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SUBCLINICAL HYPOTHYROIDISM –A REVIEW

ENT

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KEYWORDS

INTRODUCTION

Hypothyroidism is a condition of decreased level of thyroid hormones in the blood.In some conditions the features of hypothyroidism are overt and diagnosis is easily possible ,it a case of clinical hypothyroidism.In some cases the symptoms are subtle which may become severe if not diagnosed and treated in time it is called subclinical(mild) hypothyroidism. Untreated hypothyroidism increases morbidity and mortality. Autoimmune thyroid disease (Hashimoto thyroiditis) and Iodine deficiency in diet are commonest cause of hypothyroidism..

Listening the complain of patient patiencely , high suspicion and investigaion for hypothyroidism are the mainstay in making the diagnosis and treatment of the patient in time for prevention of future morbidities and even death due to Myxoedema. Today, the diagnosis of hypothyroidism is easily made with simple blood tests and can be treated with exogenous thyroid hormone.

Etiology

Hypothyroidism is divided in primary, caused by failure of thyroid function and secondary (central) due to the failure of adequate thyroid-stimulating hormone (TSH) secretion from the pituitary gland or thyrotrophin-releasing hormone (TRH) from the hypothalamus. Secondary hypothyroidism can be differentiated in pituitary and hypothalamic by the use of TRH test. In some cases, failure of hormone action in peripheral tissues can be recognized.

Primary hypothyroidism may be clinical, where free T_4 (FT_4) is decreased and TSH is increased or subclinical where FT_4 is normal and TSH is increased.

In secondary hypothyroidism FT_4 is decreased and TSH is normal or decreased.

Primary hypothyroidism is most commonly caused by chronic autoimmune thyroiditis, less common causes being radioiodine treatment and thyroidectomy. Salt iodination, which is performed routinely in many countries, may increase the incidence of overt hypothyroidism.

The incidence of clinical hypothyroidism is 0.5-1.9% in women and <1% in men and of subclinical 3-13.6% in women and 0.7-5.7% in men. It is important to differentiate between clinical and subclinical hypothyroidism as in clinical symptoms are serious, even coma may occur, while in subclinical symptoms are less and may even be absent. Subclinical hypothyroidism may be transformed to clinical and as recent research has shown it may have various consequences, such as hyperlipidemia and increased risk for the development of cardiovascular disease, even heart failure, somatic and neuromuscular symptoms, reproductive and other consequences. The administration of novel tyrosine kinase inhibitors for the treatment of neoplastic diseases may induce hypothyroidism. Hypothyroidism is treated by the administration of thyroxine and the prognosis is excellent

Causes of primary and secondary (central) hypothyroidism

Primary	Secondary (central)
	a. Pituitary
1. Chronic autoimmune thyroiditis	1. Pituitary adenomas
2. Iodine deficiency or excess	2. History of pituitary surgery or radiotherapy
3. Thyroidectomy	3. History of head trauma
4. Therapy with radioactive iodine	4. History of pituitary apoplexy
5. External radiotherapy	**b. Hypothalamus**
6. Drugs	1. Hypothalamic or suprasellar tumors
7. Thyroid agenesis or dysgenesis	2. History of hypothalamic surgery or radiotherapy

The important causes of hypothyroidism are-
Autoimmune thyroiditis—Hashimoto's thyroiditis, atrophic autoimmune thyroiditis
Iatrogenic—thyroidectomy, radioiodine therapy
Thyroiditis—subacute thyroiditis (also known as De Quervain's thyroiditis), silent
thyroiditis, postpartum thyroiditis

Iodine deficiency
Drugs—carbimazole, methimazole, propylthiouracil, iodine, amiodarone, lithium,
interferons, thalidomide, sunitinib, rifampicin
Congenital hypothyroidism—thyroid aplasia or hypoplasia, defective biosynthesis of thyroid hormones

Disorders of the pituitary or hypothalamus (secondary hypothyroidism)

