Journal of Cardiovascular Disease Research

ISSN: 0975-3583,0976-2833 VOL14, ISSUE 10 , 2023

Advancements in Understanding Thyroid Function and Disorders: Implications for Clinical Management

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ABSTRACT:

Thyroid disorders have witnessed a surge in prevalence over the last two decades, ranking as the most prevalent endocrine disorders after metabolic syndrome. These encompass hyperthyroidism, hypothyroidism, thyroiditis, and the presence of potentially benign or malignant thyroid nodules. Thyroid hormone, crucial for normal development, growth, and metabolic regulation, undergoes activation from thyroxine to triiodothyronine, influencing a myriad of genes. The cellular signaling pathway is intricately regulated, involving thyroid hormone transporters, receptor isoforms, and interactions with corepressors and coactivators. Non-genomic actions of thyroid hormone have also come to light. The hypothalamic-pituitary-thyroid axis primarily governs thyroid function and hormone levels, complemented by other feedback loops. Thyroid function tests (TFTs) encompass thyrotropin (TSH), free thyroxine (FT4), and free triiodothyronine (FT3) levels. Evolving evidence suggests that optimal thyroid hormone levels may vary within the normal range, influencing clinical outcomes. There is no universally established optimum, but mid-range levels may best signify euthyroidism. In hypothyroidism, elevated TSH levels and low FT4 and FT3 levels are indicative, while hyperthyroidism manifests with low TSH levels and elevated FT4 and/or FT3 levels. Recent research proposes a paradigm shift towards evaluating and treating hypothyroidism based on thyroxinemia rather than relying solely on TSH levels. Furthermore, metabolic syndrome, characterized by interconnected metabolic abnormalities, exhibits a heightened risk in individuals with thyroid dysfunction, particularly hypothyroidism. Insulin resistance, attributed to thyroid dysfunction, potentially underlies metabolic syndrome. Understanding these intricacies paves the way for more effective clinical management.

Keywords: thyroid disorders, thyroid hormone, hypothalamic-pituitary-thyroid axis, thyroid function tests, euthyroidism, hypothyroidism.

Over the past two decades, thyroid disorders have become increasingly prevalent, ranking as the most common endocrine disorders after metabolic syndrome. These disorders encompass hyperthyroidism, hypothyroidism, and inflammation (thyroiditis) of the thyroid gland, along with the presence of potentially benign or malignant thyroid nodules. Thyroid hormone plays a crucial role in normal development, growth, neural differentiation, and metabolic regulation in mammals. Its activation from thyroxine to triiodothyronine leads to the regulation of a wide array of genes. At the cellular level, the signaling pathway is intricate and tightly controlled due to the presence of cell and tissue-specific thyroid hormone transporters, various thyroid hormone receptor isoforms, and interactions with corepressors and coactivators. Additionally, non-genomic actions of thyroid hormone have been acknowledged. The regulation of thyroid function and hormone levels is primarily influenced by the classical pituitary-thyroid feedback loop and the hypothalamic-thyroid feedback loop, constituting the hypothalamic-pituitary-thyroid axis. Other feedback loops and mechanisms also contribute to thyroid hormone control and homeostasis.

ISSN: 0975-3583,0976-2833 VOL14, ISSUE 10 , 2023

Thyroid function tests (TFTs) encompass the levels of thyrotropin (TSH), free thyroxine (FT4), and free triiodothyronine (FT3). In cases of hypothyroidism, indicative TFT results include elevated TSH levels (unless the hypothyroidism is secondary), low levels of FT4, and, in more severe cases, low levels of FT3. Conversely, hyperthyroidism is indicated by low TSH levels (unless it is secondary) and elevated levels of FT4 and/or FT3. Current evidence suggests that previous notions regarding euthyroidism, with a primary focus on TSH levels, may no longer be tenable. Within the normal range, variations in thyroid hormone levels are associated with variations in clinical parameters and outcomes. Consequently, there are no universally established optimum levels of thyroid hormones for individuals. Levels around the midpoint of the normal population range may best signify euthyroidism. In populations primarily composed of untreated individuals, levels of thyroid hormones, particularly free thyroxine (FT4), tend to correlate more frequently with clinical parameters than levels of thyrotropin (TSH). Thus, levels of thyroid hormones may be considered the most reliable biomarkers of euthyroidism and dysthyroidism. Consequently, 'subclinical hypothyroidism' (normal FT4/raised TSH levels), instead of accurately signifying peripheral tissue hypothyroidism, more accurately denotes decreased thyroid reserve and prognosis.

