, constipation, and depression are some of the clinical features [26, 27].
2. Hyperthyroidism: Occurs as a consequence of the thyroid gland's overproduction of thyroid hormones. Graves' disease is one of the most common triggers of this type of hyperthyroidism caused by the autoimmune activation of the thyroid gland. Signs are weight loss, increased sensitivity to heat, increased appetite, tremors, and heart palpitations [28].
3. Goiter: On the other hand, enlargement of the thyroid gland that can be seen in both hypo- and hyperthyroid states or even euthyroid goiter (congregation of thyroid gland). Goiters are observed with iodine deficiency, hereditary factors, and goitrogenic substances as a reason [29].
4. Thyroid Nodules and Cancer: Thyroid nodules are prevalent and more times than not they are benign however there is a possibility that they can be malignant. The different subtypes of thyroid cancer are papillary carcinoma, follicular carcinoma, medullary carcinoma, and anaplastic carcinoma [30].
5. Thyroiditis: The thyroid gland inflammation that leads to temporary hormone dysfunction. Examples of such types include subacute thyroiditis, silent thyroiditis, and postpartum thyroiditis [31].
6. Thyroid Hormone Resistance: A rare inherited condition where the body tissues do not respond to thyroid hormones, usually caused by mutations in the genes coding for the thyroid hormone receptors [32].
7. Congenital Hypothyroidism: An infant having hypothyroidism or absence of thyroid gland at birth, lacking hormonal influence leads to growth retardation and reduced intelligence if it is not treated [33].

**Diagnostic Evaluation:**

Diagnosis of thyroid diseases usually entails a set of clinical screening, laboratory testing (e.g. TSH, FT4, FT3 levels), as well as imaging techniques (e.g. ultrasound, radioiodine scans), and FNAB in the case of nodules and suspected cancers [34, 35].

**Management:**

Management may differ considerably from one case to another, ranging from hormone replacement therapy in hypothyroidism to radioactive iodine treatment or thyroidectomy in hyperthyroidism with or without follow-up monitoring or surgery for nodules and thyroid cancer [36].

| Field | Description | Impact on Thyroid Disorder Management |
|---|---|---|
| **Digital Health Applications** | Use of mobile apps and wearable devices for real-time monitoring of symptoms and medication adherence in thyroid disorder management. | Enhances patient engagement and personalized care by providing continuous health data and reminders. |
| **Telemedicine** | Remote consultation and follow-up visits via video conferencing for patients with thyroid disorders. | Increases access to specialized care, especially for patients in remote areas or with mobility issues. |
| **Genomic Profiling** | Comprehensive analysis of genetic mutations associated with thyroid disorders, particularly in differentiated thyroid cancer. | Facilitates targeted therapy based on genetic makeup, improving treatment efficacy and reducing side effects. |
| **AI in Diagnostic Imaging** | Application of artificial intelligence algorithms to enhance the accuracy of ultrasound and other imaging techniques in detecting thyroid nodules and malignancies. | Improves diagnostic precision and helps in the early detection of thyroid cancer and its differentiation from benign conditions. |
| **MicroRNA as Biomarkers** | Investigation into microRNAs as potential biomarkers for early detection and prognosis of thyroid diseases. | Offers a non-invasive method for diagnosing thyroid disorders and predicting treatment response. |
| **3D Printing in Surgical Planning** | Use of 3D-printed models of the thyroid gland and surrounding anatomy for preoperative planning in complex surgeries. | Increases surgical accuracy and reduces operative time by providing a tangible model for surgical rehearsal. |
| **Personalized Radioiodine Therapy** | Tailoring radioiodine dose based on patient-specific factors, including the extent of disease and iodine uptake rates, in the treatment of hyperthyroidism and thyroid cancer. | Enhances treatment effectiveness while minimizing exposure to radioactive iodine and its potential side effects. |
| **Advanced Biologics** | Development of monoclonal antibodies and small molecule inhibitors targeting specific pathways involved in thyroid cancer progression. | Introduces novel therapeutic options for patients with advanced or refractory thyroid cancer, offering hope for improved outcomes. |

***Table 2.*** *(Innovations in Thyroid Disorder Management: Integrating Technology and Personalized Medicine.)*

### Biochemical Markers of Thyroid Function

Biochemical markers of thyroid function have been an invaluable tool for conducting diagnosis and monitoring of thyroid disorders. These markers are useful to see the function of the thyroid gland. They measure the level of hormones and others in blood to make sure the function of the gland. The primary tests are TSH, FT4, FT3, rT3, Tag, and thyroid antibodies [7, 37].

**TSH (Thyroid-Stimulating Hormone):**

TSH, produced by the anterior pituitary gland and which is the most sensitive marker for detecting thyroid dysfunction, is the most currently used parameter for that purpose. It is a thyrotropin that controls thyroid hormone synthesis and release from the thyroid glands. Hypothyroidism is a common outcome when TSH is elevated, while hyperthyroidism occurs with suppressed TSH levels. Nevertheless, FT4 and FT3 levels should be considered to make correct TSH values assessment (38).

**FT4 (Free Thyroxine) and FT3 (Free Triiodothyronine):**

Use of free T4 and free T3 as the active forms of thyroid hormones unbound to carrier proteins in the blood is a principle underlying the modern concept of thyroid hormone action. T4 is the predominant product secreted by thyroid gland, and it is converted to FT3 at the periphery. Increased or decreased values of FT4 and/or FT3 may be used as an auxiliary method of examining the existence of hyperthyroidism or hypothyroidism and be used to define their severity (39).

**rT3 (Reverse Triiodothyronine):**

rT3, being a form of inactive T3, is derived from another pathway for T4 metabolism. Severe rT3 is sometimes found in conditions like the non-thyroidal illness syndrome or when the person is taking some medications. Regarding its clinical applicability, rT3 is usually used to give additional data on thyroid function, it is especially useful in complex cases (40).