Pathophysiology

The most common cause of hypothyroidism is the inability of the thyroid gland to produce a sufficient amount of thyroid hormone; however, less commonly pituitary and hypothalamus may also result in thyroid dysfunction. The hypothalamus secretes thyrotropin-releasing hormone (TRH) that stimulates the pituitary gland to produce thyroid-stimulating hormone (TSH). Thyroid-stimulating hormone stimulates the thyroid gland to produce and secrete mainly T4 (approximately 100-125 nmol daily) and smaller quantities of T3. The half-life of T4 is 7-10 days, and eventually, T4 is converted to T3 peripherally by 5'-deiodination. Levels of T3 majorly and T4, to some extent, in turn, exert negative feedback on the production of TRH and TSH. Alteration in the structure and function of any of these organs or pathways can result in hypothyroidism.

The decline in the production of T4 results in an increase in the secretion of TSH by the pituitary gland, causing hypertrophy and hyperplasia of the thyroid parenchyma, thereby leading to increased T3 production.

Histopathology

Autoimmune thyroiditis causes an increase in the turn over of iodine and impaired organification. Chronic inflammation of the parenchyma leads to predominant T-cell lymphocytic infiltration. If this persists, the initial lymphocytic hyperplasia and vacuoles are replaced by dense fibrosis and atrophic thyroid follicles. Co-existing or associated malignancy, such as papillary thyroid cancer, can also be seen.

History and Physical examination

It is important to maintain a high index of suspicion for

hypothyroidism since the signs and symptoms can be mild and nonspecific and different symptoms may be present in different patients. Typical features such as cold intolerance, puffiness, decreased sweating and skin changes may not be present always.

Inquire about dry skin, voice changes, hair loss, constipation, fatigue, muscle cramps, cold intolerance, sleep disturbances, menstrual cycle abnormalities, weight gain, and galactorrhea. Also obtain a complete medical, surgical, medication and family history.

History of adverse pregnancy and neonatal outcomes should also be sought.

Symptoms of depression, anxiety, psychosis, cognitive impairments such as memory loss can be present. Patients can also present with carpal tunnel syndrome, sleep apnea, hyponatremia, hypercholesterolemia, congestive heart failure, and prolonged QT interval.

Hashimoto disease is difficult to differentiate clinically; however, some features are specific for this condition such as:

Fullness of throat, Fatigue, goiter, weight gain, dryness of skin, altered voice, slow movements, Coarse and brittle hair, Dull facial expressions, Bradycardia, Prolonged ankle reflex relaxation time.

Percentage of symptoms and signs in clinical hypothyroidism (modified)[18]

Symptoms	(%)	Signs	(%)
Fatique	88	Dry coarse skin	90
Cold intolerance	84	Voice hoarseness	87
Dry skin	77	Facial periorbital oedema	76
Voice hoarseness	74	Slowed movements	73
Decreased hearing	40	Mental impairment	54
Sleepiness	68	Bradycardia <60/min	10
Impaired memory	66	Bradycardia>60/min	90
Weight gain	72		
Paresthesia	56		
Constipation	52		
Hair loss	41		

However, most of the patients have normal thyroid examination.

In subclinical hypothyroidism most patients do not have symptoms. However, some, which approximate 30%, have. In a study performed in Sweden19 24% of patients with subclinical hypothyroidism had symptoms. As shown the diagnosis of subclinical hypothyroidism can not be performed solely on the basis of symptoms and will be performed by TSH.

Usually the reported normal limits of TSH are between 0.4-4.0 mU/l. When TSH is found in the upper normal limits it may show mild hypothyroidism which may progress to hypothyroidism, especially if antibodies are increased. Michalopoulou et al27 in individuals with hypercholesterolemia and TSH in the middle to upper normal limits found that the administration of thyroxine decreased cholesterol. Positive antithyroid antibodies predispose to the development of hypothyroidism TSH may be increased in euthyroid individuals in certain situations. Increased TSH (5-20 mU/l) is observed during convalescence from non thyroidal illness (euthyroid sick syndrome), as well in pituitary adenomas producing TSH or in isolated resistance of the pituitary to thyroid hormones. Finally, TSH increase may be observed in chronic renal failure and in primary adrenal insufficiency.

