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DISORDERS OF THYROID



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CHAPTER 1

Hypothyroidism

Subhankar Chowdhury, Partha P Chakraborty

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CASE 1 (FIG. 1)

A 24-year-old female presented with short stature, mental retardation, primary amenorrhea, and absence of secondary sexual characters. Her growth and developmental milestones were satisfactory till 5 years of age when her school performances started deteriorating gradually and she left school at the age of 10 years. On examination, she had a typical puffy face, alopecia, madarosis, and dry and coarse skin. She had severe short stature with a height standard deviation score of –5.6. Ankle jerks were grossly delayed. She had breast buds only (Tanner stage 2) and no pubic or axillary hair.



FIG. 1: A 24-year-old lady with primary hypothyroidism due to chronic Hashimoto's thyroiditis

Relevant investigations revealed the following:

- Free thyroxine (FT4): 0.2 ng/dL
- Thyroid-stimulating hormone (TSH): >150 mIU/L
- Total cholesterol (TC): 330 mg/dL
- Low-density lipoprotein cholesterol (LDL-C): 178 mg/dL
- Triglycerides (TG): 224 mg/dL

- Antithyroid peroxidase (anti-TPO) antibody: Positive
- Antithyroglobulin (anti-Tg) antibody: Negative
- Bone age: 10 years
- Neck ultrasonogram revealed a hypoplastic thyroid gland.

Diagnosis: Primary hypothyroidism due to chronic Hashimoto's thyroiditis.

CASE 2 (FIG. 2)

A 48-year-old lady got admitted to emergency ward with sudden onset disorientation following recurrent episodes of vomiting for 3 days. She was amenorrhoeic since her last child birth 27 years back and she could not breastfeed her youngest child. There were similar episodes of disorientation for several times in the past. The Glasgow Coma Scale score was 6 out of 15 with supine blood pressure of 76/42 mmHg. She had a typical pale-looking face with loss of lateral eyebrows. Pubic and axillary hairs were absent.



FIG. 2: A 48-year-old lady with secondary hypothyroidism due to Sheehan's syndrome

A detailed workup revealed the following:

- Random plasma glucose: 64 mg/dL
- Serum sodium level: 119.7 meq/L
- Potassium: 3.7 meq/L
- Morning cortisol: 2.2 µg/dL
- Triiodothyronine (T3): 55 ng/dL
- Free T4: 0.4 ng/dL
- Thyroid-stimulating hormone 0.25 mIU/L
- Follicle-stimulating hormone: 2.4 mIU/mL
- Urine spot sodium: 122 meq/L.

Magnetic resonance imaging of brain showed partial empty sella with flattened pituitary gland as a thin rim lining the sella. Patient was put on hypertonic saline, systemic steroid, and levothyroxine (LT4), following which she recovered remarkably within 48 hours.

Diagnosis: Secondary hypothyroidism due to Sheehan's syndrome.

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INTRODUCTION

Hypothyroidism, one of the common endocrine diseases across the globe, has multiple etiologies and varied clinical manifestations. It is broadly classified into overt hypothyroidism (OH) and subclinical hypothyroidism (SCH) based on the thyroid function tests (TFTs). Subclinical hypothyroidism, essentially a biochemical diagnosis, is strictly defined as elevated serum TSH with a normal serum free thyroxine (FT4) level in absence of ongoing or recent severe illness and abnormal functioning of the hypothalamic-pituitary-thyroid axis. It, probably, represents a compensated early state of primary thyroid disease where an elevated level of TSH is required to maintain serum thyroid hormones (TH) within the normal range. Though, it is called subclinical, many patients are symptomatic and significant clinical improvement is noticed after LT4 supplementation. Low FT4 combined with elevated TSH constitutes OH. Appropriate and successful treatment requires an accurate diagnosis which is also influenced by coexisting medical ailments.

ETIOLOGY

Hypothyroidism can be primary, when the disease involves the thyroid gland itself with abnormal TH synthesis and/or release; or secondary when the defect lies in the hypothalamus and/or pituitary with inappropriate thyrotropin-releasing hormone (TRH) or TSH signaling; or peripheral/consumptive which results from accelerated conversion of thyroxine (T4) to reverse T3 and T3 to diiodothyronine (T2) by excessive production of type 3 deiodinase usually from a tumor.