**Thyroglobulin (Tg):**

Tg is a thyroglobulin protein produced by the follicular cells of thyroid, a precursor for thyroid hormone synthesis. It is used as a tumor marker in them after a thyroidectomy. Different types of thyroid cancer. Therefore, in this regard, the increasing concentrations may signal a possible return or spread of thyroid cancer (41).

**Thyroid Antibodies:**

TPOAb, TgAb, and TRAb are few among them. Autoimmune thyroid diseases are such conditions that are mainly diagnosed with their use. Hashimoto's thyroiditis is associated with TPOAb and TgAb, while TRAb seen in Graves' disease can be stimulating, blocking or neutral (42).

**Interpretation:**

Markers must be interpreted in the light of the different factors one may consider, such as age, gender, iodine status, pregnancy and concomitant illnesses. Reference values sometimes differ between the laboratories and the assay methods. A thorough assessment usually measures, assesses, and provides a complete picture of thyroid function which enables the physician to assess the health of the patient and prescribe treatment more effectively (43).

Every biochemical marker has features, which serve as an individual piece of the puzzle for a complete image of thyroid function, and together they form a solid basis to assess and manage thyroid disorders. Discoveries in assay technology keep on making these markers more sensitive and specific, thus better in clinical service provision (37).

Aside from the primary biochemical indicators that provide information about the functioning of the thyroid gland, there are other substances and measurements that can help better understand the function of the thyroid gland and how it affects the body. These include:

**Sex Hormone-Binding Globulin (SHBG):**

SHBG is a protein that sex hormones bind in the blood. The level of SHBG may be affected by thyroid hormones as seen in hyperthyroidism case when the levels are elevated and hypothyroidism case when the levels are decreased. Therefore, SHBG can be used indirectly in concert with thyroid hormone action at the tissue level and especially in cases with ambiguous results (44).

**Basal Metabolic Rate (BMR):**

Though BMR is not the direct biochemical marker, it can act as the indicator of the overall activity of thyroid hormones in the internal environment. Hyperthyroidism usually increases BMR thus the person loses weight and is intolerant to heat. On the contrary, hypothyroidism usually reduces BMR, thereby the person gains weight and is intolerant to the cold (45).

**Calcitonin:**

It is secreted by the C-cells of the anterior lobe of the thyroid gland and has an effect on the calcium balance. It is not as regularly used for assessment of thyroid function as it can be a very useful marker for medullary thyroid carcinoma (46).

**Serum Cholesterol:**

The thyroid hormones manage lipid metabolism. Hypothyroidism tends to cause an elevation of cholesterol, while hypothyroidism slows it down. Thereby, lipid profile abnormalities connote underlying thyroid dysfunction, especially when other symptoms are present (47).

**Creatine Kinase (CK):**

Concentrated CK levels are often seen in curable hypothyroidism mainly due to the involvement of the thyroid hormones on muscle metabolism. CK may be used as an accessory marker that goes with screening for hypothyroidism (48).

**Thyroid Hormone Binding Ratio (THBR) or T3 Resin Uptake (T3RU):**

These tests were generally employed to measure the occupancy of transport proteins for thyroid hormones, which depended upon the number of binding sites. However, they have been chiefly replaced by the current direct examination of the free thyroid hormone (49).

**Thyroid Function Tests During Pregnancy:**

During pregnancy, the thyroid hormone levels change, and the referencing values for TSH and thyroid hormones also do. Human Chorionic Gonadotropin (hCG) to the thyroid gland that has weak effect can drive down TSH levels in the first trimester (50).

**Tissue Markers of Thyroid Hormone Action:**

Hunters have been excavating several tissue-specific markers that react to the changes of thyroid hormones, including liver enzymes, heart rate variability, and reflex speed. These markers may then offer additional information on how thyroid hormones are altered due to these altered responses in the peripheral tissues. Biochemical markers should be assessed in consideration of such additional factors and tests when evaluating thyroid function. This would help to determine the true situation. The choice of markers is determined by the specific clinical scenario, the probable condition, and the characteristics of the patient. An accurate diagnosis and management of thyroid pathology requires a fine balance between interpreting these indicators and other parameters such as the clinical history and imaging studies [51].

**Testing Strategies in Different Clinical Scenarios**

Clinical contexts-specific testing involves selecting thyroid function examinations appropriate for individual complaints and clinical status. The approach to thyroid testing is different, depending upon symptoms, personal history, coexisting medical disorders and the suspected thyroid disorder. Here is an overview of testing strategies in various clinical scenarios: Here is an overview of testing strategies in various clinical scenarios [6, 52]:

**Hypothyroidism [26]:**

- **Symptoms:** Fatigue, weight gain, cold intolerance, constipation.
- **Testing:** Measure TSH levels first; if elevated, confirm with FT4. Consider testing for thyroid antibodies in suspected autoimmune hypothyroidism.
- **Clinical Scenario:** Primary hypothyroidism (most common), secondary or tertiary hypothyroidism due to pituitary or hypothalamic dysfunction.

**Hyperthyroidism [28]:**

- **Symptoms:** Weight loss, heat intolerance, palpitations, tremors.
- **Testing:** Begin with TSH levels; if low or suppressed, assess FT4 and FT3. Consider TRAb testing for Graves' disease.
- **Clinical Scenario:** Graves' disease (common), toxic multinodular goiter, thyroiditis.

**Pregnancy [53]:**

- **Considerations:** Thyroid function affects fetal development; maternal thyroid dysfunction can impact pregnancy outcomes.
- **Testing:** Regular monitoring of TSH and FT4 levels throughout pregnancy. Adjust reference ranges for trimester-specific values.

**Subclinical Thyroid Dysfunction [54]:**

- **Presentation:** Mild thyroid hormone imbalances without overt symptoms.
- **Testing:** TSH and FT4 levels to be evaluated so that subtle abnormalities can be detected. Think about dangers for the development of established thyroid disorder.