Recent evidence suggests that treating hypothyroxinemia, regardless of TSH levels, and monitoring therapy using FT4 and/or triiodothyronine levels, depending on the replacement regimen, may lead to more effective treatment of hypothyroidism compared to relying solely on thyrotropin levels for patient selection and subsequent treatment monitoring. Targeting levels equivalent to mid-range levels of thyroid hormones, especially FT4, adjusted for individual comorbidity concerns, may serve as rational general replacement targets. These implications from the new evidence may pave the way for innovative trials of thyroid replacement therapy.[1,2]

TABLE 1 | Summary of revisions proposed for concepts and parameters related to euthyroidism.

Concept/parameter	Traditional view	Revised view
Euthyroidism	State of exposure of all tissues and organs to levels of thyroid hormones optimal for the individual	State of exposure of all tissues and organs to levels of thyroid hormones allowing normal range function, and associated with relatively modest risk profile – levels likely to be in the middle of the population range
Subclinical hypothyroidism (Raised TSH, normal FT4 levels)	State of borderline low thyroid function/mild hypothyroidism, increased risk of progression to overt hypothyroidism.	Spectrum of peripheral thyroid status from euthyroid to borderline low thyroid function. Indicates low functioning thyroid gland and risk of disease progression.
Borderline low thyroid function/mild hypothyroidism	Subclinical hypothyroidism	FT4 levels around the lower limits of the normal range
Healthy individuals' usual levels of thyroid hormones	Individual euthyroidism/set point largely directly determined genetically	Not necessarily optimal, stable balance point determined by genetically influenced stable feedback loops.
Targets for monitoring thyroid replacement	Normal range TSH levels, adjusted individually	Requires further study. Likely to be levels of FT4 +/- FT3 depending on individual factors and form of replacement therapy
TSH	Most sensitive guide to peripheral tissues thyroid status and preferred parameter for guiding replacement treatment	Inferior guide to peripheral tissues thyroid status. Differentiates primary from secondary hypothyroidism. Prognostic indicator.
FT4	Guide to thyroid status after initial classification according to TSH levels.	The most sensitive and robust measure of the thyroid status of peripheral tissues in untreated individuals. Role in monitoring replacement treatment in primary hypothyroidism requires study.
FT3	Circulating form of the active intracellular hormone. Homeostatically regulated, sensitive to non-thyroidal illness.	Sensitive measure of the peripheral tissue thyroid status. Not as robust as FT4. Requires further study.

Recent data has allowed for the formulation of a perspective on euthyroidism and its associated biomarkers. This view not only aligns with the new data but also demonstrates greater coherence with fundamental physiological principles compared to earlier paradigms. Table 1 offers an overview of these shifts concerning various concepts and parameters related to thyroid function. These modifications, in turn, hold significance for the effective clinical treatment of hypothyroidism.[2]

Relationship between thyroid function and metabolic syndrome

Metabolic syndrome encompasses a cluster of interconnected metabolic abnormalities characterized by central obesity, elevated triglycerides (TGs), low levels of high-density lipoprotein cholesterol (HDL-C), high blood pressure, and hyperglycemia. Recent studies

ISSN: 0975-3583,0976-2833 VOL14, ISSUE 10 , 2023

have identified an elevated risk of metabolic syndrome in individuals with hypothyroidism and subclinical hypothyroidism. Earlier research indicated that individuals with thyroid stimulating hormone (TSH) levels at the upper limit of the normal range (2.5-4.5 mU/L) exhibited higher rates of obesity, elevated TG levels, and an increased likelihood of developing metabolic syndrome. Therefore, it is advisable to assess healthy young women with TSH levels > 2.5 mU/L for potential presence of metabolic syndrome, even if their TSH levels fall within the normal range. A comprehensive meta-analysis of 22 studies established a significant connection between obesity and an elevated risk of hypothyroidism. Moreover, obese individuals faced an escalated risk of both overt hypothyroidism and subclinical hypothyroidism.

