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Diabetology

UNDERACTIVE THYROID AND L-THYROXINE

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KEYWORDS :

Thyroid gland and the thyroid hormones

The thyroid gland produces hormones that serve essential and critical functions in the body related to metabolism and energy utilization, maturation of the central nervous system, thermostatic control of body temperature, overall growth, bone development, and various other metabolic processes in the body [1]. Triiodothyronine (T3), tetraiodothyronine (Thyroxine, T4), and calcitonin are the hormones secreted by the thyroid gland. However, T3 and T4 are considered as the proper thyroid hormones, secreted by the follicular epithelial cells involving trace element, Iodine as the essential building block for both of them[2]. The functioning of the thyroid gland is governed by the anterior pituitary gland, and hypothalamus thus constituting a self-regulatory loop, termed a hypothalamic-pituitary-thyroid axis[3]. Thyrotropin-releasing hormone (TRH) released by the hypothalamus into the hypothalamic-hypophyseal portal system of the anterior pituitary gland, stimulates thyrotropin cells of the anterior pituitary to secrete thyroid-stimulating hormone (TSH). TSH released into the blood circulation binds to the Gs-protein coupled TSH-receptors on the basolateral aspect of the thyroid follicular cell leading to the activation of adenylyl cyclase and intracellular levels of cAMP. The elevated levels of cAMP, in turn, activates protein kinase A and causes phosphorylation of various proteins to modify their functions. The thyroid hormone binds to the intranuclear receptors in virtually every organ system in the body, including the heart, central nervous system, autonomic nervous system, bones, and gastrointestinal tract, wherein, it activates the genes for increasing metabolic rate and thermogenesis leading to increased consumption of oxygen and energy.

Hypothyroidism (Underactive thyroid)

Hypothyroidism is a common condition of insufficiency of thyroid hormones namely T3 and T4[4]. The normal value of levels of serum thyroid hormones are as follows[5]:

- T4: 4.8 to 13.2 mg/dL
- Free T4: 0.9 to 2 ng/dL
- T3: 80 to 220 ng/dL
- TSH: 0.35 to 5.50 mIU/mL

It is a common condition and is more prevalent in women, the elderly, and certain ethnic groups[6]. Hypothyroidism is more common in patients with autoimmune diseases, such as type 1 diabetes, autoimmune gastric atrophy, and coeliac disease, and can occur as part of multiple autoimmune endocrinopathies. Individuals with Downs' syndrome or Turners' syndrome have an increased risk of hypothyroidism. The symptoms of deficiency are diverse that can be readily diagnosed and effectively managed with medications. However, if untreated may lead to hypertension, dyslipidemia, infertility, cognitive impairment, and neuromuscular dysfunction and may become potentially fatal in severe cases. The simplest way of classification of hypothyroidism to understand the dysfunctional gland in the hypothalamic-pituitary-thyroid axis is as follows:

- **Primary hypothyroidism**- Decreased secretion of thyroid hormones by the thyroid gland causes a compensatory increase of TSH by the feedback mechanism. Therefore, the serum TSH level is used to screen for primary hypothyroidism in most patients. Primary hypothyroidism is further classified as[7]
  - *Clinical* / Overt- It shows raised levels of serum TSH and reduced levels of T4.
  - *Subclinical*- It shows raised levels of serum TSH, however, T4 is normal and there are no symptoms of thyroid dysfunction. It is also termed compensated hypothyroidism or mild hypothyroidism. Autoimmunity is the commonest cause of subclinical hypothyroidism [8]. This condition is more prevalent in about 10% of women of perimenopausal age.

Various causes of primary hypothyroidism are tabulated in Table 1. Iodine is an essential component of the thyroid hormone. Iodine deficiency can result in goiter, thyroid nodules, and hypothyroidism. The most severe consequence of iodine deficiency is cretinism that results in restricted mental and physical development in utero and during childhood. Iodine fortification programs are one of the safest and cheapest public health interventions for the prevention of cognitive and physical impairment [9]. Despite such efforts, suboptimal iodine status still affects large parts of underdeveloped and developing counties, as well as specific subpopulations in several developed countries—most notably, pregnant women.

In iodine-sufficient areas, the most common cause of hypothyroidism is chronic autoimmune thyroiditis called Hashimoto's disease. High concentrations of anti-thyroid antibodies mainly thyroid peroxidase antibodies and anti-thyroglobulin antibodies are present in most patients with autoimmune thyroiditis[10]. Primary hypothyroidism is diagnosed based on clinical symptoms like mental slowing, depression, dementia, weight gain, constipation, dry skin, hair loss, cold intolerance, vocal changes, irregular menstruation, infertility, muscle stiffness and muscle ache, bradycardia, and hypercholesterolemia. However, it is always confirmed with serum tests.