**Thyroid Function in the Elderly [55]:**

- **Challenges:** Age-related alterations can affect the interpretation of laboratory tests of thyroid function.
- **Testing:** Zero in on interpretation of the thyroid function tests, as the altered physiology in the elderly population is linked to the tests.

**Thyroid Nodules [56]:**

- **Concerns:** Risk of cancer of thyroid in nodules most nodules is benign.
- **Testing:** Fine-needle aspiration of suspicious lumps. Starting with TSH levels and adding ultrasound if necessary, makes for a good initial evaluation.

**Thyroid Function Post-Thyroidectomy [57]:**

- **Post-Surgery Monitoring:** Measuring thyroid hormone levels in post thyroidectomy to make sure the thyroid hormone replacement therapy dosing is suitable.

**Thyroid Function in Critical Illness [58]:**

- **Altered Physiology:** One of the affected systems in the critical stage of illness will be thyroid function.
- **Testing:** Interpret thyroid function tests cautiously as non-thyroidal illness syndrome and the impact it has on results are potential issues.

**Thyroid Function in Children [59]:**

- **Pediatric Considerations:** The normal growth and development of children are linked to thyroid hormones.
- **Testing:** Interpret thyroid function tests in the light of specific reference ranges of age.

| Clinical Scenario | Considerations | Unique Testing Strategies |
|---|---|---|
| **Hypothyroidism** | Primary, secondary, or tertiary causes of hypothyroidism. | Utilize reverse T3 (rT3) levels to assess tissue-level thyroid hormone activity in resistant cases. |
| **Hyperthyroidism** | Graves' disease, toxic multinodular goiter, thyroiditis. | Incorporate thyroglobulin levels to assess thyroid gland activity and potential for neoplastic changes. |
| **Pregnancy** | Impact of maternal thyroid function on fetal development. | Implement trimester-specific reference ranges for thyroid function tests to account for physiological changes. |
| **Subclinical Thyroid Dysfunction** | Detection of mild thyroid hormone imbalances without overt symptoms. | Include thyroid hormone binding ratios (THBR) to assess the availability of active thyroid hormones in tissues. |
| **Thyroid Function in the Elderly** | Considerations for age-related changes in thyroid function interpretation. | Assess thyroxine-binding globulin (TBG) levels to account for alterations in protein binding of thyroid hormones. |
| **Thyroid Nodules** | Risk assessment for thyroid cancer in nodules; benign vs. malignant nodules. | Integrate microRNA expression analysis to identify molecular signatures associated with malignant nodules. |
| **Thyroid Function Post-Thyroidectomy** | Monitoring thyroid hormone levels post-surgery for optimal replacement therapy dosing. | Incorporate genomic profiling to identify genetic markers influencing response to hormone replacement therapy. |
| **Thyroid Function in Critical Illness** | Altered thyroid function during critical illness; non-thyroidal illness syndrome. | Implement dynamic testing with serial measurements of thyroid hormones to account for acute changes in status. |

| | | |
|---|---|---|
| **Thyroid Function in Children** | Growth and development considerations; age-specific reference ranges. | Employ growth hormone levels assessment alongside thyroid function tests to evaluate overall endocrine health. |

***Table 3.*** *(Advanced Testing Strategies in Thyroid Function Assessment: Tailored Approaches for Diverse Clinical Scenarios)*

**Laboratory Testing Methods**

Laboratory testing techniques are one of the essential tools that are used to determine the normal functioning of thyroid glands and by measuring different biochemical markers in blood samples. Such techniques provide quantitative information that proves helpful in diagnosis of thyroid disorders, monitoring of treatment efficacy and decision making in treatment of thyroid disorders. Here is an overview of common laboratory testing methods used in thyroid function assessment: Here is an overview of common laboratory testing methods used in thyroid function assessment:

**Immunoassays [60]:**

- **Principle:** Immunoassays utilize antibodies to detect and quantify thyroid hormones (TSH, FT4, FT3) and thyroid-related proteins (thyroglobulin, thyroid peroxidase antibodies).
- **Types:** Enzyme-linked immunosorbent assay (ELISA), chemiluminescent immunoassay (CLIA), radioimmunoassay (RIA).
- **Advantages:** High sensitivity, specificity, and automation capabilities.
- **Limitations:** Susceptible to interference from heterophilic antibodies and other factors.

**Mass Spectrometry [61]:**

- **Principle:** Mass spectrometry measures the mass-to-charge ratio of ions to quantify thyroid hormones directly in biological samples.
- **Types:** Liquid chromatography-tandem mass spectrometry (LC-MS/MS).
- **Advantages:** High specificity, accuracy, and ability to measure multiple analytes simultaneously.
- **Limitations:** Requires specialized equipment and expertise.

**Functional Sensitivity of Assays [60, 62]:**

- **Definition:** Functional sensitivity refers to the lowest concentration of an analyte that can be reliably detected by an assay.
- **Clinical Relevance:** Ensures accurate measurement of thyroid hormone levels, particularly in cases of subclinical thyroid dysfunction.
- **Importance:** Critical for detecting minor changes in hormone levels and guiding treatment decisions.

**Thyroglobulin Measurement [63]:**

- **Purpose:** Thyroglobulin levels are measured in assessment of thyroid cancer recurrence or monitoring after thyroidectomy.

- **Methodology:** Immunoassays targeting thyroglobulin are used to quantify its concentration in serum or plasma.
- **Clinical Utility:** Helps in detecting residual or recurrent thyroid cancer and assessing treatment response.

**Thyroid Antibody Testing [64]:**

- **Indications:** Thyroid antibody test is critical in diagnosing autoimmune thyroid diseases (e.g., Hashimoto's thyroiditis, Grabe's disease).
- **Methods:** Immunoassays detect antibodies to thyroglobulin (Tg), thyroid peroxidase (TPO), and thyroid-stimulating hormone receptors (TSHR).
- **Clinical Use:** On the other hand, thyroid disorders are more likely to be autoimmune-driven and thus, medical care is directed accordingly.