In a study investigating the correlation between thyroid function status and the prevalence of metabolic syndrome, a total of 62,408 subjects aged ≥18 years were included. The cumulative evidence indicates that thyroid dysfunction influences lipid and glucose metabolism, blood pressure, and body weight. These factors are linked to various metabolic parameters and may contribute to the onset or exacerbation of components of metabolic syndrome. Overall, women with hypothyroidism exhibit a higher susceptibility to metabolic syndrome compared to men. Metabolic syndrome displays sex-specific variations, and the characteristics of the condition differ between men and women. Particularly in postmenopausal women, both overt and subclinical hypothyroidism primarily elevate the risk of metabolic syndrome by increasing the likelihood of abdominal obesity and hypertriglyceridemia. A gender discrepancy is observed in the relationship between thyroid dysfunction and lipid levels. Following menopause, women experience heightened levels of follicle-stimulating hormone (FSH). Serum FSH levels demonstrate a positive correlation with total cholesterol (TC) levels, and the incidence of hypercholesterolemia in perimenopausal women is notably higher compared to premenopausal women.[3]

Insulin resistance stemming from thyroid dysfunction could serve as a significant underlying cause of metabolic syndrome. Hyperthyroidism may induce insulin resistance because it entails the breakdown of excessive thyroid hormones, potentially influencing components of metabolic syndrome like body weight and lipid levels. Conversely, hypothyroidism is linked with decreased insulin sensitivity. The explanation for this apparent contradiction may be found in the distinct impacts of thyroid hormones on the liver and peripheral tissues. Thyroid hormones serve as both insulin-like agents (in muscle tissue) and opposing agents (in the liver) in various organs. An excess of thyroid hormone (or potentially a deficiency) disrupts this equilibrium, leading primarily to hepatic insulin resistance, resulting in elevated glucose production, glycogen breakdown, and glucose intolerance.[3]

Hyperthyroidism

Hyperthyroidism, even in its subclinical form, poses long-term risks like osteoporosis and atrial fibrillation, especially in older individuals, and generally should not be left untreated. The choice of treatment approach for hyperthyroidism should prioritize the patient's preferences, the underlying pathology, and the availability of expert surgical care.

Initial investigations and management should commence with a thorough medical history, focusing on identifying or ruling out thyroid eye disease and any other systemic effects of excess thyroid hormone. Antithyroid medications like propylthiouracil and methimazole/carbimazole can be initiated initially. Thyrotrophin receptor antibodies play a crucial role in distinguishing between autoimmune thyrotoxicosis and transient hyperthyroidism, which can occur in post-viral situations or in the early inflammatory stages of autoimmune hypothyroidism.[4]

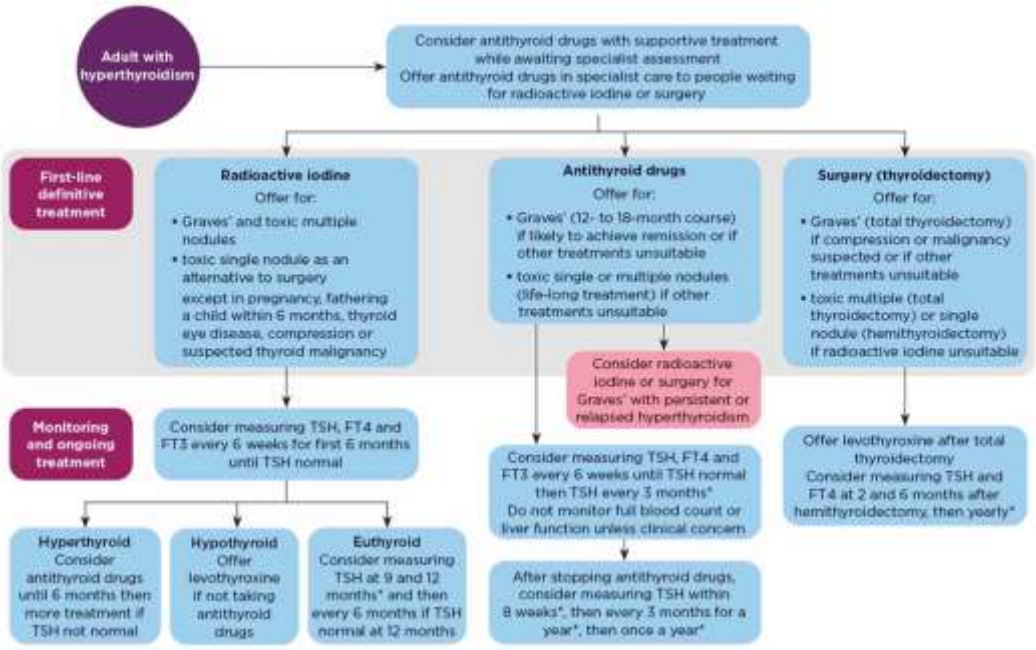
In a departure from previous approaches, NICE (National Institute for Health and Care Excellence) recommends discussing the potential use of radioactive iodine (RAI) with

