Section A-Research paper

A Brief Insight about Hypothyroidism

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Abstract

Background: Hypothyroidism is a condition that characterized by abnormally low thyroid hormone production. There are many disorders that result in hypothyroidism. These disorders may directly or indirectly involve the thyroid gland. Because thyroid hormone affects growth, development, and many cellular processes, inadequate thyroid hormone has diffuse consequence for the body. Hypothyroidism is the commonest pathological hormone decrease, the variety of end-organ effects and wide range of disease severity make it an elusive clinical entity. The early assessment of hypothyroidism remains a big aim, particularly when the decrease in thyroid function is gradual. In some instances, the manifestations were simply attributed to the effects of aging in the elderly. Infrequently, hypothyroidism may progress to myxedema coma; a state characterized by defective thermoregulation and altered mental status to the point of coma after a precipitating event. The symptoms of hypothyroidism are often not specific (which means they can like the symptoms of many other conditions). Symptoms generally become more evident as the condition worsens and a lot of these complaints are related to a metabolic slowing of the body. Common symptoms are : Fatigue , Depression, weight gain, Excessive sleepiness, Cold intolerance, Constipation, Dry, course hair, Dry skin, low concentration, Swelling of the legs, Vague aches and pain, uscle cramps. The treatment goals for hypothyroidism are to invert clinical progression and correct metabolic derangements, as evidenced by normal blood levels of thyroid-stimulating hormone (TSH) and free thyroxine (T4). Thyroid hormone is administered to replace endogenous production. In general, hypothyroidism can be adequately treated with a constant daily dose of levothyroxine (LT4).Thyroid hormone can be started at a full replacement doses in individuals who are young and otherwise healthy. In elderly patients and those with known ischemic heart disease, treatment should begin with one fourth to one half the expected dosages, and the dosage should be adjusted in small increases.

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Introduction

Thyroid hormones are produced by the thyroid gland. This gland is located in the lower part of the neck, below the Adam's apple. The gland enwraps around the trachea and has a shape that is similar to a butterfly - formed by lobes and attached by a middle part called (isthmus) **(1).**

The thyroid gland is covered by a thin fibrous capsule, which has an inner and an outer layer. The inner layer extrudes into the gland and forms the septa that divide the thyroid tissue into microscopic lobules. The outer layer is continuous with the pretracheal fascia, attaching the gland to the cricoid and thyroid cartilages via a thickening of the fascia to form the posterior suspensory ligament of thyroid gland, also known as Berry's ligament. This causes the thyroid to move up and down with the movement of these cartilages when swallowing occurs **(2).**

The thyroid hormones organize the metabolism of proteins, lipids and carbohydrates, and control the activity of membrane bound enzymes. This hormone can also organize the transcription of numerous genes

encoding both myofibrillar and calcium-regulatory proteins in myofibers. A thyroid disease is a medical condition impairing the function of the thyroid **(2).**

The primary function of the thyroid is the production of the iodine-containing thyroid hormones, triiodothyronine (T_3) and thyroxine or tetraiodothyronine (T_4) and the peptide hormone calcitonin. The thyroid hormones are created from iodine and tyrosine. T_3 is so named because it contains three atoms of iodine per molecule and T_4 contains four atoms of iodine per molecule. The thyroid hormones have a wide range of effects on the human body,These include: **(3).**

Hypothyroidism is a condition that characterized by abnormally low thyroid hormone production. There are many disorders that result in hypothyroidism. These disorders may directly or indirectly involve the thyroid gland. Because thyroid hormone affects growth, development, and many cellular processes, inadequate thyroid hormone has diffuse consequence for the body. **(4)**

Hypothyroidism is the commonest pathological hormone decrease, the variety of end-organ effects and wide range of disease severity make it an elusive clinical entity. The early assessment of hypothyroidism remains a big aim, particularly when the decrease in thyroid function is gradual. In some instances, the manifestations were simply attributed to the effects of aging in the elderly. Infrequently, hypothyroidism may progress to myxedema coma; a state characterized by defective thermoregulation and altered mental status to the point of coma after a precipitating event **(5).**

It is evaluated that 3% to 5% of the population has some form of hypothyroidism. The condition is more common in women than in men, and its extent increases with age. Below is a list of some of the common causes of hypothyroidism in iodine rich countries like United States.