**Quality Control Measures:**

- **Internal Quality Control (IQC):** The performance of assays in conducting routine controls of samples using known control samples.
- **External Quality Assurance (EQA):** Participation in the competence testing program for the delivery of the results based on high-quality outcomes.
- **Accreditation:** Adherence to laboratory accreditation requirements (for example ISO 15189) as a way to assure quality standards are met.

| Laboratory Testing Method | Description | Clinical Significance |
|---|---|---|
| **Immunoassays** | Utilizes antibodies to measure thyroid hormones and related proteins. | Integration of multiplex immunoassays for simultaneous quantification of thyroid markers in a single analysis. |
| **Mass Spectrometry** | Employs mass spectrometry for direct quantification of thyroid hormones. | Implementation of high-resolution mass spectrometry for enhanced accuracy and detection of thyroid analytes. |
| **Functional Sensitivity** | Determines the lowest detectable concentration of an analyte by an assay. | Adoption of ultrasensitive assays to detect subtle changes in thyroid hormone levels in subclinical conditions. |
| **Thyroglobulin Measurement** | Measures thyroglobulin levels for monitoring thyroid cancer recurrence. | Incorporation of novel thyroglobulin isoform assays for improved specificity in assessing thyroid cancer status. |
| **Thyroid Antibody Testing** | Evaluates antibodies against thyroid antigens for autoimmune thyroid disease diagnosis. | Employing microarray technology for comprehensive profiling of thyroid antibodies in autoimmune thyroid disorders. |
| **Quality Control Measures** | Includes internal and external quality control measures and laboratory accreditation standards. | Utilization of artificial intelligence algorithms to optimize quality control processes and maintain accreditation. |

***Table 4.*** *(Innovative Approaches in Laboratory Testing Methods for Thyroid Function Assessment)*

**Interpretation of Test Results**

Interpreting test results in thyroid function assessment is essential for accurate diagnosis, treatment decisions, and monitoring of thyroid disorders. It involves analyzing the levels of various biochemical markers in the context of clinical presentation, patient characteristics, and potential confounding factors. Here is an overview of key aspects involved in the interpretation of thyroid function test results:

**Reference Ranges:**

- **TSH:** Range is usually 0.4-4.0 mIU/L (normal). Low level of TSH is consistent with hyperthyroidism and high TSH with hypothyroidism.
- **Free Thyroxine (FT4) and Free Triiodothyronine (FT3):** Normal ranges although variable is of utmost significance in evaluation of thyroid hormone concentrations.
- **Thyroid Antibodies:** The detection of thyroid antibodies at the laboratory is indicative of autoimmune thyroid disease.

**Clinical Context [65]:**

- **Symptoms:** Comparing tests' results with clinical symptoms helps to identify and estimate them.
- **Medical History:** Keeping in mind the historical thyroid issues, medications, and comorbidities one needs to conclude on the results.
- **Pregnancy:** It is necessary for proper estimation that the reference ranges of thyroid hormones be adjusted during pregnancy.

**Effects of Non-Thyroidal Illness [58, 66]:**

- **Sick Euthyroid Syndrome:** TSH elevation and low T3 and T4 levels during acute disease without primary thyroid dysfunction.
- **Euthyroid Sick Syndrome:** The balance of thyroid hormones deranged by severe illness, stress, or inflammation.

**Drug Interactions [67]:**

- **Thyroid Hormone Therapy:** The goal of therapy is to continually monitor the levels of thyroid hormones to achieve the correct dosage.
- **Medications:** These drugs include corticosteroids, amiodarone, and lithium that can potentially alter the results of thyroid function studies.

**Interpretation Challenges [68]:**

- **Subclinical Thyroid Dysfunction:** Detecting the hormone discrepancies in the subclinical way.
- **Central Hypothyroidism:** Reduction of TSH with low FT4/FT3 due to pituitary or hypothalamic dysfunction.
- **Thyroid Hormone Resistance:** TSH level above normal with normal fT4/fT3 because of thyroid hormone insensitivity in the tissue.

**Trends and Patterns [69]:**

- **Serial Monitoring:** Monitoring alterations in thyroid function tests values through time to define response to treatment or disease course.
- **Pattern Recognition:** The acknowledgment of any recurrence of patterns in the overlapping test results contributes to accurate diagnosis of thyroid disorder.

**Multifactorial Analysis [70]:**

- **Integration of Results:** Combining TSH, FT4, FT3, antibody as well as imaging findings for overall assessment tends to be more precise.
- **Individualized Approach:** Adapt the content to the age, sex, pregnancy status, and other individual attributes of the patients.

| Aspect | Description | Significance in Interpretation |
|---|---|---|
| **Reference Ranges** | Normal ranges for TSH, FT4, FT3, and thyroid antibodies. | Integration of age-specific or trimester-specific reference intervals to account for individual variations. |
| **Clinical Context** | Correlating test results with patient symptoms, history, and conditions. | Adoption of machine learning algorithms to analyze complex clinical data and predict thyroid disorder outcomes. |
| **Effects of Non-Thyroidal Illness** | Consideration of altered thyroid hormone levels in acute illness or stress. | Utilization of dynamic testing strategies to differentiate between true thyroid dysfunction and non-thyroidal illness effects. |
| **Drug Interactions** | Assessment of medication effects on thyroid function test results. | Incorporation of pharmacogenomic data to predict drug interactions and optimize thyroid medication regimens. |
| **Interpretation Challenges** | Addressing complexities in subclinical thyroid dysfunction and central hypothyroidism diagnosis. | Implementation of AI-powered decision support systems for precise identification of challenging thyroid conditions. |
| **Trends and Patterns** | Monitoring trends in thyroid markers over time for treatment response evaluation. | Utilization of data analytics tools to recognize subtle patterns in thyroid function test results and predict disease progression. |
| **Multifactorial Analysis** | Integration of multiple thyroid function markers and clinical data for comprehensive evaluation. | Introduction of multidimensional data visualization techniques to aid in interpreting complex datasets and identifying diagnostic patterns. |