ISSN: 0975-3583,0976-2833 VOL14, ISSUE 10 , 2023

patients during the initial consultation. RAI is indicated for Graves' disease and cases of toxic multiple nodules or toxic single nodules, offering an alternative to surgery. However, exceptions exist for cases involving pregnancy, planning to father a child within 6 months, thyroid eye disease, compression, or suspected thyroid malignancy. Otherwise, the recommendation still stands for a course of antithyroid drugs for 12–18 months, while keeping the option open for RAI or surgery in cases of hyperthyroidism that proves difficult to control. Surgery should also be considered in the presence of any evidence of compression on local structures or suspected/confirmed malignancy.[5]

When investigating the underlying cause of thyrotoxicosis, it is standard practice to include tests for Thyroid Stimulating Hormone (TSH), Free Thyroxine (FT4), Free Triiodothyronine (FT3), and thyroid antibodies, including thyroid receptor antibodies (TRAb). If subacute thyroiditis is suspected, as indicated by a tender and painful thyroid, it is advisable to also check C-reactive protein levels. Thyroid uptake scans can offer valuable insights if the diagnosis remains unclear based on clinical features and blood test results. However, thyroid sonography plays a limited role in assessing patients with thyrotoxicosis and is not a necessary component of routine evaluation.[4]

NICE (National Institute for Health and Care Excellence) has provided a concise summary sheet for quick guidance on management, which can be referred to (see figure 1). This summary encompasses the monitoring protocol post-treatment with radioactive iodine (RAI) or surgical definitive treatment.[5]



According to the most recent guidelines from the European Thyroid Association, it is recommended to conduct regular testing for mothers experiencing reduced fertility. The goal is to achieve an optimal thyrotropin level of less than 2.5mIU/l. When it comes to the utilization of levothyroxine in patients undergoing assisted reproductive techniques, the emphasis is primarily on enhancing success rates for patients with a thyrotropin level exceeding 4.0mIU/l.[5]

Recent Advances in Thyroid Cancer Research

Thyroid carcinoma, or thyroid cancer (TC), is a malignant tumor arising from the glandular tissue of the thyroid gland. It represents the most common form of malignancy within the endocrine (hormonal) system, albeit being quite rare, accounting for approximately

ISSN: 0975-3583,0976-2833 VOL14, ISSUE 10 , 2023

1% of all malignant tumors. However, there has been a notable increase in its incidence in recent years. TC encompasses various categories: (1) differentiated TC (DTC), which includes papillary (PTC), follicular (FTC), and Huerthle cell tumors, (2) medullary TC (MTC), and (3) anaplastic TC. The long-term survival rate for patients with differentiated TC stands at around 90%, whereas those with poorly differentiated TC types exhibit a long-term survival rate of less than 10%, largely due to their resistance to standard treatment options. The established therapeutic approaches for advanced and radioiodine-refractory TC involve immunotherapy, chemotherapy, and kinase inhibitors. Unfortunately, the survival rate remains low, underscoring the need for innovative research avenues employing novel technologies.