The commonest type of hypothyroidism is primary hypothyroidism; its usual causes are:

- Autoimmune thyroiditis
- Iodine deficiency
- Surgical removal or radioiodine ablation of the thyroid gland
- Medications.

Usual causes of secondary hypothyroidism are:

- Sellar or suprasellar space-occupying lesions
- Vascular insult to the pituitary
- Inflammatory disorders of the hypothalamic-pituitary region.

PRESENTATION

The signs and symptoms of hypothyroidism have poor sensitivity and specificity and vary according to the degree of thyroid dysfunction. They are subjective and commonly include fatigue, somnolence, aches and pains, menstrual irregularities, cold intolerance, dry skin, constipation, vocal changes, and non-pitting edema.

Hypothyroidism, at times, may have monosymptomatic presentation like short stature in children, infertility, galactorrhea, polyserositis, and hypoosmolar euvolemic hyponatremia (secondary hypothyroidism).

Atypical presentations, like Van Wyk-Grumbach syndrome (combination of primary hypothyroidism, peripheral isosexual precocity, delayed bone age, feedback pituitary adenoma, and ovarian cysts), Kocher-Debre-Semelaigne syndrome (primary hypothyroidism with pseudomuscular hypertrophy in children), Hoffman's syndrome (primary hypothyroidism with pseudomuscular hypertrophy in adults), and delayed ejaculation, are not uncommonly encountered in clinical practice.[1,2]

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HYPOTHYROIDISM AND COMORBIDITIES

A number of comorbidities are commonly associated with hypothyroidism of which dyslipidemia, cardiovascular morbidities, menstrual irregularities, infertility, depression, and diabetes are of significant clinical importance.

Thyroid hormones play an important role in different steps of cholesterol metabolism. It stimulates hepatic cholesterol synthesis by inducing 3-hydroxy-3-methylglutaryl-coenzyme A reductase. On the other hand, TH increases hepatic low-density lipoprotein receptor expression and decreases intestinal cholesterol absorption, and thereby, decreases serum TC and LDL-C concentration. Thyroid hormones can potentially decrease high-density lipoprotein cholesterol (HDL-C) concentration by stimulating cholesteryl ester transfer protein and hepatic lipase activity. However, effects on cholesterol clearance predominates over cholesterol synthesis; so, hypothyroidism, both overt and subclinical, are associated with increased TC, TG, very-low-density lipoprotein cholesterol, LDL-C, HDL-C, and lipoprotein(a) [Lp(a)] levels. There are suggestions of qualitative abnormalities of LDL-C particles in hypothyroidism as well. What is of interest is that even in patients with TSH level within the so-called reference range, lipid levels are more deranged as the TSH rises.

Patients of hypothyroidism have more cardiovascular risks due to underlying atherogenic lipid profile, abnormal hemodynamics, endothelial dysfunction, hypercoagulability, and abnormal nontraditional risk factors [elevated Lp(a), homocysteine, and C-reactive protein]. The trend is same for both OH and SCH; SCH with TSH more than 10 μIU/mL is considered as definite cardiovascular risk factor.

Hypothyroidism has long been associated with depression. Thyroid hormones has an established role in central nervous system (CNS) function and the prevalence of depression has been shown to be significantly high even in patients with SCH. Interestingly, patients with autoimmune hypothyroidism are more prone to mental disturbances compared to patients with hypothyroidism secondary to other etiologies as evidenced by a positive correlation of depression scores with elevated anti-thyroid peroxidase (anti TPO) antibody even in patients with normal TFT. Levothyroxine, though alone is ineffective in inducing complete remission, can enhance the effect of concurrent antidepressant medications. Conversely, patients with endogenous depression may manifest abnormal TFTs characterized by higher T4 and reverse T3 (rT3) with lower T3 and TSH. Absent nocturnal surge of TSH and blunted TSH response to TRH explain the suppressed value in those patients. Elevated circulatory glucocorticoids and resultant reduced activity of peripheral deiodinases alter the TH metabolism and the TFT resembles a state seen in sick euthyroid syndrome.