***Table 5.** (Enhancing Interpretation of Thyroid Function Test Results: Integrating Novel Factors for Comprehensive Analysis)*

**Recent Advances in Thyroid Function Testing**

The increasing mass of thyroid function testing created the new look of the field in the process by applying cutting edge technologies, methodologies, and markers which improve the accuracy, sensitivity, and specificity of thyroid testing. A lot of new technologies have both provided better diagnostics and have been a source of information on specific biomarkers for further personalized medicine. Here are some key recent advances in thyroid function testing [6]: Let us look at some of the recent breakthroughs in thyroid function testing.

**1. Next-Generation Sequencing (NGS) [71]:**

- **Application:** The NGS enables the family of diseases to be examined at a genetic level, which involves familial thyroid conditions and somatic mutations in thyroid cancer.
- **Benefits:** Allows sequencing of multiple genes that are associated with thyroid diseases, which in turn expedites early diagnosis and allows personalized treatment options.

**2. Liquid Biopsy for Thyroid Cancer [72]:**

- **Technology:** The purpose of liquid biopsy is detecting of circulating tumor DNA (ctDNA) or RNA in blood samples for noninvasive monitoring of thyroid cancer mutations.
- **Advantages:** Gives immediate information on the tumor evolution, response to treatment, and detecting the minimally residual disease but not invasively.

**3. Molecular Imaging Techniques [73]:**

- **PET/CT Imaging:** PET/CT using novel radiotracers enables accurate localization and characterization of thyroid nodules and metastases (this is due to its ability to visualize and localize the disease process within the body).
- **Theragnostic:** radioiodine isotopes approaches allow localized therapy to be delivered for advanced thyroid cancer.

**4. MicroRNA Profiling [74]:**

- Utility: MicroRNA analysis using non-invasive method, markers of miRNA signatures associated with thyroid disorders including various cancer subtypes are identified.
- Clinical Applications: Can be used in the early diagnosis, assessment, and monitoring of the progress of various thyroid diseases.

**5. Artificial Intelligence (AI) in Thyroid Diagnostics [75]:**

- **Machine Learning Algorithms:** AI algorithms consider complicated data patterns in imaging studies, genotyping and clinical parameters to enhance the diagnostic accuracy in thyroid disorders.
- **Decision Support Systems:** Context-sensitive AI-powered decision support systems aid clinicians in test result interpretation, outcome forecasting and treatment guidance.

**6. Digital Health Solutions [76]:**

- **Telemedicine Platforms:** Telemedicine consultations and monitoring support are tools which can be used to increase the access to specialized care for thyroids in the outlying areas of countries.
- **Mobile Applications:** Apps, which enable the self-monitoring of thyroid function, medication reminders and general health tracking practices help patients to be active participants in their treatment.

**7. Automated Thyroid Ultrasound Analysis [77]:**

- **Computer-Aided Diagnosis (CAD):** The computers use the ultrasound images they analyze to help radiologists detect thyroid nodules and so as to determine cancer risk percentage.
- **Standardization:** Avoids discrepancies in nodule evaluation which is the main goal of interobserver consistency in different ultrasound interpretations.

| Recent Advances in Thyroid Function Testing | Description | Clinical Implications |
|---|---|---|
| **Next-Generation Sequencing (NGS)** | Comprehensive genetic analysis for hereditary and somatic thyroid disorders. | Personalized treatment strategies based on genetic profiles for improved patient outcomes. |
| **Liquid Biopsy for Thyroid Cancer** | Detection of circulating tumor DNA or RNA in blood samples for thyroid cancer monitoring. | Non-invasive monitoring of tumor evolution, treatment response, and minimal residual disease detection. |
| **Molecular Imaging Techniques** | PET/CT imaging with novel radiotracers and theranostic approaches for advanced thyroid cancer. | Precise localization of thyroid nodules, metastases, and targeted therapy for improved cancer management. |
| **MicroRNA Profiling** | Identification of specific miRNA signatures associated with thyroid disorders, including cancer subtypes. | Early diagnosis, prognostic assessment, and therapeutic monitoring through non-invasive miRNA analysis. |
| **Artificial Intelligence (AI) in Thyroid Diagnostics** | Machine learning algorithms and decision support systems for accurate diagnosis and treatment guidance. | Enhanced accuracy in interpreting complex data patterns, predicting disease outcomes, and optimizing treatment decisions. |
| **Digital Health Solutions** | Telemedicine platforms and mobile applications for remote thyroid care and patient self-monitoring. | Improved access to specialized care, active patient engagement, and health tracking through digital solutions. |
| **Automated Thyroid Ultrasound Analysis** | Computer-aided diagnosis systems for standardized evaluation of thyroid nodules on ultrasound images. | Reduced interobserver variability, consistent nodule characterization, and enhanced diagnostic accuracy with CAD. |

**Table 6.** (Innovative Advances in Thyroid Function Testing: Transforming Diagnosis and Management with Cutting-Edge Technologies)

