REVIEW ARTICLE

Hypothyroidism - new aspects of an old disease

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Abstract

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. Hippokratia 2010; 14 (2): 82-87

Key words: hypothyroidism, chronic autoimmune thyroiditis, postpartum thyroiditis, antithyroid antibodies, myxedema coma, congenital neonatal hypothyroidism

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Hypothyroidism is the most common disorder arising from hormone deficiency. According to the time of onset it is divided in congenital and acquired, according to the level of endocrine dysfunction in primary and secondary or central and according to the severity in severe or clinical and mild or subclinical hypothyroidism. The distinction between subclinical and clinical hypothyroidism is of major significance as in clinical hypothyroidism symptoms are more severe even coma may occur, while in subclinical hypothyroidism symptoms are less serious and may even be absent. The diagnosis may be easily performed by the measurement of blood levels of thyroid hormones. Therapy of choise is the administration of thyroxine and the prognosis is very good.

Cellular and biochemical pathophysiology

Thyroxine (T_4) and triiodothyronine (T_3) are produced from the thyroid gland. T_4 is produced only from the thyroid, whereas T_3 from the thyroid and from T_4 deiodination in extrathyroidal tissues. T_3 deficiency is responsible for the clinical and biochemical manifestations of hypothyroidism. Thus, basic intracellular functions such as oxygen consumption by the mitochondria and calorigenesis are slowed down. The decrease in energy metabolism and heat production is reflected in the low basal metabolic rate, decreased appetite, cold intolerance, and slightly low basal body temperature.

T_4, which is the main product of the thyroid and circulates in plasma, is converted to T_3, T_4 being in many respects considered as a prohormone for the more potent T_3. This is performed in the cytoplasm and the nuclei of target tissue cells by three specific deiodinases with the subtraction of a molecule of iodine from the peripheral ring of T_4[1]. Deiodinases have a diverse localization in tissues, diverse substrates and diverse behaviour in various drugs and diseases. It is believed that the effect of T_3 in target tissues is mediated genomically by T_3 binding to one of the T_3 receptor isoforms[2].

There is increasing evidence for non-genomic effects of T_3 in addition to the transcriptional effects mediated by the nuclear receptors[3].

Aetiology

The commonest causes which are responsible for the development of primary and secondary or central hypothyroidism are shown in Table 1.

Table 1: 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

Primary hypothyroidism

Primary hypothyroidism is due to a disorder of the thyroid gland causing decreased synthesis and secretion of thyroid hormones. Hypothyroidism, which in 50% of the cases is of autoimmune aetiology, is observed in chronic autoimmune thyroiditis. In the remaining 50% it is due to other causes or drugs. Recently, postpartum thyroiditis and silent thyroiditis, which may cause hypothyroidism, are considered as manifestations of chronic autoimmune thyroiditis.

Chronic autoimmune thyroiditis affects 3-5 times more frequently women than men, usually middle aged or older, as well as children. The role of autoimmunity is supported by the histological findings of diffuse lymphocytic infiltration of the thyroid gland and by the circulation of specific antibodies in almost all patients[4]. Increased levels of anti-TPO antibodies are found in 95% and antithyroglonulin antibodies in 60% of the cases being higher in the atrophic than the goitrous form of the disease. The prevalence of Hashimoto's thyroiditis is great in micronodular goiter. Yeh et al[5] in patients with micronodules 1- 6.5 mm in diameter detected antithyroid antibodies in 94.7% of the cases. Increased levels of antithyroid antibodies are found in other thyroid diseases, as well, but at a lower prevalence. In chronic autoimmune thyroiditis both types of antithyroid antibodies are usually detected, rarely, only one type being detected. Takamatsu et al[6] in 437 patients, found both types of autoantibodies positive in 316, only one in 85 and none in 36. Amongst patients positive for autoantibodies 50-75% are euthyroid, 25-50% have subclinical hypothyroidism, and 5-10% clinical hypothyroidism. Genetic and exogenous factors predispose to the development of chronic autoimmune thyroiditis. The genetic factors recognized so far are few, including genes encoding the major histocompatibility complex (HLA)[7] and the gene encoding antigen 4 of cytotoxic T lymphocytes (CTLA-4)[8]. The mechanisms by which these genes contribute to increased susceptibility to Hashimoto's thyroiditis remain obscure. A polygenic factor for autoimmune thyroiditis is suggested by linkage of the disorder to several genetic loci in affected kindreds[9]. The recognition of the above genes does not fully explain the heritability observed in families of patients with Hashimoto's thyroiditis. Other genetic factors seem to exist within the human genome which predispose to the development of chronic autoimmune thyroiditis. Infection and iodine intake have been most studied amongst exogenous factors predisposing to the development of chronic autoimmune thyroiditis. There is some evidence that infectious agents may predispose to the development of autoimmune thyroiditis. Thus antibodies against Epstein-Barr virus have been found in children with autoimmune thyroid disease[10] and acute parvovirus B19 infection has been found to be associated with Hashimoto's thyroiditis in children[11]. Infectious agents may cause autoimmunity via tissue destruction or molecular mimicry. Higher incidence of antithyroid antibodies has been found in residents of areas with iodine sufficiency than in those with iodine insufficiency, while in cases of iodine insufficiency the presence of autoimmune thyroiditis was correlated with higher iodine excretion in the urine[12]. Salt iodination has been found to increase the incidence of overt hypothyroidism. The antigenicity of thyroglobulin increases when it is rich in iodine[13] and iodine may react with active oxygen metabolites and produce free iodine radicals with proinflammatory actions[14].

