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Review Article

Management of Hypothyroidism in Adults

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ABSTRACT

Hypothyroidism is a common endocrine disorder. Lifelong replacement with Levothyroxine is the standard treatment of primary hypothyroidism. It has a long half-life of seven days making it a convenient daily dosage for the patient. Full anticipated doses of thyroid hormone can be started in young adults and otherwise healthy individuals. 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 increments after no less than 4-6 weeks.

Subsequent monitoring is also simple with TSH estimation. Once the desired TSH level in achieved, annual monitoring can be done. A small subgroup of patients well controlled on levothyroxine monotherapy with TSH in euthyroid range still complain of persistent symptoms suggesting that a combination of thyroxine and triiodothyronine may improve the quality of life in such patients.

Key Words: Hypothyroidism, Thyroxine, Triiodothyronine.

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INTRODUCTION

Hypothyroidism is one of the most common endocrine disorder of thyroid function where in the thyroid gland is unable to synthesize and secrete sufficient amount of thyroid hormone to meet the requirement of human body.

Hypothyroidism can be either subclinical or overt. Subclinical hypothyroidism is basically a biochemical entity characterized by a TSH level which is above the reference limit of normal along with normal levels of FT4 and FT3.

Definition of Overt and Subclinical Hypothyroidism[1, 2]

THYROID DISORDER	Free T3	Free T4	TSH
▪ **Overt hypothyroidism**	Reduced	Reduced	Elevated
▪ **Subclinical hypothyroidism**	Normal	Normal	Elevated

Overt hypothyroidism is characterized by an elevated serum concentration of TSH along with low FT4and FT3. This article shall deal with the management of overt hypothyroidism in non-pregnant adults.

EPIDEMIOLOGY

The incidence of hypothyroidism is estimated to be 4-5 per thousand per year for women and 0.6 to 0.9 per thousand per year for men[1] .The prevalence of overt hypothyroidism is 1%-2% in women and 0.1% in men[2]. Hypothyroidism is ten times more common in women compared to men and occurs more frequently in elderly women.

CAUSE OF OVERT HYPOTHYROIDISM

Iodine deficiency has been the most common cause of hypothyroidism world over. In areas of Iodine sufficiency chronic autoimmune thyroiditis is the most common cause of hypothyroidism. Chronic lymphocytic thyroiditis is characterized by elevated titer of Thyroid Peroxidase Antibodies (TPO). In patients with Subclinical hypothyroidism, TPO positivity predicts the risk of progression to overt hypothyroidism.

The risk of progression to overt hypothyroidism is 4.3 % per year in females who are positive for TPO Antibodies and 2.6% per year in women who are negative for anti TPO antibodies[3]. Patients suffering from chronic lymphocytic thyroiditis may also suffer from other autoimmune diseases like type 1 diabetes, Rheumatoid arthritis, Systemic lupus erythematosis, Addison`s disease, Celiac disease and Myasthenia gravis[4].(Table 1) The most common cause of hypothyroidism is Chronic lymphocytic thyroiditis which is characterized by elevated titer of Thyroid Peroxidase Antibodies (TPO).

In patients with Subclinical hypothyroidism, TPO positivity predicts the risk of progression to overt hypothyroidism.

Surgical removal of the thyroid gland, radioactive iodine ablation of thyroid gland or external beam radiation of head and neck

region can also lead to hypothyroidism. Congenital hypothyroidism can occur due to thyroid agenesis or hypo genesis or dysgenesis. Congenital hypothyroidism can also occur due to functional defects in thyroid hormone biosynthesis. It may be due to a loss of function mutation in genes encoding for TSH receptor, thyroglobulin, TPO etc. It affects 1 in 4000 live births[5].

Table 1: Causes of Hypothyroidism

1)Auto immune Thyroiditis
2)Thyroid Injury(post ablative)
➢ **Thyroidectomy**
➢ **Radio Active Iodine Therapy**
➢ **External Radio Therapy of head and neck region**
3)Drugs
➢ **Lithium**
➢ **Amoidarone**
➢ **Interferon α**
➢ **Interleukin 2**
➢ **Tyrosine kinase inhibitors**
➢ **Radio graphic contrast agents**
4)Thyroid infiltrative Disease
➢ **Sarcoidosis**
➢ **Amyloidosis**
➢ **Cystinosis**
➢ **Haemochromatosis**
➢ **Primary Thyroid lymphoma**
5)Genetic Factor
➢ **Loss of Function mutation in TSHR,TTf-1(thyroid transcription factor)**
➢ **Inactivating PAX8 mutations.**

Table 2--SIGNS AND SYMPTOMS OF OVERT HYPOTHYROIDISM[6]