Diabetes and hypothyroidism are the two most frequently encountered endocrinological disorders and thyroid dysfunction is more common in diabetes, in particular type 1 diabetes. About 20% of children with type 1 diabetes may have antithyroid antibodies and 3–8% suffer from hypothyroidism. Thyroid hormones has its role in glucose homeostasis. It increases hepatic glucose output and stimulates intestinal glucose absorption, and thereby tends to increase blood glucose levels. It also stimulates peripheral utilization of glucose minimally. A particular polymorphism of type 2 deiodinase is associated with insulin resistance. The effect of hypothyroidism on blood glucose level, thus, varies but hypothyroidism is known to adversely affect the cardiovascular and nephropathy risks in patients with diabetes. Glycolsylated hemoglobin is a commonly used biochemical marker of long-term glycemic control; it could be spuriously high in patients with OH, making it unreliable as a glycemic marker.

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Menstrual irregularities and infertility are common in hypothyroidism and the prevalence of infertility is estimated to be around 10–15% due to abnormal function of the hypothalamic-pituitary-gonadal axis. Abnormal pulsatility of the gonadotropins, hyperprolactinemia, and structural abnormalities of the ovaries are the important underlying mechanisms. Levothyroxine administration normalizes these abnormalities, reverses menstrual abnormalities, and improves chances of spontaneous fertility.

Obesity and Hypothyroidism

About a quarter of overweight or obese patients have abnormal TFTs which mimic SCH. In individuals with normal body mass index (BMI), T4 produces equal amount of T3 and rT3. There is increased T3 production and decreased rT3 production in obesity. The high leptin level in obesity is perhaps the main underlying mechanism for elevated TSH. Leptin stimulates TRH, proopiomelanocortin/cocaine- and amphetamine-regulated transcript (POMC/CART) neurons and inhibits neuropeptide Y/agouti-related protein (NPY/AGRP) neurons and pituitary conversion of T4 to T3, and thus, elevates serum TSH. The other postulations for elevated TSH in obesity are injury of thyroid cells and sodium-iodide symporter due to chronic systemic inflammation, low levels of TH receptors in hypothalamus/pituitary with resultant TH resistance, derangement of hypothalamic-pituitary axis with secretion of immunoreactive but bioinactive TSH, TSH receptor mutation, and impaired mitochondrial function and coexisting thyroid disease.

These patients usually have a TSH value of less than 10 μIU/mL and usually do not require LT4 therapy. Thyroid-stimulating hormone and BMI have a positive correlation, and with reduction of weight, the TSH value falls within the reference range.

DIAGNOSIS

Diagnosis of hypothyroidism is confirmed by simple laboratory test. It is suggested that when the clinical suspicion of hypothyroidism is high, a combination of FT4 and TSH should be ordered; however, as a routine screen for thyroid dysfunction, serum TSH alone is sufficient. A combination of elevated TSH and low FT4 fulfils the diagnostic criteria of overt primary hypothyroidism. Subclinical hypothyroidism is said to be present when TSH is elevated but the FT4 is within the laboratory reference range. Low FT4 with low or inappropriately normal or mildly elevated TSH constitutes secondary (pituitary) or tertiary (hypothalamic) hypothyroidism and should ask for imaging of the hypothalamus and pituitary gland, and ensuring normal serum cortisol level before starting on levothyroxine therapy. Though at present, TSH is commonly measured using a third-generation chemiluminescence assay, older generation assays are sufficient enough to diagnose primary hypothyroidism. There is much controversy worldwide as far as normal reference range of TSH is concerned and a value between 0.3 and 5.0 mIU/L is commonly used as the normal reference range. A monograph by the National Academy of Clinical Biochemistry suggested that 95% of euthyroid volunteers had a serum TSH between 0.4 and 2.5 mIU/L on routine screening.[3] Alterations in TFTs in different clinical situations mimicking primary or secondary hypothyroidism have been summarized in table 1.

Measuring thyroid autoantibodies (anti-TPO and anti-Tg) in hypothyroid patients not only helps to determine the underlying etiology of primary hypothyroidism, it can assess the risk of progression of SCH to OH. Though anti-TPO antibodies are commonly present in patients of chronic autoimmune thyroiditis, a subset of patients who are

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TABLE 1: Alteration in thyroid function tests in disorders of hypothalamo-pituitary-thyroid axis and non-thyroidal illnesses mimicking primary or secondary hypothyroidism