Diagnosis of Hypothyroidism

The diagnosis of primary hypothyroidism is confirmed by an increase in the serum thyroid stimulating hormone concentration above the upper limit of the reference range. Adults presenting with symptomatic hypothyroidism often have a thyroid stimulating hormone level in excess of 10 mU/l, coupled with a reduction in the serum free or total thyroxine concentration below the reference range. Some body have less severe hypothyroidism, with a serum thyroid stimulating hormone that is increased (typically between 5 mU/l and 10 mU/l) but a serum thyroxine concentration within the reference range. This is termed subclinical hypothyroidism (also called mild hypothyroidism) and in many patients it represents a state of compensated or mild thyroid failure. About a 30% diurnal variation occurs in thyroid stimulating hormone levels, with a trough around 2. 00 pm and rising during the hours of darkness. This variability is conserved in mild hypothyroidism, sometimes giving the impression of fluctuating disease A small variability also exists between the different assays used for measuring thyroid stimulating hormone levels and the reference ranges quoted by different laboratories. Serum triiodothyronine concentration is often normal even in severe hypothyroidism and is not a helpful investigation in this situation. If the cause is autoimmune, circulating antibodies directed at thyroid peroxidase (formerly known as microsomal antibodies) or thyroglobulin are detectable in more than 90% and about 70% of patients, respectively.

Evaluation

Serum TSH level is used to screen for primary hypothyroidism in most patients. In overt hypothyroidism, TSH levels are elevated, and free T4 levels are low. In subclinical hypothyroidism, TSH levels are elevated, and free T4 levels are normal.[2]

Central hypothyroidism is of pituitary or hypothalamic origin. TSH produced can be biologically inactive and can affect the levels of bioactive TSH, hence the diagnosis of central hypothyroidism should be based on free T4 rather than TSH.

Labs should include evaluation for autoimmune thyroid diseases with levels of anti-thyroid antibodies such as the thyroid peroxidase antibodies.

Patients with subclinical hypothyroidism and thyroid peroxidase antibody positivity have a greater risk of developing overt hypothyroidism. The studies have shown that 50% of the patients will develop primary hypothyroidism in the course of 20 years. The decision to follow up periodically with clinical evaluation as well as lab tests is based on clinical judgment as there are no clear cut guidelines in this regard.

Hospitalized patients should undergo TSH testing only when thyroid dysfunction is suspected. Slight abnormalities of TSH in sick patients during their hospital stay should hint towards euthyroid sickness. However, if the values of TSH are very high, it does suggest hypothyroidism. "Reverse T3" will be elevated when the patient has euthyroid sickness; however, it is not routinely checked in clinical practice.

Laboratory workup may reveal hyperlipidemia, elevated serum CK, elevated hepatic enzymes, and anemia. BUN, creatinine, and uric acid levels can also be elevated.[10]

Imaging studies (ultrasound) of the neck are not routinely recommended for hypothyroidism

Indication of Screening for Hypothyroidism

While there are no universal guidelines on screening the public for thyroid disease, the American Thyroid Association recommends that screening should commence at the age of 35 and should continue every five years. Individuals at high risk for hypothyroidism include the following:

- Women over the age of 60
- Pregnancy
- Patients with a prior history of head and neck irradiation
- Patients with autoimmune disorders and/or type 1 diabetes
- Positive thyroid peroxidase antibodies
- Family history