- Hashimoto's thyroiditis
- Lymphocytic thyroiditis (which may occur after hyperthyroidism)
- Thyroid destruction (from radioactive iodine or surgery)
- Pituitary or hypothalamic disease.
- Medications.
- Severe iodine deficiency **(6).**

Hashimoto's Thyroiditis is the commonest cause of hypothyroidism in the United States is an inherited disease; the thyroid gland is usually enlarged (goiter) and has a decreased ability to make thyroid hormones. Hashimoto's is an autoimmune disease in which the body's immune system inappropriately attacks the thyroid tissue. In part, this condition is believed to have a genetic base. This means that the way toward developing Hashimoto's thyroiditis can run in families. Hashimoto's is 5 to 10 times more common in women than in men. Patients with this disease show an increased number of antibodies to the enzyme, thyroid peroxidase (anti-TPO antibodies). Since the basis for autoimmune diseases may have a common origin, it is usual to find that a patient with Hashimoto's thyroiditis has any other autoimmune diseases such as diabetes or pernicious anemia (B12 deficiency). Hashimoto's can be detected by presence of anti-TPO antibodies in the blood and/or by performing a thyroid scan **(7).**

HT was first described by a Japanese physician, Haraku Hashimoto, in 1912. He found that thyroid tissue was infiltrated by lymphocytes with increased volume of the gland, naming this disease as “struma lymphomatosa”. Hashimoto's struma lymphomatosa was not considered a specific clinical entity until 1931, when Allen Graham described the condition as an autonomous pathology. In 1956, Rose and Witebsky demonstrated that rabbit immunization with extracts of rabbit thyroid induced histologic modification on thyroid tissue similar to HT, identifying anti-thyroglobulin antibodies in the serum. In the same year, Roitt, Doniach et al. isolated anti-thyroglobulin antibodies from the serum of patients with HT and stated that patients with HT may have an immunological reaction to thyroglobulin, concluding that Hashimoto's goiter should be considered an autoimmune disease of the thyroid gland . **(8).**

Lymphocytic Thyroiditis following Hyperthyroidism, Thyroiditis means inflammation of the thyroid gland. When the inflammation caused particularly by a lymphocyte, the condition is referred to as lymphocytic thyroiditis. This condition is more common after pregnancy and can actually affect up to 8% of women after they deliver. In these cases, there is usually a hyperthyroid phase (in which excessive amounts of thyroid hormone go out from the inflamed gland), which is followed by a hypothyroid phase that can last for up to six months. A lot of affected women finally return to a state of normal thyroid function, although there is a possibility of remaining hypothyroid **(9).**

The exogenous reason for hypothyroidism is the low intake of iodine. Hypothyroidism is also caused by surgical removal of the thyroid gland, thyroid ablation with radioactive iodine, and external irradiation. It is also associated with diabetes, infertility, obesity and certain drugs (such as lithium and interferon); being more common in females than males and may manifest in severe or subclinical form **(10).**

Severe hypothyroidism can be detected in 5% to 15% of the population, in areas of the world where there is an iodine decrease in the diet; Examples of these areas include India and Chile. Severe iodine deficiency is also seen in remote mountain areas such as the Himalayas. **(11).**

Diagnosis of hypothyroidism :-

The symptoms of hypothyroidism are often not specific (which means they can like the symptoms of many other conditions). Symptoms generally become more evident as the condition worsens and a lot of these complaints are related to a metabolic slowing of the body. Common symptoms are : Fatigue , Depression, weight gain, Excessive sleepiness, Cold intolerance, Constipation, Dry, course hair, Dry skin, low concentration, Swelling of the legs, Vague aches and pain, Muscle cramps **(12).**