Recent published studies have delved into different types of TC cells (TCC). One study focused on medullary thyroid cancer cells (MTC). The investigation was motivated by the observation that inhibiting mortalin led to the suppression of human MTC cells both in laboratory cultures and in mouse xenografts, inducing apoptosis and downregulating RET. Additionally, the agent MKT-077, which inhibits mortalin, produced similar effects, though it is known to be toxic in animals. Various MKT-077 analogs (JG-98 and JG-194) hindered the propagation of TT and MZ-CRC-1 cells in both 2D and 3D cultures. These analogs also effectively reduced the viability of TT and MZ-CRC-1 progenies resistant to vandetanib and cabozantinib. Furthermore, JG-231 demonstrated the suppression of TT and MZ-CRC-1 xenografts in mice. These findings suggest the potential of mortalin as a target for designing molecular therapy for MTC.

Another study examined FOXE1-induced transcriptional changes in thyroid cells lacking endogenous FOXE1 expression. The authors demonstrated FOXE1-dependent regulation of macrophage chemotaxis by thyroid cells, both in vitro and in vivo. This study established a connection between FOXE1 and the recruitment of macrophages in the TCC microenvironment. The results indicate a role for this gene in the interaction between TCC and immune cells in the context of tumor development and progression.[6]

The study centered on elucidating how inhibition of V600EBRAF triggers autophagy through the activation of the LKB1-AMPKULK1 pathway. Furthermore, it was observed that autophagy exhibits cell-protective characteristics, and blocking it enhances PLX4720-induced cell death in thyroid cancer cells carrying the V600EBRAF mutation, both in laboratory settings and in animal models. These findings suggest potential treatment strategies involving targeting the AMPK pathway and/or autophagy, which could augment the effectiveness of V600EBRAF inhibitors and potentially overcome acquired resistance to these compounds in thyroid cancer.

In a clinical investigation, the molecular mechanism and clinical significance of ZNF677 expression were examined in over 1200 cases of Middle Eastern papillary thyroid cancer (PTC) and 15 metastatic tissues. The study revealed frequent downregulation of ZNF677 in primary PTC (13.6%, 168/1235), and the complete loss of ZNF677 expression was significantly associated with aggressive clinicopathological features like extrathyroidal extension and distant metastases. Furthermore, the absence of ZNF677 was an independent predictor of distant metastasis in PTC. The data also indicated that ZNF677 operates as a tumor suppressor, exerting its effects by inhibiting AKT phosphorylation. The authors highlighted the pivotal role of ZNF677 in the development of cancer and the formation of metastases in Middle Eastern PTC patients. This review provides clinicians with an extensive update on clinical signs, diagnostic assessments, and current approaches to managing secondary cancers affecting the thyroid gland. Targeted therapies, such as multikinase inhibitors (MKIs) and immune checkpoint inhibitors, have shown effectiveness in certain patients. Another study delved into the use of MKIs like lenvatinib, sorafenib, and cabozantinib in patients with thyroid cancer refractory to radioactive iodine (RAI). The

ISSN: 0975-3583,0976-2833 VOL14, ISSUE 10 , 2023

authors provided an overview of the current understanding of MKIs in iodine-refractory differentiated thyroid cancer (DTC), with a specific focus on the occurrence, mechanisms, and management of treatment-induced hypertension (TE-HTN). The adverse event of TE-HTN was observed across all compounds, but it was found to be well manageable, as demonstrated in recent clinical trials. This was underscored by the widespread use of lenvatinib as the preferred first-line treatment, despite its higher incidence of TE-HTN.[6]

New biomarkers: prospect for diagnosis and monitoring of thyroid disease

Thanks to the rapid progress in high-throughput molecular biology techniques, there is now an opportunity to discover novel biomarkers for thyroid neoplasms. These markers can complement traditional imaging methods in postoperative follow-up and assist in the preoperative cytology examination of uncertain or follicular lesions. While established circulating biomarkers like Tg or TgAb are commonly used in postoperative monitoring, they fall short in distinguishing between benign and malignant neoplasms or between low- and high-risk malignant lesions at the preoperative stage. A number of promising targets are emerging as potential prognostic circulating biomarkers for thyroid cancers. The evidence of miRNA, lncRNA, and circRNA dysregulation in various thyroid neoplasms, and their potential as sensitive diagnostic and prognostic indicators, is particularly intriguing. However, the existing data in the literature stems from small-scale clinical studies focused on specific patient groups. Therefore, further validation is imperative to establish their potential for clinical use. Extensive studies on a larger scale are necessary to verify and confirm the utility of novel biomarkers, such as miRNAs, lncRNAs, and circRNAs, in the diagnosis, prognosis, and monitoring of thyroid neoplasms.[1]