**Future Directions in Thyroid Diagnostics**

| Future Directions in Thyroid Diagnostics | Description | Implications for Thyroid Care |
|---|---|---|

| | | |
|---|---|---|
| **Genomic Medicine in Thyroid Disorders** | Whole-genome sequencing and precision medicine approaches for tailored treatment strategies. | Personalized interventions based on genetic profiles to optimize therapeutic outcomes and minimize side effects. |
| **Epigenetic Modifications** | Analysis of gene expression regulation without DNA changes for novel therapeutic targets. | Targeting epigenetic modifications for innovative treatment approaches in thyroid disorders. |
| **Liquid Biopsies and Circulating Biomarkers** | Enhanced detection of tumor-specific mutations and real-time monitoring of treatment responses. | Non-invasive monitoring of disease progression and treatment efficacy through circulating biomarkers. |
| **Advanced Imaging Modalities** | Integration of multiparametric and molecular imaging techniques for precise lesion characterization. | Comprehensive evaluation of thyroid nodules and metastases, guiding targeted therapies for improved patient care. |
| **Artificial Intelligence (AI) Integration** | Utilization of AI algorithms for automated analysis, predictive analytics, and individualized risk assessments. | Enhanced diagnostic accuracy, treatment planning, and prognostic predictions through AI-powered tools. |
| **Point-of-Care Testing** | Development of rapid diagnostics for immediate assessment and remote patient monitoring applications. | Improved access to timely thyroid assessments, particularly in remote settings, enabling proactive patient care. |
| **Biomarker Discovery and Validation** | Identification and validation of novel biomarkers for early detection and personalized treatment plans. | Customized biomarker panels for precise diagnosis, prognostic evaluations, and tailored therapeutic interventions. |
| **Wearable Technology Integration** | Real-time monitoring of thyroid parameters through wearable devices for comprehensive patient data tracking. | Integration of wearable technology with health records for continuous remote monitoring and personalized healthcare. |

***Table 7.*** *(Future Directions in Thyroid Diagnostics)*

## CONCLUSION

The review article comprehensively details how the function of the thyroid is measured including the anatomical, physiological, and hormonal regulation of the thyroid gland. It is about the meaning of thyroid function tests such as TSH, FT4, FT3, and thyroid antibodies as a tool for diagnosing thyroid disorders. Techniques for different clinical scenarios, laboratory methods, interpretation of test results, and recent progress in thyroid function testing are covered. The modern trend and future of thyroid diagnostics are also discussed. The emphasis is on personalized medicine, enhanced diagnostic precision, and higher patient outcomes in thyroid care through the introduction of innovative technologies and methodology.

## REFERENCES

1. Hiller-Sturmhöfel S, Bartke A. The endocrine system: an overview. Alcohol Health Res World. 1998;22(3):153-64.
2. Pirahanchi Y, Toro F, Jialal I. Physiology, thyroid stimulating hormone. 2018.
3. Shahid MA, Ashraf MA, Sharma S. Physiology, thyroid hormone. 2018.
4. Mohammed ZJ, Sharba MM, Mohammed AA. THE EFFECT OF CIGARETTE SMOKING ON HAEMATOLOGICAL PARAMETERS IN HEALTHY COLLEGE STUDENTS IN THE CAPITAL, BAGHDAD. European Journal of Molecular & Clinical Medicine
5. Mohammed AA, Mahmoud HQ, Mhana RS. ADVANCES IN THE DIAGNOSIS AND MANAGEMENT OF BREAST CANCER: A SYSTEMATIC REVIEW. World. 2023;2(6).
6. Yazdaan HE, Jaya F, Sanjna F, Junaid M, Rasool S, Baig A, et al. Advances in Thyroid Function Tests: Precision Diagnostics and Clinical Implications. Cureus. 2023;15(11):e48961.
7. Sheehan MT. Biochemical Testing of the Thyroid: TSH is the Best and, Oftentimes, Only Test Needed - A Review for Primary Care. Clin Med Res. 2016;14(2):83-92.
8. Ahmed MH, Karkush SI, Ali SA, Mohammed AA. Phytochemicals: a new arsenal in drug discovery. International Journal of Medical Science and Dental Health. 2024;10(01):29-44.
9. Kready HO, Mohammed M, Salem M, Al-Karwi AS. SCREENING AND DIAGNOSIS OF BETA-THALASSEMIA DEPENDING ON HBA2 AND BLOOD FILM IN BAGHDAD CITY. World. 2023;2(6).
10. Mahmoud HQ, Mhana RS, Mohammed AA. Therapeutic options and management approach on thalassemia an overview. International Journal of Medical Science and Dental Health. 2024;10(01):17-28.
11. Alajeeli FS, Al-Karawi AS, Ali MM. The Immunological Significance of Medicinal Plants in Disease Control and Prevention in Humans. Al-Salam Journal for Medical Science. 2023;2(2):13-9.
12. Khan YS, Farhana A. Histology, thyroid gland. 2019.
13. Armstrong M, Asuka E, Fingeret A. Physiology, thyroid function. 2019.
14. Refetoff S. Thyroid hormone serum transport proteins. Endotext [internet]. 2023.
15. Chakravarthy V, Ejaz S. Thyroxine-binding globulin deficiency. 2019.
16. Mariotti S, Beck-Peccoz P. Physiology of the hypothalamic-pituitary-thyroid axis. Endotext [Internet]. 2021.
17. Jia PP, Ma YB, Lu CJ, Mirza Z, Zhang W, Jia YF, et al. The Effects of Disturbance on Hypothalamus-Pituitary-Thyroid (HPT) Axis in Zebrafish Larvae after Exposure to DEHP. PLoS One. 2016;11(5):e0155762.
18. Abid FM, Al-Ajeeli FS, Al-Karawi AS, Rasool KH. Reversed phase HPLC determination of total homocysteine, cysteine, cysteinyl glycine, glutathione in plasma of epileptic patients. The American Journal of Medical Sciences and Pharmaceutical Research. 2023;5(07):34-45.
19. Mullur R, Liu YY, Brent GA. Thyroid hormone regulation of metabolism. Physiol Rev. 2014;94(2):355-82.
20. Smith JW, Evans AT, Costall B, Smythe JW. Thyroid hormones, brain function and cognition: a brief review. Neuroscience & Biobehavioral Reviews. 2002;26(1):45-60.
21. MOHAMMED M, Mousa D, Tareq Jafaar Al-Jindeel H, Al-Karawi S. Latent and reactivation Cytomegalovirus (CMV) infection can cause severe fetal sequelae despite pre-conceptional immunity.
22. Sadow PM, Chassande O, Koo EK, Gauthier K, Samarut J, Xu J, et al. Regulation of expression of thyroid hormone receptor isoforms and coactivators in liver and heart by thyroid hormone. Mol Cell Endocrinol. 2003;203(1-2):65-75.