Postpartum thyroiditis, which appears during the first year after delivery and affects 5%-10% of women, is due to the presence of antithyroid antibodies which increase after delivery. It presents with mild hyperthyroidism which may be transformed to hypothyroidism and may subside without therapy or may present only with hypothyroidism and should be managed by thyroxine for a duration of up to 6 months. However in 25% of cases hypothyroidism may persist for up to 4 or more years.

Silent thyroiditis presents with mild, of recent onset hyperthyroidism. It is due to the secretion of thyroid hormones in the circulation, due to cell lysis and subsides in 6-12 weeks or is transformed in 50% of the cases to transient hypothyroidism, which subsides in 2-12 weeks. Rarely, in up to 5% of the cases, hypothyroidism becomes permanent.

Iodine insufficiency is a common cause of hypothyroidism[15]. These patients usually have a large goiter. Transient hypothyroidism may occur after the ingestion of large amounts of iodine and is referred to as Wolff-Chaicoff effect, due to the inhibition of hormone synthesis within the thyroid. It appears that there is a mild enzyme disorder which is corroborated by the ingestion

of iodine agents. Increased amounts of iodine are found in contrast agents and in the drug amiodarone.

In partial thyroidectomy for hyperthyroidism clinical hypothyroidism has been found in 17% and subclinical in 51.3% whereas in partial thyroidectomy for various disorders clinical hypothyroidism has been found in 27%. In Graves' disease mild and sometimes transient hypothyroidism is observed during the first 6 months after radioiodine therapy.

External radiotherapy of the head and neck, as well as whole body irradiation may cause damage to the thyroid and lead to hypothyroidism. Hypothyroidism appears after a rather large time period[16].

Various drugs may cause hypothyroidism, the commonest being the widely used drugs amiodarone and lithium. Interferon-a may also cause hypothyroidism, usually mild. The new tyrosine kinase inhibitor Sunitinib, an anticancer agent, has been shown to cause hypothyroidism[17].

Children and infants may develop hypothyroidism due to thyroid agenesis or dysgenesis and a disorder of thyroid hormone biosynthesis. Antithyroid drug therapy in pregnant women who have hyperthyroidism may lead to hypothyroidism in newborn infants.

Generalized resistance to thyroid hormones is a rare, autosomal recessive disorder caused by a mutation in the T_3 receptor gene. The TSH level is usually normal and T_3 and T_4 levels are elevated. Patients are usually euthyroid and do not require thyroid hormone replacement.

Secondary (central) hypothyroidism

Secondary hypothyroidism is caused by a disorder of the pituitary or the hypothalamus, leading to decreased TSH secretion and consequently to decreased synthesis and secretion of thyroid hormones. Secondary hypothyroidism is also reported as central and is divided in secondary and tertiary when the causes are in the pituitary and the hypothalamus, respectively.

A variety of disorders can cause secondary hypothyroidism. The most common causes are pituitary adenomas as well as surgery and/or radiotherapy, used to treat them.

Diagnosis

The diagnosis of hypothyroidism is made from the history, the clinical picture and the laboratory measurements.

History and clinical picture

The symptoms and signs of clinical hypothyroidism are shown in Table 2[18]. The appearance of symptoms depends on the degree of its severity. This is related to the degree of alteration in biochemical examinations. In the beginning manifestations are mild, may be differentiated with difficulty from those of euthyroid patients and may be aggravated with time. In a study, only 30% of hypothyroid patients had some of the symptoms, 17% of euthyroid patients having at least one. The evaluation of symptoms is performed either when they are newly developed, or when recent aggravation of already existing symptoms is observed. Many times the question arises as to whether an increase in body weight is related to hypothyroidism. This symptom should be evaluated under the condition that it is a small increase in body weight in the order of 3 to 6 kg and not an excessive weight gain and that there are other coexisting symptoms. It should be noted that hypothyroid individuals may also exhibit a decrease in body weight in the order of 2 to 13%. In severe hypothyroidism there are various clinical manifestations such as congestive heart failure, pericarditis, pleural effusion, intestinal obstruction and pseudo-obstruction, as well as coagulation disorders. Neurologic manifestations may also develop such as depression, psychosis, ataxia, seizures and coma. Neurocognitive deficits may also develop, particularly in memory.