- **Secondary hypothyroidism**- It is a pituitary gland disorder causing decreased TSH release, thus decreased levels of T3 and T4.

- **Tertiary hypothyroidism**- It is caused by a hypothalamic disorder that results in decreased TRH levels, leading to decreased TSH, and corresponding T3 and T4 levels. Usually, secondary and tertiary hypothyroidism are collectively termed as central hypothyroidism [11]. Central hypothyroidism is rare and affects both sexes equally. It is more often associated with the pituitary than hypothalamic disorders but frequently involves both [12]. The diagnosis of central hypothyroidism involves testing of levels of free T4 rather than TSH. TRH stimulation test analyzing the delayed TSH response to TRH also supports the diagnosis. Various etiological factors responsible for central hypothyroidism are tabulated in Table 1.

Table 1. Causes of different types of hypothyroidism[4,13]

Causative factor	Examples of causative factors
Primary hypothyroidism	
Iodine	Either severe iodine deficiency or excess iodine in the body
Autoimmune diseases	Chronic autoimmune thyroiditis called Hashimoto's thyroiditis and atrophic thyroiditis
Drugs	Amiodarone, lithium, tyrosine kinase inhibitors, IFN-α, IL-2 thalidomide, monoclonal antibodies like ipilimumab and nivolumab, antiepileptics like valproic acid, and antitubercular drugs used as a second-line of therapy for MDR-TB
Iatrogenic treatment	Radioiodine (I131) treatment for Graves' disease or toxic nodular disease, hemithyroidectomy, radiotherapy, or surgery in the treatment of head and neck cancer
Transient thyroiditis	Destructive thyroiditis, post-partum, silent thyroiditis, a viral infection like De Quervain's syndrome
Thyroid gland infiltration	Mycoplasma infections, thyroid malignancy, lymphoma, sarcoidosis, Riedel's thyroiditis

Genetic	Autoimmunity related genes like HLA class I region, PTPN22, SH2B3, and VAV3), general and thyroid-specific genes like FOXE1, ATXN2, and PDE8B
Central hypothyroidism	
Pituitary tumors	Secreting non-secreting tumors as in pituitary adenoma, Metastatic pituitary lesions
Extra-pituitary factors	Primary intracranial craniopharyngioma, meningioma, germinoma
Pituitary dysfunction	Sheehan's syndrome
Hypothalamic dysfunction	Post-pituitary surgery, Post-external radiation therapy
Drugs	Dopamine, somatostatins, glucocorticosteroids, bexarotene, retinoid X receptor-selective ligands, salicylates, and drugs interfering with the neuro-dopaminergic system and dopamine
Hormonal resistance	Resistance to TSH or TRH
Increased TSH	Leptin stimulation
Genetic	Pituitary-specific transcription factor defects such as PIT-1, PROP-1 LHX3 or HESX1, Isolated TRH deficiency, Mutations in the TSH-(beta) subunit gene, inactivating mutation in TRH receptor gene
Peripheral hypothyroidism	
Tissue-specific	Decreased sensitivity to thyroid hormone due to mutations in MCT8. SECISBP2, THRA, THRB
Consumptive	High levels of D3 expression by neoplastic tissues

Hypothyroidism is the most common pregnancy-related thyroid disorder, affecting 3–5% of pregnant women. Subclinical hypothyroidism is more common than the clinical / overt hypothyroidism, and shows serum TSH concentration greater than the pregnancy-specific reference range for each laboratory value, or serum TSH concentrations greater than 2·5 mIU/L in the 1st trimester and greater than 3 mIU/L in the 2nd and 3rd trimesters[14].

Hypothyroidism is common in the elderly population too, affecting 5–20% of women and 3–8% of men. It is highly prevalent in Caucasians and populations with a high iodine intake[15]. Treatment of subclinical hypothyroidism shows some improvement in lipid profile too. However, there is no evidence that it will decrease cardiovascular or all-cause mortality in elderly patients. Close monitoring of thyroid function could be the best option for patients at high risk of progression from subclinical to overt disease[16].

Clinical features of hypothyroidism

The presenting symptoms and signs of hypothyroidism (Figure 1) are diverse, reflecting the widespread tissue actions of thyroid hormones. However, the symptoms are not specific to hypothyroidism. Commonly observed symptoms of hypothyroidism in adults are tiredness, lethargy, cold intolerance, weight gain, constipation, change in voice, and dry skin, but the clinical presentation can include a wide variety of symptoms that differ with age, sex, and time between onset and diagnosis.

Figure 1. Various clinical implications of hypothyroidism on other systems of the body

In elderly patients, the symptoms for the diagnosis of hypothyroidism are non-specific, and are fewer and less classic signs and symptoms than observed younger individuals. Hypothyroidism has clinical implications related to nearly all major organs (Figure 1), but the cardiovascular system is the most studied. Hypothyroidism results in increased vascular resistance, decreased cardiac output, decreased left ventricular function, and changes in several markers of cardiovascular contractility.