Treatment of Hypothyroidism

Hypothyroidism is mainly treated with levothyroxine monotherapy. Replacement levothyroxine dose is 1.6 mcg/kg per day; however, in elderly and atrial fibrillation patients, it is important to reduce the dose. In order to help the absorption, levothyroxine should be taken 30-45 minutes before breakfast and at least 3 hours post-meal at bedtime which are the convenient times for most patients. . Moreover, elemental supplements such as calcium, magnesium, to name a few, do affect the absorption of levothyroxine. Commonly used medications such as proton pump inhibitors also have a negative impact on levothyroxine absorption. Maintaining a consistent formulation or brand of levothyroxine is essential.There can be slight variations in the dose of the generic formulations, which can have clinical impact in a small sub-set of very sensitive hypothyroid patients.

Drugs preventing absorption of levothyroxine

- Calcium salts
- Ferrous sulphate
- Aluminium hydroxide
- Cholestyramine

Drugs increasing clearance of levothyroxine

- Phenytoin
- Carbamazepine
- Phenobarbitone
- Rifampicin

Advice to patients with newly diagnosed hypothyroidism

- Levothyroxine has a half life of seven days in the blood stream and it will take a week or more to start to feel better. Conversely, if one tablet is missed out, there will be no noticeable effect
- If muscle weakness, stiffness, or cognitive defects are present these may take up to six months to fully resolve
- Levothyroxine should be taken on an empty stomach to maximise absorption
- Treatment is generally life long and only small changes in levothyroxine dosage are likely over that time, as determined by yearly measurements of thyroid stimulating hormone Levels.

Based on the 2012 Clinical Practice Guidelines for Hypothyroidism in Adults by American Association of Clinical Endocrinologists and the American Thyroid Association, therapy should be monitored and titrated based on TSH measurements. Serum-free T4 can also be used. Labs should be drawn every 4 to 8 weeks until target levels are achieved after starting the treatment, after any dose changes, changes in formulation or brand of levothyroxine after starting or stopping of any medications that may affect levels. If stable, then the monitoring interval can be extended to 6 months, and afterward if still, it is stable then, further monitoring can be extended to 12 months or can be done at shorter intervals on a case-to-case basis along with clinical evaluation. Central hypothyroidism should be monitored based on free T4 rather than TSH.

Patients with cardiac disease should be monitored for the development of any symptoms of angina and atrial fibrillation.If a patient is overly treated with thyroid replacement for an extended period of time, screening for osteoporosis is warranted.

Effective treatment helps to achieve a clinical improvement of signs and symptoms, along with an improved sense of patient well-being and normal TSH (or free T4 levels as applicable).However, since the symptoms of hypothyroidism are non-specific, if a patient's labs are normalized while on thyroid replacement treatment, it signifies that symptoms are not from hypothyroidism. This is a difficult situation that providers need to deal with and strong counseling skills are of great help.

A comprehensive workup for other differentials is recommended for unresolved symptoms in the presence of biochemical euthyroidism. There is a lack of strong evidence supporting the routine inclusion of triiodothyronine (T3) preparations with levothyroxine in the treatment of hypothyroidism.FDA has approved treatment options such as armor or nature thyroid; however, it is important to understand that these formulations increase risks of cardiac arrhythmias. Moreover, these formulations are not approved for pregnant patients due to the T3 component as well as in thyroid cancer patients, where strict TSH goals are required.

If symptoms persist despite normalization of TSH/free T4 levels, then non-endocrine etiologies should be considered.