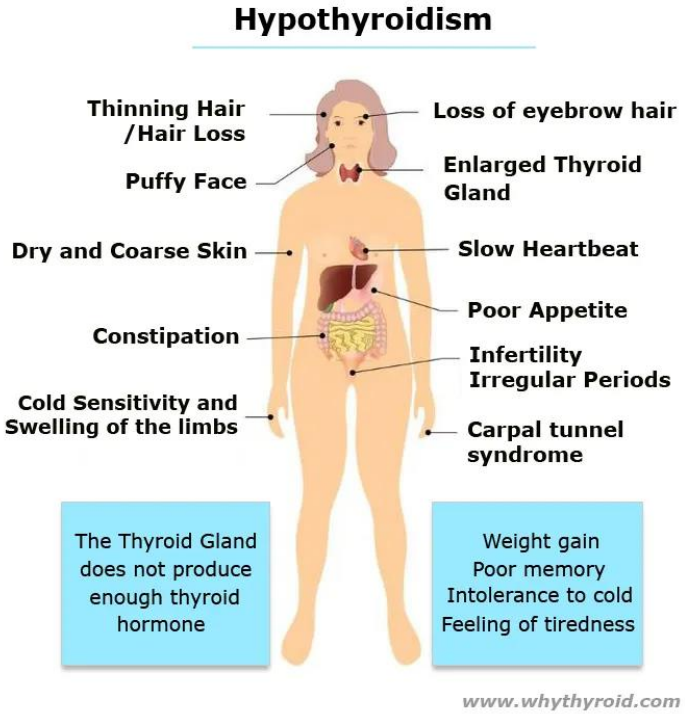

Figure 1:- Diagnosis of hypothyroidism (12).

As the disease becomes more severe, there may be puffiness around the eyes, bradycardia, low body temperature, and heart failure. In its most profound form, severe hypothyroidism may lead to a life-threatening

coma (myxedema coma). In a severely hypothyroid individual, a myxedema coma tends to be exaggerated by severe illness, surgery stress, or traumatic injury. This condition requires hospitalization and immediate treatment with thyroid hormones given by injection. On the other hand, untreated hypothyroidism can lead to cardiomyopathy, worsening heart failure, and pleural effusion **(13).**

The symptoms of hypothyroidism are varied and depend on the severity and duration of thyroid hormone decrease. Assessment of these patients should include an evaluation of their thyroid status. The sensitive TSH study is the most useful laboratory study in the diagnosis of hypothyroidism. A diagnosis of hypothyroidism can be doubted in patients with fatigue, cold intolerance, constipation, and dry skin. A blood test is needed to confirm the diagnosis **(3).**

When hypothyroidism is present, the blood levels of thyroid hormones can be measured directly and are usually decreased. However, in early hypothyroidism, the level of thyroid hormones (T3 and T4) may be normal. Therefore, the main tool for the detection of hyporthyroidism is the measurement of the TSH, the thyroid stimulating hormone. As mentioned before, TSH is secreted by the pituitary gland. If a decrease of

thyroid hormone occurs, the pituitary gland reacts by producing more TSH and the blood TSH level increases in a trial to help thyroid hormone production. This increase in TSH cans occure before the fall in thyroid hormones by months or years. Thus, the measurement of TSH should be elevated in cases of hypothyroidism **(14).**

Diagnosis

Patients with altered sensorium, hypothermia, or absence of fever despite infectious disease, clinical and biochemical features of hypothyroidism, those who had a history of hypothyroidism and are currently not on treatment, in the setting of a precipitating factor, should be identified with a high index of suspicion. The treating physician should not hesitate in starting replacement therapy while waiting for serum TSH and serum T4. An active search for precipitating causes should be initiated, and appropriate investigations should be ordered based on patient's clinical presentation. White blood cell counts, urine routine and microscopy, blood and urine culture, serum electrolytes, serum creatinine, chest X-ray, and electrocardiogram should be obtained **(15).**

Management of Hypothyroid patient:-

The treatment goals for hypothyroidism are to invert clinical progression and correct metabolic derangements, as evidenced by normal blood levels of thyroid-stimulating hormone (TSH) and free thyroxine (T4). Thyroid hormone is administered to replace endogenous production. In general, hypothyroidism can be adequately treated with a constant daily dose of levothyroxine (LT4).Thyroid hormone can be started at a full replacement doses in individuals who are young and otherwise healthy. In elderly patients and those with known ischemic heart disease, treatment should begin with one fourth to one half the expected dosages, and the dosage should be adjusted in small increases **(16).**

- The average dose of T4 replacement in adults is approximately 1.6 micrograms per kilogram per day. This translates into approximately 100 to 150 mg per day.
- In young, healthy patients, the full amount of T4 replacement hormone may be initially started.
- In patients with preexisting heart disease, this method of thyroid

replacement may increase the underlying heart condition in about 20% of cases.

- In older patients without known heart disease, starting with a full dose of thyroid replacement may result in uncovering heart disease, leading to chest pain or a heart attack. For this reason, patients with a history of heart disease or those doubted of being at high risk are started with 25 mg or less of replacement hormone, with an increase the dose at 6 weeks interval gradually.