In general, the clinical manifestations of hypothyroidism range from no signs or symptoms-to-life threatening like Myxedema coma. It was first described in the late 1900s as an outcome of long-standing untreated and severe hypothyroidism, which is a rare condition. Myxedema coma leads to an altered mental status, hypothermia, progressive lethargy, and bradycardia and can eventually result in multiple organ dysfunction syndrome and death[17]. Therefore, early recognition of the disease and initiation of thyroid hormone therapy and other supportive measures. Although very rare, severe primary hypothyroidism can lead to pituitary hyperplasia with concomitant pituitary pathologies like secondary adrenal insufficiency and symptoms like amenorrhea. Concerning laboratory findings in various types of hypothyroidism, levels of various thyroid hormones are summarized in table 2.

Table 2. Levels of various thyroid hormones in different types of hypothyroidism[5]

Hypothyroidism	TRH	TSH	Free T4	Free T3	Reverse T3
Primary	High to normal	High	Low	Low to Normal	Normal
Secondary	High	Normal to low	Low	Low to Normal	Normal
Tertiary	Low to Normal	Low to normal	Low	Low to Normal	Low to normal
Peripheral	Normal to high	Normal	Normal	Low	Normal to high

Management of hypothyroidism with Levothyroxine

Hypothyroidism is a permanent condition in most patients, therefore requiring lifelong thyroid hormone replacement. Pharmacological mamangement of hypothyroidm is started once the diagnosis has been confirmed. Synthetic levothyroxine is the drug of choice for the treatment of hypothyroidism. The chemical structure of levothyroxine was first identified by Edward Kendal in 1914, whereas, it was successfully synthesized by Harrington in 1927[18].

The synthesized molecule was acid and has less solubility and bioavailability and thus its water-soluble sodium salt was developed for oral therapy. The dose is taken orally on empty stomach. The half-life of levothyroxine is 9–10 days in patients with hypothyroidism and is eliminated slowly by kidneys and the conjugated metabolites were eliminated in feces. Approximately 20% of levothyroxine is eliminated in the feces[19]. After starting the levothyroxine therapy, TSH levels should be monitored every 6-8 weeks. Based on the levels of TSH, the dose of levothyroxine should be tailored. Once TSH is stabilized, serum level monitoring may be delayed for up to 4-6 months and thereafter annually.

Levothyroxine is a replacement therapy in hypothyroidism of any etiology, except for transient hypothyroidism during the recovery phase of subacute thyroiditis. It is also effective in the suppression of pituitary TSH secretion in the treatment or prevention of various types of euthyroid goiters, including thyroid nodules, Hashimoto's thyroiditis, and multinodular goiter, and as supplemental therapy in the treatment of thyrotropin-dependent well-differentiated thyroid cancer.

The objective of levothyroxine therapy is to restore physical and psychological well-being while maintaining normal levels of TSH. Levothyroxine therapy is usually started with a dose of 1.5 to 1.8 µg/kg body weight of the patient (Figure 2).

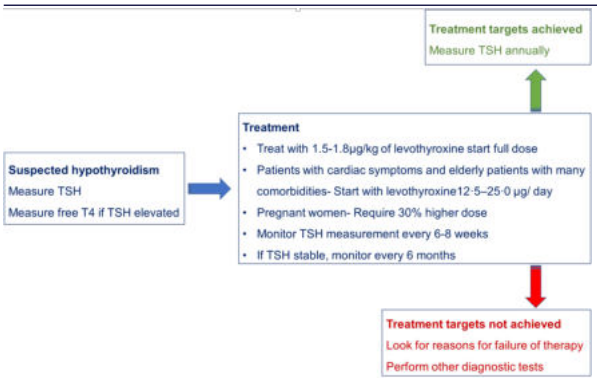

Figure 2. Decision making flow chart for treatment of hypothyroidism [13]

Concluding remarks

Although lot of research is done in the area of identification of causes, knowledge of clinical implications, diagnosis, and treatment of hypothyroidism, several unanswered questions remain, especially regarding diagnosis and treatment. Numerous risk factors are identified for abnormal TSH concentrations, free thyroxine concentrations, and thyroid disease, but a huge proportion of the variability is yet to be answered. Therefore, identification of risk factors is important. Increasing evidence shows that endocrine-disrupting chemicals might be casual factors for endocrine diseases. Several chemicals disrupt the functioning of thyroid gland and human body is exposed to such chemicals from variety of sources namely environmental exposure like flame retardants, and dietary items like food packaging material.