In subclinical hypothyroidism most patients do not have symptoms. However, some, which approximate 30%, have[19]. In a study performed in Sweden[19] 24% of patients with subclinical hypothyroidism had symptoms. As shown the diagnosis of subclinical hypothyroidism can

Table 2: 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		

not be performed solely on the basis of symptoms and will be performed by TSH measurement. Subclinical hypothyroidism is a risk factor for cardiovascular disease. This increased risk is attributed to the increase in cholesterol.

Flak et al[20] in elderly women found that subclinical hypothyroidism is a risk factor for atherosclerosis and myocardial infarction, irrespective of total cholesterol levels, high density lipoprotein, smoking and various other factors. Brenta et al[21] while did not find a cholesterol increase in subclinical hypothyroidism, they found decreased activity of hepatic lipase and of LDL cholesterol/LDL-triglyceride ratio suggesting a proatherosclerotic index. In a recent study it was found that subclinical hypothyroidism in older adults increases the risk of heart failure[22]. In subclinical hypothyroidism besides the cardiovascular effects, various disorders have been found such as disorders of nerve conduction and muscular function, disorders of the reproductive system, fertility problems[23], increased placental detachment and premature labor[24], decreased infant birth weigh[25] and others.

In congenital neonatal hypothyroidism hypothermia, bradycardia, jaundice, feeding unwillingness, apathy, voice hoarseness, constipation and omphalocele are mainly observed. However, in early stages there may be few symptoms. Thus, measurement of thyroid hormones is considered necessary. In children growth retardation, mental retardation, voice hoarseness, constipation and either retarded or premature sexual maturation are mainly observed. Diagnosis and management of congenital hypothyroidism should be performed with caution. Kempers et al[26] measured T_4, TSH and TBG in 430,764 newborn infants and found congenital permanent, permanent primary, permanent central and transient hypothyroidism in 1:2200, 1:2500, 1:21000 and 1:12000 respectively, while they had a large proportion of false positive results due to serious disorders and TBG deficiency.

Laboratory evaluation

TSH and FT_4 measurement are the laboratory examinations necessary for the diagnosis of hypothyroidism and the differential diagnosis between primary (clinical or subclinical) and secondary one.

When TSH is increased and FT_4 is decreased or normal hypothyroidism is primary. In this case increased anti-TPO or anti-Tg antibodies point to the cause of hypothyroidism, which is autoimmune thyroiditis. Primary hypothyroidism is divided in clinical when TSH is increased and FT_4 is decreased and in subclinical when TSH is increased and FT_4 is normal. When TSH is normal or decreased and FT_4 is low hypothyroidism is secondary (central). In order to discriminate whether the cause is in the pituitary or the hypothalamus a test with the TSH releasing factor is performed (TRH test). In the first case the response is normal, while in the second it is abnormal. In central hypothyroidism imaging studies of the brain and the pituitary are performed aiming at finding its cause.

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 al[27] 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.

Therapy

Hypothyroidism therapy is performed with the administration of thyroxine, which is transformed by 80% in peripheral tissues to T_3.

The daily dose of thyroxine in the initiation of substitution therapy depends on various factors, such as body weight, age, the presence of coronary artery disease and cardiac arrhythmias. In adults the dose is about 1.8 μg/kg body weight, is higher in neonates and young children (3.8 μg/kg) and lower in the elderly (0.5 μg/kg). The dose is higher in individuals having been subjected to thyroidectomy than those with chronic autoimmune thyroiditis, as in those there are remnants of functioning thyroid tissue. In subclinical hypothyroidism the dose is low (0.5 μg/kg). In pregnancy, finally, a larger dose is required (2 μg/kg). During pregnancy the increase in dose that may be required is 25-47% more than the one before pregnancy and it is observed during the 4^{th} to 6^{th} week.

In young and healthy adults therapy may be commenced with the complete dose and not necessarily with small doses. However, in the elderly or patients with coronary artery disease 25-50 μg are administered daily and the dose is increased by 12.5 or 25 μg every 2 weeks. TSH measurement after the initiation of therapy is performed every 4-6 weeks until TSH becomes normal. The follow-up is performed by TSH measurement once every year. In pregnancy the first TSH measurement should be performed when pregnancy is diagnosed and thereafter every 3-4 weeks during the first half of the pregnancy and every 6 weeks thereafter. TSH in primary hypothyroidism on substitution therapy should be in the mean levels to lower normal limits (approximately 1.0 mU/l), whereas in secondary TSH measurement does not help. FT_4 and sometimes FT_3 measurement is performed and the values should be in the upper half of the normal range.