Ideally, synthetic T4 replacement should be taken in the morning, 30 minutes before eating .Drugs containing iron or antacids should be prevented, because they affect absorption **(8).** Therapy for hypothyroidism is observed at approximately six week intervals until stable. Follow up TSH to determine if the appropriate amount of thyroid replacement is being given. The goal is to maintain the TSH within normal values. Depending on the lab used, the absolute values may vary, but in general, a normal TSH range is between 0.5 to 5.0uIU/ml. Once patient became stable, the TSH can be monitored yearly. Over-treating hypothyroidism with excessive thyroid medication is potentially harmful and can cause problems with heart palpitations and blood pressure control and can also lead to osteoporosis. Every effort should be made to keep the TSH within the normal range **(17).**

Levothyroxine (LT4) treatment is a widely accepted hypothyroidism therapy. Recently more studies done to evaluate treatment with alone or combined with triiodothyronine (T3) in the outpatient setting. Initial LT4 replacement with gradual dose elevation is classically needed for outpatients. But in myxedematous coma patients need more aggressive treatment, because that is a life-threatening condition and there is a difficult intestinal absorption. Appropriate hypothyroidism therapy may be determinant for intensive care patients with regard to hemodynamic conditions and mechanical ventilation-dependent respiratory failure **(18).**

Another group of patients are those without a diagnosis of hypothyroidism that may have critical illness adaptive changes that looklike hypothyroidism (euthyroid sick syndrome). LT4-compensated hypothyroidism patients should be managed carefully, as they rely on fixed LT4 oral doses and may eventually not be able to self-adjust **(19)**

Subclinical hypothyroidism: Subclinical hypothyroidism (SCH) is a commonly laboratory finding in clinical practice, characterised by elevated levels of thyroid-stimulating hormone (TSH) in serum in the presence of normal serum levels of free thyroxine (FT4), as compared with population-based reference ranges for
these values **(20).**
Definition of SCH according to TSH level has widely been reinvestigated as TSH testing has remarkably developed through several generations of tests but the upper decision limit has not been yet settled, especially in the elderly. Epidemiological studies reported that the upper limit of the expected normal TSH increases with age **(21).** Subclinical (without obvious symptoms) hypothyroidism (low thyroid function) describes a situation in which thyroid function is only mildly low, so that the blood level of thyroxine remains within the normal range, but the blood level of TSH is elevated, indicating mild thyroid dysfunction.
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Subclinical (without obvious symptoms) hypothyroidism (low thyroid function) describes a situation in which thyroid function is only mildly low, so that the blood level of thyroxine remains within the normal range, but the blood level of TSH is elevated, indicating mild thyroid failure **(15).**
Estimates for the prevalence of (SCH) differed by sex, age, race, and geographic location (range, 0.4–16.9%). Higher rates of (SCH) were consistently reported in women (0.9–16.9%) and older individuals (2.7– 16.9%) **(23).**
The proportion of SCH was 9.7%. A higher incidence was observed in the ≥60y (11.7%) compared to <60y individuals (8.4%), SCH subjects were more likely to have TPOAbs than euthyroid individuals. Subclinical hypothyroidism may progress to overt hypothyroidism in approximately 2-5% cases annually. All patients with overt hypothyroidism and subclinical hypothyroidism with TSH >10 mIU/L should be treated **(24)**.

Condition	**TSH mIU/L**
Mild	4–6
Moderate	6–10
Severe	Above 10

Clinical features: Subclinical term may be inexact as some of the patients have symptoms. In the elderly a diagnosis of hypothyroidism may be delayed by wrongly referring the symptoms of, for example, fatigue and constipation to ageing. Clinical manifestations can be demonstrated by assuming that a T4 level of 6-7 mcg/dL, although inside the normal range, may represent a significant decrease from a previous normal of 10 mcg/dL, and is low for this certain patient **(25).**
Individuals classified as having SCH are usually asymptomatic; although signs and symptoms of hypothyroidism, such as dry skin, fatigue, cold sensitivity, constipation and muscle cramps, are sometimes present **(23).**
No significant differences in cognitive function or hypothyroid symptoms were observed between patients and controls, whereas patients scored better than controls on the General Health Questionnaire (GHQ-30) for emotional function. In a survey carried out in Pomerania, which included 3790 participants with known

thyroid disease, 27 subjects with SHypo did not differ from controls in their mental and physical complaints. However, autoimmune thyroiditis in 47 patients was associated with negative effects on health also in euthyroid subjects. A cross-sectional study of 5865 patients at least 65 years of age with known thyroid disease (168 with SHypo defined by TSH > 5.5 mIU/liter) was done in primary care practices in England to assess the relation with cognitive function, depression, and anxiety. This study provides good evidence that Subclinical thyroid dysfunction is not associated with depression, anxiety, or cognition **(26).**

In contrast, functional magnetic resonance imaging (MRI) was used to evaluate brain function in overt and SHypo patients in comparison with euthyroid subjects. Working memory (but not other memory functions) is impaired by SHypo, and impairment is more severe in overt hypothyroidism **(27).**

Diagnosis:

Subclinical hypothyroidism is diagnosed using blood tests to measure the TSH and thyroid hormone levels.An elevated level of TSH without change in the level of thyroid hormone referes to the presence of subclinical hypothyroidism **(24)**.