➢ **DRY COARSE SKIN**	➢ **DEPRESSION**
➢ **COLD INTOLERANCE**	➢ **CARPEL TUNNEL SYNDROME**
➢ **WEIGHT GAIN**	➢ **HEARING IMPAIRMENT**
➢ **FACIAL PUFFNESS**	➢ **BRADYCARDIA**
➢ **WEAKNESS**	➢ **SLOW RELAXING TENDON REFLEXES**
➢ **FATIGUE**	➢ **DYSLIPIDEMIA**
➢ **LETHARGY**	➢ **IMPAIRED CONSCIOUSNESS (MYXOEDEMA COMA)**
➢ **DYSPONEA**	➢ **GOITRE**
➢ **ANOREXIA**	➢ **HOARSENESS OF VOICE**
➢ **MENORRHAGIA**	➢ **PRIMARY INFERTILITY**
➢ **CONSTIPATION**	
➢ **HAIR LOSS**	

SIGNS AND SYMPTOMS OF OVERT HYPOTHYROIDISM

Overt biochemical hypothyroidism may have minimum signs and symptoms because the disease usually has an insidious onset. Moreover, the symptoms of hypothyroidism are non-specific and include fatigue, constipation, dryness, cold intolerance, menstrual irregularities and weight gain.[6] (Table 2)

Hypothyroidism can have age and sex specific symptoms for example in children it manifests as impaired growth velocity, in women of reproductive age it can lead to mennorhagia and in elderly individuals hypothyroidism can lead to impaired memory and cognitive dysfunction. Hypothyroidism has profound effect on dermis, epidermis, hair and nail. Hair becomes dry, coarse and brittle with generalized alopecia. There could be Thinning of lateral portion of eyebrows. Vitiligo, an auto immune disorder can also occur in association with hypothyroidism. Hypothyroidism reduces gastro intestinal tract motility leading to constipation .Thyroid hormone deficiency can cause poor concentration, impaired memory and cognitive dysfunction. Physical signs in overt hypothyroidism include periorbital puffiness, cold skin, hoarseness of voice, slow pulse and slowing of recovery phase of ankle jerk.

In severe hypothyroidism patient may present with congestive cardiac failure, pericardial effusion, pleural effusion and intestinal obstruction.

Myxedema coma is a rare but life threatening complication of untreated hypothyroidism. Signs and symptoms include hypothermia, bradycardia, hypotension, altered mental status and eventual respiratory failure from hypoventilation and carbon dioxide retention.

HISTORICAL ASPECTS OF TREATMENT OF HYPOTHYROIDISM

China is one of most ancient civilizations to have used seaweed for the treatment of Goiter. Dry seaweed was imported into the Andrean highlands which was endemic for Goiter at that time.

In the year 1891 George Murray for the first time treated Hypothyroidism with a subcutaneous injection of sheep thyroid extract. A year later, he showed that oral administration of sheep extract was as effective as inject able treatment[7]. It was in year 1914 that Edward Kendall isolated and crystallized thyroxine. But it was only in 1926 when C R Harrington identified the chemical structure of this hormone and named it Thyroxin. It was only after the synthesis of sodium salt of Levothyroxine in 1949 that levothyroxine became the mainstay of therapy for hypothyroidism as this salt was better absorbed than T4 itself. Year 1952 saw the discovery of second more potent hormone Liothyronine (T3)[8]. The credit of discovery of T3 goes to Gross and Pitt-Rivers in the United Kingdom. Although synthetic hormone was made available for clinical use since 1930s but desiccated thyroid preparation continued to be the preferred treatment for hypothyroidism till 1960.It was only in 1970s that synthetic levothyroxine replaced desiccated porcine and bovine thyroid extract as the most commonly employed therapy for primary hypothyroidism.

TREATMENT OF HPOTHYROIDISM

Treatment of hypothyroidism has several objectives .The most important goal is to normalize serum TSH, to relive the symptoms of hypothyroidism and to restore euthyroid state in the body.

Levothyroxine is the treatment of choice for hypothyroidism. Levothyroxine is chemically stable and absorption after oral route is fairly acceptable. The half-life of the tablet is seven days allowing a convenient once daily dose.

GOALS OF MANAGEMENT OF HYPOTHYROIDISM

- **Normalization of serum TSH**
- **Restoration of euthyroid status in body**
- **To relive the symptoms of hypothyroidism**
- **To avoid over treatment and under treatment of hypothyroidism**

When treating young healthy adults, we can start with a full replacement dose of 1.6 mcg/Kg/day. As we know Levothyroxine has a long half-life of seven days, the dose has to be taken once daily on an empty stomach in the morning. Steady state concentrations are achieved in six weeks' time and therefore in order to titrate the dose repeat TSH should be performed only after 6 -8 weeks of initiation of replacement therapy[9].