Machine learning system for thyroid dysfunction

A significant challenge in treating thyroid dysfunction lies in avoiding oversight or misinterpretation of these conditions. Both excess and deficiency of thyroid hormones are frequently misunderstood and unfortunately overlooked or misdiagnosed. Hyperthyroidism diagnoses may be delayed or overlooked because certain symptoms can be mistakenly attributed to other factors like stress, leading to potential misdiagnoses as cardiac issues or gastrointestinal malignancies. On the other hand, hypothyroidism can manifest with vague constitutional and neuropsychiatric complaints. Patients with hypothyroidism often receive misdiagnoses, such as dementia, cardiac problems, liver issues, or high cholesterol, which can hinder them from receiving the appropriate treatment. The American Association of Clinical Endocrinologists has estimated that approximately 4.78% of the U.S. population has undiagnosed thyroid dysfunction. It is believed that around 15 million adults may have unrecognized thyroid disease. In recent years, various computer-aided diagnosis techniques have been proposed to aid doctors in more accurate diagnosis of thyroid dysfunction. These techniques employ different types of input to make such diagnoses. Machine learning, recognized for its effectiveness in predictive analytics, is a popular approach due to its success in diagnosis, prediction, and treatment selection. Several studies have also sought to evaluate the effectiveness of detecting misdiagnosed diseases, including thyroid dysfunction. They have found strong, multiple correlations between a set of routine clinical parameters and FT4 levels in patients with both overt hyperthyroidism and overt hypothyroidism. These studies utilized pattern recognition methods like neural networks to predict the likelihood of thyroid dysfunction based on routine clinical tests. However, despite these efforts, there remain several concerns regarding the application of machine learning in disease diagnosis. These include issues related to data cleaning, completing missing values, defining dysfunction criteria, integrating datasets from multiple hospitals, and validating and interpreting machine learning models.[7]

ISSN: 0975-3583,0976-2833 VOL14, ISSUE 10 , 2023

Conclusion:

Approximately two hundred million individuals worldwide grapple with some form of thyroid disorder, with women being particularly susceptible. Human thyroid function displays variations among populations, individuals, and over the course of a person's life. In order to offer patients the most tailored and effective care, it is imperative to conduct research into the factors contributing to thyroid variability across these various levels. The utilization of big data and digital health applications can potentially unlock previously untapped sources of variation, leading to a more comprehensive understanding of the connections between an individual's life history, environment, and changes in thyroid function and associated symptoms. By enhancing our comprehension of the natural variations in thyroid function, it becomes possible to deliver more personalized care, prioritizing attention to the underlying causes of thyroid dysfunction over rigid adherence to standardized reference values.[8]

Abbreviations: AE-Adverse effect, AKT- Proteinkinase B/AKT serine/threonine kinase 1, AMPK-5′ adenosine monophosphate-activated protein kinase, BRAF-v-Raf murine sarcoma viral oncogene homolog B1, D-Day, ERK-Extracellular-signal regulated kinases, FOXE1-Forkhead box E1, FTC-Follicular thyroid cancer, HTN-Hypertension, ISS-International Space Station, LKB1-Liver kinase B1, MCS-Multicellular spheroids, MKIs-Multikinase inhibitors, MTC- Medullary thyroid cancer, mTOR-Mammalian target of rapamycin, PTC-Papillary thyroid cancer, r-µg-Real microgravity, SI-Special Issue, TC-Thyroid cancer, TCC-Thyroid cancer cells, TE-HTN- Treatment-emergent hypertension, 2D- Two-dimensional, 3D-Three-dimensional, ULK1-Unc-51 like autophagy activating kinase, ZNF677-Zinc finger protein 677

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