Treatment:

A mildly elevated TSH level does not necessarily need treatment, especially if the patient lacks other risk factors for developing overt hypothyroidism **(23).**

Subclinical hypothyroidism may be treated with a single daily dose of thyroxine. This treatment needs monitoring of the thyroid hormone levels within the blood for several months. However, it's not certain whether it's necessary to treat subclinical hypothyroidism at all. Treatment may well be secured, especially if the blood TSH level is above10 mU/L **(24)**.

Other pituitary hormones should be evaluated in patients with central hypothyroidism, especially assessment of the hypothalamic- pituitary-adrenal axis, since hypocortisolism, if present, needs to be corrected prior to initiating thyroid hormone replacement. Levothyroxine (LT4) monotherapy remains the current standard for management of primary, as well as central, hypothyroidism. The full calculated dose can be started with for most young patients. However, treatment should be started at a low dose in elderly patients, patients with coronary artery disease and patients with long-standing severe hypothyroidism. Treatment in primary hypothyroidism is followed up with serum TSH; with a target of 0.5-2.0 mIU/L.Treatment in patients with central hypothyroidism is adapted according to free or total T4 levels, which should be preserved in the upper half of the normal range for age. In patients with persistently elevated TSH despite an apparently adequate replacement dose of LT4, poor compliance, malabsorption and the presence of drug interactions should be noted. Over-treatment is common in clinical practice and is associated with increased risk of osteoporosis and atrial fibrillation, and hence should be avoided **(24)**.

Performance of Submaximal cardiopulmonary exercise improves after six months of TSH normalisation and this improvement may help enhance the ability to carry out daily life activities **(28).**

Myxedema coma:

Myxedema coma, the extreme manifestation of hypothyroidism, is an uncommon but potentially lethal condition. Patients with hypothyroidism may exhibit a number of physiologic alterations to compensate for the lack of thyroid hormone. If these homeostatic mechanisms are overwhelmed by factors such as infection, the patient may decompensate into myxedema coma. Patients with hypothyroidism typically have a history of fatigue, weight gain, constipation and cold intolerance. Physicians should include hypothyroidism in the differential diagnosis of every patient with hyponatremia **(29).**

Workup in myxedema coma (30):-

Laboratory studies are important to confirm the diagnosis of myxedema coma. Results include the following:

- Thyroid-stimulating hormone (TSH) is elevated in most patients, indicating a primary thyroid disorder
- Free thyroxine (T4) and free triiodothyronine (T3) levels are low
- Hyponatremia with low serum osmolality
- Because of decreased renal perfusion, serum creatinine levels are usually elevated

Assessment of adrenal function should be performed, as should a complete blood count (CBC). Leukocytosis may not be seen because of hypothermia. A white blood cell differential may be one of the few clues to the presence of infection.

Chest radiography may show signs of cardiomegaly, pericardial effusion, congestive heart failure, or pleural effusion.

Electrocardiography may reveal sinus bradycardia, low-amplitude QRS complexes, a prolonged QT interval, flattened or inverted T waves, or arrhythmias.

Management of myxedema coma (31):-

Medical care in myxedema coma includes the following:

- Airway management
- Thyroid hormone replacement - The ideal mode of therapy and doses of thyroid hormone therapy in myxedema coma remain controversial due to the rarity of the condition and lack of clinical trials
- Glucocorticoid therapy - Patients with primary hypothyroidism may have concomitant primary adrenal insufficiency, while patients with secondary hypothyroidism may have associated hypopituitarism and secondary adrenal insufficiency; the other rationale for treatment with corticosteroids is the potential risk of precipitating acute adrenal insufficiency caused by the accelerated metabolism of cortisol that follows T4 therapy
- Supportive measures - Treat hypothermia with passive rewarming; treat associated infection; correct severe hyponatremia with saline and free water restriction; correct hypoglycemia with intravenous dextrose; hypotension is usually corrected with thyroid hormone therapy

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