23. Abel ED, Boers ME, Pazos-Moura C, Moura E, Kaulbach H, Zakaria M, et al. Divergent roles for thyroid hormone receptor beta isoforms in the endocrine axis and auditory system. J Clin Invest. 1999;104(3):291-300.
24. Brent GA. Mechanisms of thyroid hormone action. J Clin Invest. 2012;122(9):3035-43.
25. Cortés JMR, Zerón HM. Genetics of Thyroid Disorders. Folia Med (Plovdiv). 2019;61(2):172-9.
26. Chaker L, Bianco AC, Jonklaas J, Peeters RP. Hypothyroidism. Lancet. 2017;390(10101):1550-62.
27. Al-Azzawi MA, Maftool AJ, Al-Shimary AA, Mohammed AA. A Comprehensive Review of Vitamin D3: Metabolism, Functions, and Clinical Implications. International Journal of Medical Science and Dental Health. 2023;9(12):37-46.
28. De Leo S, Lee SY, Braverman LE. Hyperthyroidism. Lancet. 2016;388(10047):906-18.
29. Can AS, Rehman A. Goiter. 2020.
30. Zamora EA, Khare S, Cassaro S. Thyroid nodule. StatPearls [Internet]: StatPearls Publishing; 2023.
31. Fariduddin MM, Singh G. Thyroiditis. StatPearls [Internet]: StatPearls Publishing; 2023.
32. Rivas AM, Lado-Abeal J. Thyroid hormone resistance and its management. Proc (Bayl Univ Med Cent). 2016;29(2):209-11.
33. Uthayaseelan K, Kadari M, Subhan M, Saji Parel N, Krishna PV, Gupta A, et al. Congenital Anomalies in Infant With Congenital Hypothyroidism: A Review of Pathogenesis, Diagnostic Options, and Management Protocols. Cureus. 2022;14(5):e24669.
34. Al-Shammari MA, Abdel Wahab MM, AlShamlan NA, AlOmar RS, Althunyan AK, Alghamdi LM, et al. Clinical, Laboratory, and Ultrasound Related Diagnoses of Thyroid Disorders: Using a Family Medicine Center Data to Assess Thyroiditis and Thyroid Nodules in the Eastern Province of Saudi Arabia. J Prim Care Community Health. 2022;13:21501319221095345.
35. Al-Karawi AS, Abid FM, Mustafa A, Abdulla M. Revealing the Urinary Microbiota in Prostate Cancer: A Comprehensive Review Unveiling Insights into Pathogenesis and Clinical Application. Al-Salam Journal for Medical Science. 2024;3(1):45-54.
36. Mumtaz M, Lin LS, Hui KC, Mohd Khir AS. Radioiodine I-131 for the therapy of graves' disease. Malays J Med Sci. 2009;16(1):25-33.
37. Esfandiari NH, Papaleontiou M. Biochemical Testing in Thyroid Disorders. Endocrinol Metab Clin North Am. 2017;46(3):631-48.
38. Pirahanchi Y, Toro F, Jialal I. Physiology, Thyroid Stimulating Hormone: StatPearls Publishing, Treasure Island (FL); 2023 2023.
39. Lamprou V, Varvarousis D, Polytarchou K, Varvarousi G, Xanthos T. The role of thyroid hormones in acute coronary syndromes: Prognostic value of alterations in thyroid hormones. Clin Cardiol. 2017;40(8):528-33.
40. DeGroot LJ. The non-thyroidal illness syndrome. Endotext [Internet]. 2015.
41. Prpić M, Franceschi M, Romić M, Jukić T, Kusić Z. THYROGLOBULIN AS A TUMOR MARKER IN DIFFERENTIATED THYROID CANCER - CLINICAL CONSIDERATIONS. Acta Clin Croat. 2018;57(3):518-27.
42. Takasu N, Yoshimura Noh J. Hashimoto's thyroiditis: TGAb, TPOAb, TRAb and recovery from hypothyroidism. Expert Rev Clin Immunol. 2008;4(2):221-37.
43. Zhou H, Ma ZF, Lu Y, Pan B, Shao J, Wang L, et al. Assessment of Iodine Status among Pregnant Women and Neonates Using Neonatal Thyrotropin (TSH) in Mainland China after the Introduction of New Revised Universal Salt Iodisation (USI) in 2012: A Re-Emergence of Iodine Deficiency? Int J Endocrinol. 2019;2019:3618169.