In congenital hypothyroidism according to Rose et al[28] the measurement and therapy should be performed during the first 2 weeks of life for the avoidance of the consequences of hypothyroidism. This measurement

has been instituted in various places of the world, and in Greece, but not everywhere. In neonates the initial dose is 10-15 μg/kg. Thereafter frequent TSH measurement is needed, which should be normal and T_4 or FT_4, which should be in the upper half of normal values during the first 3 years of life.

In subclinical hypothyroidism there is no consensus as to whether thyroxine should be administered. In guidelines from various associations and colleges of physicians (Table 3)[29-33] as to whether therapy is needed or not for subclinical hypothyroidism, all agree, apart from the American College of Physicians, which does not hold a definitive position, that thyroxine should be administered if antibodies are positive.

Table 3. Practical guidelines from Medical Societies and Colleges of Physicians regarding the need for therapy of subclinical hypothyroidism, in relation to the presence or absence of antibodies

Subclinical hypothyroidism (Therapy)				
Antibodies	AACE[29]	ATA[30]	ACP[31-32]	RCP[33]
Positive	Yes	Yes	?	Yes
Negative	Yes (No)	Yes / No	No (Yes)	No (Yes)

AACE (American Association of Clinical Endocrinologists): In manycases yes especially if antibodies positive, caution in elderly or in cardiac failure with slightly increased TSH.
ATA (American Thyroid Association): Possibly yes, especially if anti-TPO antibodies positive or yearly follow-up.
ACP (American College of Physicians): Generally not justified. Yes in women over the age of 50 if symptoms exist including high cholesterol, no in young women and men or if slightly increased TSH (0.6-9 mU/l) as it is not beneficial.
RCP (Royal College of Physicians United Kingdom): Yes, if anti-TPO positive or TSH> 10 mU/l, follow up if anti-TPO negative and TSH< 10 mU/l.

In myxedema coma, which is the most severe form of hypothyroidism and occurs in long-term not treated hypothyroidism the danger of death was 60-70% in 1985 but it has decreased to 20-25%, owing to the timely diagnosis and the referral of patients to acute care units. Intravenous thyroxine is administered at a dose of 200-400 μg during the first 2 days and thereafter at normal doses. During the first day of treatment hydrocortisone 100 mg every 8 hours is also administered and hypothermia, hypoglycemia, hypotension, hyponatremia and hypercalcemia are appropriately treated.

Great caution is needed in substitution therapy with thyroxine as dose overestimation has consequences. It has been observed that more than one fifth of the patients have clinical or subclinical hyperthyroidism. These consequences are atrial fibrillation, aggravation of coronary artery disease and a decrease in bone mineral density, fractures of the spine and the hip being observed in women >65 years.

Hypothyroidism is not always properly treated by the administration of thyroxine, as there are differences in the activity, stability and bioavailability between different batches of thyroxine which may even be provided by the same manufacturer. Koutras[34] commenting on the aforementioned problems suggests the following: a) authorities should insist on bioavailability studies of thyroxine preparations, b) physicians should instruct their patients to take thyroxine while fasting for at least 4 hours, and avoid food for at least 20-30 minutes, as well as to avoid other drugs for at least 30 min after the thyroxine tablet and be aware of food items or fruit juices that may interfere with thyroxine absorption, c) physicians should not frivolously change from one thyroxine brand to another on the assumption that 100 μg thyroxine from brand A equals 100 μg from brand B d) physicians should report to the authorities if they have suspicious results in several patients.

Hypothyroidism is not always permanent and a percentage of patients exists in whom thyroid function may be normal after thyroxine discontinuation. The normalization of thyroid function may be more related to the antibodies to TSH receptor than to anti-TPO or anti-Tg antibodies, the titles of which very little may be influenced by thyroxine administration. The percentage of hypothyroidism normalization after thyroxine administration is between 0-24%, mean 10%.

In conclusion, hypothyroidism is a frequent disease, affecting more women than men. The negative consequences of hypothyroidism, which are frequent, dictate its timely diagnosis. The measurement of thyroid hormones in women after the age of 50, in pregnancy and after delivery, in women and men with hypercholesterolemia, in patients having had neck radiotherapy, in patients having been given drugs, such as amiodarone and lithium, appears appropriate. Therapy is long term, usually life long and is performed by the administration of thyroxine.

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Conflict of Interest Statement

No conflict of interest is declared by any of the authors.