Tips for non-specialists

- It may take several months before symptoms of hypothyroidism are resolved after biochemical correction of hypothyroidism.
- If thyroid stimulating hormone level is persistently raised after an adequate dose of levothyroxine, suspect poor compliance (concordance), the presence of drug interference, or malabsorption (for example, undiagnosed coeliac disease)
- If a new drug is started, think whether the drug would interfere with thyroxine absorption or thyroid hormone action; ferrous and calcium salts are common culprits
- Monitoring replacement with serum thyroid stimulating hormone alone is adequate in most patients with hypothyroidism; the important exception being those with pituitary or hypothalamic disease
- Consider referring to a specialist if symptoms do not improve or worsen after treatment with levothyroxine, if serum thyroid stimulating hormone level remains persistently raised while the patient is receiving a full dose of thyroxine, if other morbidity or complications exist (such as active and unstable ischaemic heart disease), or in pregnancy

Treating hypothyroidism in older patients and those with ischaemic heart disease Because people with longstanding hypothyroidism may have bradycardia, which can mask substantial but asymptomatic coronary artery disease,31 levothyroxine should be replaced cautiously in older patients (>60 years) or those with known ischaemic heart disease. Particular attention is required in those with profound and longstanding hypothyroidism (thyroid stimulating hormone level >50 mU/l). In these instances, or in someone with active angina pectorisor acute coronary syndrome, the starting dose of levothyroxine should be 12.5 or 25 µg daily, which should then be increased every three to six weeks until euthyroidism is achieved.

Hypothyroidism in pregnancy

Maternal hypothyroidism in pregnancy is associated with adverse obstetric outcomes and long term developmental sequelae.

The prevalence of hypothyroidism during pregnancy is 2.5%, with the most frequent form being subclinical hypothyroidism. The most common cause of hypothyroidism in women of reproductive age is AITD (Hashimoto's hypothyroidism). A history of total or subtotal thyriodoectomy, radioiodine ablation, or transient thyroiditis accounts for most of the remaining cases of hypothyroidism in pregnant women.

Risks of hypothyroidism to the fetus

Preterm delivery has been found to be three-fold more common in hypothyroid pregnant women and has also been associated with an increase in spontaneous abortions, fetal death, placental abruption, preterm delivery, and postpartum hemorrhage.

Another worrying danger associated with maternal hypothyroidism (especially when present during the first trimester) is the adverse consequence to child neuro psychointellectual development.

- **Screening of hypothyroidism during pregnancy**

Documentation of an elevated serum TSH level confirms the diagnosis of primary hypothyroidism. The presence of thyroid auto antibodies (Tabs) is a useful confirmatory finding. Serum TSH>2.5mU/L in pregnant women should be used as a guide for thyroid dysfunction. If the serum TSH is >4 mU/L irrespective of the presence (or absence) of TAbs, there is no doubt about the existence of hypothyroidism during pregnancy.

The American Association of Clinical Endocrinologists advises that all pregnant women be screened for thyroid problems. They recommend, specifically, the following:

- Anyone considering becoming pregnant should have her thyroid checked in advance.
- All pregnant women with a family history or symptoms of a thyroid disease should be tested.

A disadvantage of screening during pregnancy is of course that the fetal brain is dependent on maternal T4 from conception and by the time testing is possible (probably at the booking antenatal visit at around 14 weeks), damage may already have occurred.Nevertheless, maternal T4 is still an important source of thyroid hormone for the fetal brain during the rest of period.

Prevention of hypothyroidism: Adequate iodine supplementation is crucial to preventing maternal hypothyroidism. Fertile women with normally functioning thyroid glands should have an average iodine intake of 150 mcg/day. During pregnancy and breast feeding, women should increase their iodine intake to 250 mcg daily.23

Hypothyroid pregnant women already on LT4 replacement therapy will require a dose increase from 25% to 50% on average to maintain desirable TSH level < 2.5 mIU/L during pregnancy because they have inadequate thyroid reserve. Most hypothyroid pregnant women need a dose increase during the first trimester. In the second trimester, there is generally a plateau in LT4 requirements, but 25-40% of women may need a further dose increase during the third trimester. The increase is at least partly dependent on the thyroid reserve of the patient but also the size of the distribution space and the number of babies. Therefore, women with a history of total thyriodoectomy will be most dependent. Generally, patients with ongoing Hashimoto's thyroiditis require a 25% increase in LT4 dose, whereas the increase is more likely to be 50% in women with total thyriodctomy. Adjustments of the thyroxin

dose are made by increasing LT4 by 25-50 mg/day. Serum TSH and FT4 should always be evaluated 3-4 weeks after every change of dosage. Possible LT4 interactions with coexisting diseases such as gastritis, or medications such as iron supplements, calcium, vitamins, or omeprazole, may reduce LT4 absorption. It is best to advise a 4-hour delay between the medications and LT4 and to take the LT4 on empty stomach.