Because of the well-known poor consistency between TSH and thyroid function testing [56], each patient's thyroid function should be periodically assessed on an individual basis, with the subject's entire clinical picture kept in mind, while TSH monitoring at regular intervals is recommended to avoid overtreatment.

REFERENCES

[1] Diaz, A., Lipman Diaz, E. G. (2014). Hypothyroidism. Pediatrics in review, 35(8), 336–349. https://doi.org/10.1542/pir.35-8-336
[2] InformedHealth.org [Internet]. Cologne, Germany: Institute for Quality and Efficiency in Health Care (IQWiG); 2006-. How does the thyroid gland work? 2010 Nov 17 [Updated 2018 Apr 19]. https://www.ncbi.nlm.nih.gov/books/NBK279388/
[3] Shahid, M.A., Ashraf, M.A., Sharma, S. Physiology, Thyroid Hormone. [Updated 2020 May 18]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing;. https://www.ncbi.nlm.nih.gov/books/NBK500006/
[4] Gilbert, J., (2017), Hypothyroidism. Medicine, 45 (8) 506-509 https://doi.org/10.1016/j.mpmed.2017.05.009
[5] Pizzorno, J.E., Murray, M.T., Joiner-Bey, H. (2016) Hypothyroidism. Chapter 40. In The Clinician's Handbook of Natural Medicine. 458-472. https://doi.org/10.1016/B978-0-7020-5514-0.00049-X
[6] Almandoz, J. P., & Gharib, H. (2012). Hypothyroidism: etiology, diagnosis, and management. The Medical clinics of North America, 96(2), 203–221. https://doi.org/10.1016/j.mcna.2012.01.005
[7] Nygaard B. (2010). Hypothyroidism (primary). BMJ clinical evidence, 2010, 0605. PMID: 21726489; PMCID: PMC2907600. https://pubmed.ncbi.nlm.nih.gov/21726489/
[8] Redford, C., Vaidya, B. (2017). Subclinical hypothyroidism: Should we treat?. Post reproductive health, 23(2), 55–62. https://doi.org/10.1177/2053369117705058
[9] Bougma, K., Aboud, F. E., Harding, K. B., & Marquis, G. S. (2013). Iodine and mental development of children 5 years old and under:a systematic review and meta-analysis. Nutrients, 5(4), 1384–1416. https://doi.org/10.3390/nu5041384
[10] Hollowell, J. G., Staehling, N. W., Flanders, W. D., Hannon, W. H., Gunter, E. W., Spencer, C. A., Braverman, L. E. (2002). Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). The Journal of clinical endocrinology and metabolism, 87(2), 489–499. https://doi.org/10.1210/jcem.87.2.8182
[11] Gupta, V., Lee, M. (2011). Central hypothyroidism. Indian journal of endocrinology and metabolism, 15(Suppl 2), S99–S106. https://doi.org/10.4103/2230-8210.83337
[12] Persani L. (2012). Clinical review: Central hypothyroidism: pathogenic, diagnostic, and therapeutic challenges. The Journal of clinical endocrinology and metabolism, 97(9), 3068–3078. https://doi.org/10.1210/jc.2012-1616
[13] Chaker, L., Bianco, A. C., Jonklaas, J., Peeters, R. P. (2017). Hypothyroidism. Lancet (London, England), 390(10101), 1550–1562. https://doi.org/10.1016/S0140-6736(17)30703-1
[14] Teng, W., Shan, Z., Patil-Sisodia, K., & Cooper, D. S. (2013). Hypothyroidism in pregnancy. The lancet. Diabetes & endocrinology, 1(3), 228–237. https://doi.org/10.1016/S2213-8587(13)70109-8
[15] Duntas, L. H., & Yen, P. M. (2019). Diagnosis and treatment of hypothyroidism in the elderly. Endocrine, 66(1), 63–69. https://doi.org/10.1007/s12020-019-02067-9
[16] Bensenor, I. M., Olmos, R. D., Lotufo, P. A. (2012). Hypothyroidism in the elderly: diagnosis and management. Clinical interventions in aging, 7, 97–111. https://doi.org/10.2147/CIA.S23966
[17] Dutta, P., Bhansali, A., Masoodi, S. R., Bhadada, S., Sharma, N., Rajput, R. (2008). Predictors of outcome in myxoedema coma: a study from a tertiary care centre. Critical care (London, England), 12(1), R1. https://doi.org/10.1186/cc6211
[18] Hennessey J. V. (2017). The emergence of levothyroxine as a treatment for hypothyroidism. Endocrine, 55(1), 6–18. https://doi.org/10.1007/s12020-016-1199-8
[19] Grater, R. (2014) Levothyroxine. Part 2. Compound Articles. Handbook of Metabolic Pathways of Xenobiotics. https://doi.org/10.1002/9781118541203.xen313