Free thyroxine	Free triiodothyronine	Thyroid-stimulating hormone	Possibilities
Low	Low/normal	High	Primary hypothyroidism
Normal	Normal	High	SCH/recovery from sick euthyroid syndrome/ recovery from thyroiditis/heterophile antibody against TSH/macro-TSH/partial TSH resistance
Low	Low	Low/normal	Secondary hypothyroidism/sick euthyroid syndrome/drug effect like dopamine, steroid/ patients of hyperthyroidism treated with antithyroid drugs or radioiodine in recent past
Low	Low	Mildly elevated (Usually <20 mIU/L)	Rule out secondary hypothyroidism/sick euthyroid syndrome

TSH, thyroid-stimulating hormone; SCH, subclinical hypothyroidism.

negative for anti-TPO antibody are tested positive for anti-Tg antibody. It has to be kept in mind that a minority of patients with histologically confirmed autoimmune hypothyroidism are negative for both antibodies. Thyroid scintigraphy and ultrasound do not provide any extra information in patients of hypothyroidism; the latter has a role to characterize any associated thyroid nodule.

It would be relevant to rule out hypothyroidism before embarking on statin treatment for dyslipidemia (especially, if any clinical suspicion). It is because if frankly hypothyroid, thyroxine treatment may be enough to correct or at least to improve the dyslipidemia, and the risk of statin-induced myopathy is significantly higher in untreated hypothyroidism.

TREATMENT

The initiating dose of LT4 replacement varies depending on etiology of hypothyroidism, age, body weight, and associated comorbidities. Neonates and infants with hypothyroidism should be initiated with a higher dose whereas children with long-standing severe hypothyroidism and elderly individuals should be put on a significantly lower dose of LT4 at the beginning. Caution should also be exercised when initiating and titrating LT4 therapy in individuals with known or suspected coronary artery disease to avoid development of new onset angina or worsening of preexisting ischemic heart disease. A typical starting dosage of 25–50 µg per day followed by a slow up-titration every 4–6 weeks is recommended in patients with underlying heart disease. Patients with complete absence of functional thyroid tissues typically require a replacement dose of 1.6–1.8 µg/kg/day and the calculation should be made using the ideal body weight.[4,5]

Thyroxine has a plasma half-life of about 6.7 days and provided that there is an intact hypothalamic-pituitary-thyroid axis, the dose adjustment is usually done every 8–12 weeks to allow achievement of a new steady state which requires 5–6 half-lives. However, in special circumstances like in pregnancy or in infants and children, dose titration every 4–6 weeks is recommended.

Many a time, patients on a stable dose of LT4 present with elevated TSH with normal FT4. A detailed history to ensure compliance is of importance before increasing the dose of LT4.

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In nonpregnant, non-elderly individuals, the dose of LT4 is adjusted to maintain the TSH level within the normal reference range for the performing laboratory. Though, there are some suggestions for aiming a TSH within the lower half of the reference range (0.4–2.0 mIU/L), this level of TSH has not been consistently associated with symptomatic improvement, better quality-of-life scores or clinical outcomes.[6,7] However, a minority of patients prefer LT4 dosages that result in low-normal or even sub-normal serum TSH values.[8,9]

A recent reanalysis of the third National Health and Nutrition Examination Survey data, using age, sex, and ethnicity specific TSH reference limits, the 97.5 percentile for TSH values in whites between 70 and 79 years old was 5.6 mIU/L, and for those over age 80, it was 6.6 mIU/L. This age-dependent increase in serum TSH and the fact that longevity has been reported to be associated with high serum TSH should make the target TSH level in elderly individuals somewhat higher than the general population.

The current American Thyroid Association (ATA) guidelines for pregnancy and postpartum management of thyroid disease recommend that if trimester-specific TSH reference ranges are not available, the following target TSH ranges may be used: first trimester 0.1–2.5 mIU/L; second trimester 0.2–3.0 mIU/L; third trimester 0.3–3.0 mIU/L.

Many factors including food, medications, and disease processes are known to adversely affect the absorption of LT4. A number of commonly used drugs, like gastric antisecretory agents, antacids, calcium carbonate, and iron preparations, interfere with absorption of LT4. It is commonly advised that LT4 should be taken on an empty stomach, without other medications, supplements, or food for 1 hour to allow consistent absorption and to maintain serum TSH within a narrow target range.[10] Levothyroxine may also be taken in a similar fashion 4 hours after the last meal or at bed time with identical clinical and biochemical outcomes. In fact, it has been seen that the nocturnal absorption of LT4 is better because of higher basal secretion of gastric acid and slower intestinal motility overnight combined with the fasting state.[11]

However, considering the food habits of the majority of Indian population, patients should be instructed to take LT4 tablets at empty stomach in the morning, and bed time administration of LT4 should not be entertained. Poor compliance and difficulty with adherence to a daily regimen is common in clinical practice. Study with randomized crossover design has shown that euthyroidism can be achieved with once-weekly dosing of LT4, at a dose slightly higher than 7 times the usual daily dose, without systemic side effects,[12] and once-weekly LT4 administration may be tried only in exceptional cases to counteract noncompliance.