- Postpartum: After delivery, LT4 dosing generally can be returned to pre-pregnancy requirements.

Differential Diagnosis

Owing to the subtle signs and symptoms of hypothyroidism, the list of differential diagnoses is extensive. Differential diagnosis is based on signs and symptoms; for instance, fatigue can point to iron deficiency anemia, sleep apnea, depression, and rheumatological diseases.[14]

The following disorders may have to be considered in the differentials:

- Euthyroid sick syndrome
- Goiter
- Myxedema coma
- Anemia
- Riedel thyroiditis
- Subacute thyroiditis
- Thyroid lymphoma
- Iodine deficiency
- Addison disease
- Chronic fatigue syndrome
- Depression
- Dysmenorrhea
- Erectile dysfunction
- Familial hypercholesterolemia
- Infertility

Complication

Severe hypothyroidism may present as myxedema coma and is an endocrine emergency. Prompt recognition and early treatment in the intensive care unit (ICU) are essential, and even then, mortality reaches 25% to 60%.

Myxedema crisis should be suspected in cases where there is encephalopathy, hypothermia, seizures, hyponatremia, hypoglycemia, arrhythmias, cardiogenic shock, respiratory failure, and fluid retention.

Factors leading to an increased risk of myxedema crisis include inadequate doses of thyroid hormone, interruption in treatment, undiagnosed hypothyroidism, or presence of acute illness such as sepsis ,perhaps due to increased metabolic demands.

Supportive treatment should be provided in the intensive care unit with fluid and electrolyte management, ventilator support, vasopressors, treatment of coexisting acute illness, and hypothermia.

Thyroid replacement treatment is with intravenous hydrocortisone at stress doses followed by intravenous levothyroxine then switched to oral levothyroxine after clinical improvement. The reason to give steroids is that these patients may have adrenal insufficiency, which can lead to an Addisonian crisis if the thyroid deficiency is replaced without addressing adrenal insufficiency. It is recommended to check for Adrenal insufficiency but wait for the results and start treatment with steroids.

If the treatment is effective, this should result in cardiopulmonary and cognitive improvement. There should also be an associated improvement in laboratory derangements, including an up-trending of free T4, which should be measured every 1 to 2 days during the initial treatment period. Low dose intravenous liothyronine (T3) can be considered until initial improvement. TSH may not reflect changes in such cases as it can take up to 4 weeks to normalize, hence it may not be helpful.

SUMMARY POINTS

In adults with newly diagnosed hypothyroidism who are under 60 and without ischaemic heartb disease it is safe and efficient to start on a full replacement dose of levothyroxine Levothyroxine replacement dose is related to body mass; a daily dose of about 1.6 µglevothyroxine/kg body mass is adequate replacement for most adults (equivalent to 100 µgdaily or 125 µg daily for an average size woman or man, respectively)

Elderly people and those with ischaemic heart disease should start on a small dose of levothyroxine, and the dose increment should be gradual Current evidence does not support a clinical benefit from the use of a combination of levothyroxine and liothyronine (triiodothyronine) over levothyroxine alone in the treatment of hypothyroidism.

Prognosis

Without treatment, hypothyroidism may have a risk of high morbidity and mortality. It can eventually lead to coma or even death. In children, failure to treat hypothyroidism can result in severe mental retardation. A leading cause of death in adults is heart failure. With treatment, most patients have a good prognosis, and the symptoms usually reverse in a few weeks or months.

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