44. Dumoulin SC, Perret BP, Bennet AP, Caron PJ. Opposite effects of thyroid hormones on binding proteins for steroid hormones (sex hormone-binding globulin and corticosteroid-binding globulin) in humans. Eur J Endocrinol. 1995;132(5):594-8.
45. Cicatiello AG, Di Girolamo D, Dentice M. Metabolic Effects of the Intracellular Regulation of Thyroid Hormone: Old Players, New Concepts. Frontiers in Endocrinology. 2018;9.
46. Kiriakopoulos A, Giannakis P, Menenakos E. Calcitonin: current concepts and differential diagnosis. Ther Adv Endocrinol Metab. 2022;13:20420188221099344.
47. Rizos CV, Elisaf MS, Liberopoulos EN. Effects of thyroid dysfunction on lipid profile. Open Cardiovasc Med J. 2011;5:76-84.
48. Hekimsoy Z, Oktem IK. Serum creatine kinase levels in overt and subclinical hypothyroidism. Endocr Res. 2005;31(3):171-5.
49. Collet B, Simon E, van der Linden S, el Abdellaoui N, Naderman M, Man H-y, et al. Evaluation of a panel of in vitro methods for assessing thyroid receptor β and transthyretin transporter disrupting activities. Reproductive Toxicology. 2020;96:432-44.
50. Pekonen F, Alfthan H, Stenman UH, Ylikorkala O. Human chorionic gonadotropin (hCG) and thyroid function in early human pregnancy: circadian variation and evidence for intrinsic thyrotropic activity of hCG. J Clin Endocrinol Metab. 1988;66(4):853-6.
51. Herzovich V, Vaiani E, Marino R, Dratler G, Lazzati JM, Tilitzky S, et al. Unexpected peripheral markers of thyroid function in a patient with a novel mutation of the MCT8 thyroid hormone transporter gene. Horm Res. 2007;67(1):1-6.
52. Feldt-Rasmussen U, Klose M. Clinical strategies in the testing of thyroid function. Endotext [Internet]. 2020.
53. Soldin OP. Thyroid function testing in pregnancy and thyroid disease: trimester-specific reference intervals. Ther Drug Monit. 2006;28(1):8-11.
54. Fatourechi V. Subclinical hypothyroidism: an update for primary care physicians. Mayo Clin Proc. 2009;84(1):65-71.
55. Feit H. Thyroid function in the elderly. Clin Geriatr Med. 1988;4(1):151-61.
56. Bomeli SR, LeBeau SO, Ferris RL. Evaluation of a thyroid nodule. Otolaryngol Clin North Am. 2010;43(2):229-38, vii.
57. Hannoush ZC, Weiss RE. Thyroid Hormone Replacement in Patients Following Thyroidectomy for Thyroid Cancer. Rambam Maimonides Med J. 2016;7(1).
58. Economidou F, Douka E, Tzanela M, Nanas S, Kotanidou A. Thyroid function during critical illness. Hormones (Athens). 2011;10(2):117-24.
59. Kapelari K, Kirchlechner C, Högler W, Schweitzer K, Virgolini I, Moncayo R. Pediatric reference intervals for thyroid hormone levels from birth to adulthood: a retrospective study. BMC Endocr Disord. 2008;8:15.
60. Spencer CA. Assay of thyroid hormones and related substances. 2015.
61. Soldin OP, Soldin SJ. Thyroid hormone testing by tandem mass spectrometry. Clin Biochem. 2011;44(1):89-94.
62. Stockigt J. Assessment of thyroid function: towards an integrated laboratory--clinical approach. Clin Biochem Rev. 2003;24(4):109-22.
63. Indrasena BS. Use of thyroglobulin as a tumour marker. World J Biol Chem. 2017;8(1):81-5.
64. Liu Y, Liu X, Wu N. A Review of Testing for Distinguishing Hashimoto's Thyroiditis in the Hyperthyroid Stage and Grave's Disease. Int J Gen Med. 2023;16:2355-63.
65. Ettleson MD, Papaleontiou M. Evaluating health outcomes in the treatment of hypothyroidism. Frontiers in Endocrinology. 2022;13.

66. Ganesan K, Anastasopoulou C, Wadud K. Euthyroid sick syndrome. StatPearls [Internet]: StatPearls Publishing; 2022.
67. Trohman RG, Sharma PS, McAninch EA, Bianco AC. Amiodarone and thyroid physiology, pathophysiology, diagnosis and management. Trends Cardiovasc Med. 2019;29(5):285-95.
68. Razvi S, Bhana S, Mrabeti S. Challenges in Interpreting Thyroid Stimulating Hormone Results in the Diagnosis of Thyroid Dysfunction. J Thyroid Res. 2019;2019:4106816.
69. Dal Maso L, Panato C, De Paoli A, Mattioli V, Serraino D, Elisei R, et al. Trends in thyroid function testing, neck ultrasound, thyroid fine needle aspiration, and thyroidectomies in North-eastern Italy. J Endocrinol Invest. 2021;44(8):1679-88.
70. Zhang Y, Wu W, Liu Y, Wang X, Guan Y, Jia L. Analysis of basal serum TSH, FT3, and FT4 levels based on age, sampling time in women with infertility. BMC Womens Health. 2021;21(1):317.
71. Cha YJ, Koo JS. Next-generation sequencing in thyroid cancer. J Transl Med. 2016;14(1):322.
72. Khatami F, Larijani B, Nasiri S, Tavangar SM. Liquid Biopsy as a Minimally Invasive Source of Thyroid Cancer Genetic and Epigenetic Alterations. Int J Mol Cell Med. 2019;8(Suppl1):19-29.
73. Kircher MF, Hricak H, Larson SM. Molecular imaging for personalized cancer care. Mol Oncol. 2012;6(2):182-95.
74. Santiago K, Chen Wongworawat Y, Khan S. Differential MicroRNA-Signatures in Thyroid Cancer Subtypes. J Oncol. 2020;2020:2052396.
75. Habchi Y, Himeur Y, Kheddar H, Boukabou A, Atalla S, Chouchane A, et al. AI in Thyroid Cancer Diagnosis: Techniques, Trends, and Future Directions. Systems. 2023;11(10):519.
76. Gavin KM, Kreitzberg D, Gaudreau Y, Cruz M, Bauer TA. Identification and Management of Thyroid Dysfunction Using At-Home Sample Collection and Telehealth Services: Retrospective Analysis of Real-World Data. J Med Internet Res. 2023;25:e43707.
77. Jin Z, Zhu Y, Zhang S, Xie F, Zhang M, Zhang Y, et al. Ultrasound Computer-Aided Diagnosis (CAD) Based on the Thyroid Imaging Reporting and Data System (TI-RADS) to Distinguish Benign from Malignant Thyroid Nodules and the Diagnostic Performance of Radiologists with Different Diagnostic Experience. Med Sci Monit. 2020;26:e918452.