Different brands of LT4 are available in the market with different bioequivalence, and changes in LT4 brands are strongly discouraged as such a wide difference in bioequivalence may put patients at risk for incorrect dosing, if different brands are used interchangeably.

Animal studies have demonstrated that LT4 therapy in post-thyroidectomy subjects may not achieve euthyroidism in all tissues simultaneously and required the combination of LT4 and liothyronine.[13,14] However, randomized clinical trials comparing LT4 monotherapy with LT4 plus liothyronine combination therapy were unable to support the superiority of the combination therapy in general.[15] The positive outcome of combination therapy in some of the studies may be explained by favorable effects of combination therapy in a subset of patients harboring genetic polymorphism in relevant TH transporters or deiodinase enzymes resulting in low levels of T3 in the tissues.

In some of the studies, weight loss was somewhat higher in patients receiving combination therapy or desiccated thyroid compared to LT4 monotherapy[16,17] and was thought

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to be the explanation for patients' preference for combination therapy or desiccated thyroid which contains significant amount of T3. Though the determinants of patients' preferences for combination therapy still remain unknown, it has been speculated that higher serum and tissue T3 levels might be associated with improvement in T3-dependent functions of the CNS, including regulation of body weight. Despite all these evidences, only the European Thyroid Association have offered specific guidance for the use of LT4 and liothyronine combination therapy, but still consider it experimental.[18] On a futuristic note, based on a landmark study published in 2012 that has described the generation of functional thyroid tissue from embryonic stem cells, we can speculate that hypothyroid patients can also be treated with thyroid-generating stem cells in the coming years.[19]

CONCLUSION

Hypothyroidism may be primary, secondary, or peripheral. Biochemically, it can also be classified into overt or subclinical. Primary hypothyroidism is the most commonly encountered form of the disease while peripheral type is rare. Signs and symptoms of hypothyroidism are nonspecific and a high degree of clinical suspicion is required for diagnosis. Monosymptomatic presentations or atypical presentations are not uncommon. A number of comorbidities like dyslipidemia, cardiovascular disease, menstrual irregularities and infertility, depression, and diabetes are commonly associated with hypothyroidism, both overt and subclinical. One-fourth of overweight or obese patients have altered thyroid function, manifesting biochemically as SCH. Excess weight itself alters the hypothalamic-pituitary-thyroid axis by a number of mechanisms. There are significant controversies regarding management of SCH which requires individualization of therapy. The usual indications of treatment are pregnancy, infertility, cosmetically unaccepted goiter, TSH more than 10 µIU/mL, elevated antithyroid antibodies and dyslipidemia. Therapy with LT4 may also be tried in symptomatic patients of SCH if those are suggestive of hypothyroidism. Levothyroxine is the mainstay of therapy, which should preferably be taken at empty stomach in the morning. Changing of brands is discouraged. The target TSH in LT4-treated, nonpregnant patients depends on age, presence of comorbidities, and clinical scenarios. Trimester-specific TSH ranges provided by ATA may be used in pregnant patients.