Once the desired TSH is achieved a repeat TSH can be safely repeated after 6 months to ensure that euthyroid state is maintained. Some patients may be having under replacement or over replacement of the dose and may require the titration of dose to bring the patient to euthyroid state. Continuing therapy with this correct dose shall then maintain the desired TSH .Stable patients can be monitored on an annual basis.

Levothyroxine is taken on empty stomach and an acidic P^H in the stomach is required for subsequent intestinal absorption of Levothyroxine .When Levothyroxine is co administered with food, there is reduced absorption of Levothyroxine

In patients known to have ischemic heart disease treatment of overt hypothyroidism is started with lower doses such as 12.5-25 micro grams per day. In patients who have hypothyroidism and Adrenal insufficiency, cortisol replacement should be started concurrently with levothyroxine to avoid precipitation of adrenal crisis.

Approximately 40% to 48% patients of hypothyroidism taking levothyroxine are either undertreated or over treated[10]. Overtreatment with levothyroxine is associated with a significant increased risk of fractures due to osteoporosis. The other main adverse effect of overtreatment with levothyroxine is the development of atrial fibrillation. The elderly people are particularly susceptible to it, while the post-menopausal women are especially prone to bone loss and osteoporosis. Therefore monitoring the dose of levothyroxine especially in elderly patients is important to avoid overtreatment in this population[11].

TREATMENT OF HYPOTHYROIDISM IN PREGNANCY

Hypothyroid women willing to get pregnant ought to receive optimal replacement with levothyroxine prior to conception. Treating physicians should try to achieve a target TSH of 0.5-2.0 m IU/L in the preconception period .In women with known hypothyroidism, a serum TSH must be done immediately as soon as the pregnancy is confirmed. At least 50%of women with hypothyroidism will require an increase in their usual replacement doses during pregnancy. The recommended dosage of levothyroxine for treatment of overt hypothyroidism in pregnancy is 1.6-1.8 µg/Kg/day. The dose is 25% to 50% higher in pregnancy.TSH should be monitored regularly at an interval of 4 weeks until TSH is normalized. The goal of treatment is to normalize maternal serum TSH values within the trimester-specific pregnancy reference range for TSH, as defined in populations with optimal iodine intake. If trimester-specific reference ranges for TSH are not available in the laboratory, the following reference ranges are recommended: first trimester, 0.1–2.5 mIU/L; second trimester, 0.2–3.0 mIU/L; third trimester, 0.3–3.0 mIU/L11[12].

FUTURE INSIGHTS INTO THYROID HORMONE REPLACEMENT THERAPY

Thyroxine monotherpy is the mainstay of treatment of primary overt hypothyroidism. However, few patients adequately treated with thyroxine monotherapy still complain of non-specific symptoms even when the serum TSH levels are within normal range. It is possible that levothyroxine monotherapy may not be able to normalize serum T 3levels and therefore triiodothyronine may be used in such sub group of patients.

In1999, Bunevicius described an increase in general well-being of the patients who were given a combination of T4 and T3 compared to those who were treated with thyroxine montherpy[13]. A meta-analysis of 11 randomized controlled trials with a total of 1216 patients indicated that T4/T3 combination therapy provided no advantage when compared to standard thyroxine monotherpy in improving the psychological symptoms or improving the lipid parameters of hypothyroid patients[14]. A second meta-analysis including 1243 patients suggested that T4/T3 combination therapy is beneficial for the psychological well-being of patients previously treated levothyroxine monotherapy[15]. So, different trials have given conflicting results and until clear advantage of levothyroxine plus triiodothyronine is demonstrated, the administration of levothyroxine alone should remain the treatment of choice for replacement therapy of hypothyroidism.

Several studies have shown that polymorphism in D2 gene (D2Thr92Ala) is associated with a better response in terms of both physical and psychological well-being when treated with a combination therapy of levothyroxine and triiodothyronine[16].

The potential benefits of combination therapy with levothyroxine and triiodothyronine can only be addressed by performing large scale randomized control trials using a correct ratio of T4 to T3 keeping in mind that the endogenous thyroid gland secretes T4 to T3 in the ratio of 14:1.

SUMMARY POINTS

- **Adult hypothyroidism is a widely prevalent endocrine disorder**
- **All adults with overt hypothyroidism should be treated with levothyroxine monotherapy**
- **Full replacement doses of 1.6µg/kg may be initiated in young adults not suffering from other co morbid conditions.**
- **Levothyroxine is taken on an empty stomach as first thing in the morning with few sips of water.**
- **Repeat TSH is done after 8 weeks for dose titration.**
- **Elderly patients or patients suffering from ischemic heart disease, heart failure or arrhythmias should be initiated with low doses of levothyroxine (12.5-25µg)**
- **Once target TSH is achieved ,repeat TSH levels should only be repeated after 6-12 months**

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