REFERENCES

1. Van Wyk JJ, Grumbach MM. Syndrome of precocious menstruation and galactorrhea in juvenile hypothyroidism: An example of hormonal overwrap in pituitary feed-back. J Pediatr. 1960;57:416-35.
2. Werner SC, Ingbar SH, Braverman LE, Utiger RD. In: Werner and Ingbar's The Thyroid: A Fundamental and Clinical Text, 9th edition. Philadelphia: Lippincott Williams and Wilkins; 2005. pp. 894-5.
3. Baloch Z, Carayon P, Conte-Devolx B, Demers LM, Feldt-Rasmussen U, Henry JF, et al. Laboratory medicine practice guidelines. Laboratory support for the diagnosis and monitoring of thyroid disease. Thyroid. 2003;13(1):3-126.
4. Fish LH, Schwartz HL, Cavanaugh J, Steffes MW, Bantle JP, Oppenheimer JH. Replacement dose, metabolism, and bioavailability of levothyroxine in the treatment of hypothyroidism. Role of triiodothyronine in pituitary feedback in humans. N Engl J Med. 1987;316(13):764-70.
5. Santini F, Pinchera A, Marsili A, Ceccarini G, Castagna MG, Valeriano R, et al. Lean body mass is a major determinant of levothyroxine dosage in the treatment of thyroid diseases. J Clin Endocrinol Metab. 2005;90(1):124-7.
6. Boeving A, Paz-Filho G, Radominski RB, Graf H, Amaral de Carvalho G. Low-normal or high-normal thyrotropin target levels during treatment of hypothyroidism: a prospective, comparative study. Thyroid 2011;21(4):355-60.

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7. Walsh JP, Ward LC, Burke V, Bhagat CI, Shiels L, Henley D, et al. Small changes in thyroxine dosage do not produce measurable changes in hypothyroid symptoms, well-being, or quality of life: results of a double-blind, randomized clinical trial. J Clin Endocrinol Metab. 2006;91(7):2624-30.
8. Carr D, McLeod DT, Parry G, Thornes HM. Fine adjustment of thyroxine replacement dosage: comparison of the thyrotrophin releasing hormone test using a sensitive thyrotrophin assay with measurement of free thyroid hormones and clinical assessment. Clin Endocrinol (Oxf). 1988;28(3):325-33.
9. Toft AD, Beckett GJ. Thyroid function tests and hypothyroidism. Measurement of serum TSH alone may not always reflect thyroid status. BMJ. 2003;326:295-6.
10. Bach-Huynh TG, Nayak B, Loh J, Soldin S, Jonklaas J. Timing of levothyroxine administration affects serum thyrotropin concentration. J Clin Endocrinol Metab. 2009;94(10):3905-12.
11. Vanderpump M. Pharmacotherapy: hypothyroidism-should levothyroxine be taken at bedtime? Nat Rev Endocrinol. 2011;7(4):195-6.
12. Grebe SK, Cooke RR, Ford HC, Fagerström JN, Cordwell DP, Lever NA, et al. Treatment of hypothyroidism with once weekly thyroxine. J Clin Endocrinol Metab. 1997;82(3):870-5.
13. Escobar-Morreale HF, Obregón, MJ, Escobar del Rey F, Morreale de Escobar G. Replacement therapy for hypothyroidism with thyroxine alone does not ensure euthyroidism in all tissues, as studied in thyroidectomized rats. J Clin Invest. 1995;96(6):2828-38.
14. Escobar-Morreale HF, del Rey FE, Obregón, MJ, de Escobar GM. Only the combined treatment with thyroxine and triiiodothyronine ensures euthyroidism in all tissues of thyroidectomized rat. Endocrinology. 1996;137(6):2490-502.
15. Grozinsky-Glasberg, S, Fraser A, Nahshoni E, Weizman A, Leibovici L. Thyroxine-triiodothyronine combination therapy versus thyroxine monotherapy for clinical hypothyroidism: meta-analysis of randomized controlled trials. J Clin Endocrinol Metab. 2006;91(7):2592-9.
16. Nygaard B., Jensen EW, Kvetny J, Jarløv A, Faber J. Effect of combination therapy with thyroxine (T4) and 3,5,3›-triiodothyronine versus T4 monotherapy in patients with hypothyroidism, a double-blind, randomised cross-over study. Eur J Endocrinol. 2009;161(6):895-902.
17. Hoang TD, Olsen CH, Mai VQ, Clyde PW, Shakir MK. Desiccated thyroid extract compared with levothyroxine in the treatment of hypothyroidism: a randomized, double-blind, crossover study. J Clin Endocrinol Metab. 2013;98(5):1982-90.
18. Wiersinga WM, Duntas L, Fadeyev V, Nygaard B, Vanderpump MP. 2012 ETA guidelines: the use of L-T4 + L-T3 in the treatment of hypothyroidism. Eur Thyroid J. 2012;1:55-71.
19. Antonica F, Kasprzyk DF, Opitz R, Iacovino M, Liao XH, Dumitrescu AM, et al. Generation of functional thyroid from embryonic stem cells. Nature. 2012;491:66-71.

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