Review Article

Optimal management of Hypothyroidism

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Hypothyroidism was the first of the endocrine disease treated by replacement of the deficient hormone with extracts of animal thyroid glands. The development of more purified and synthetic thyroid hormone preparations have made it possible to mimic the function of thyroid gland with thyroid hormone replacement. The treatment of hypothyroidism with synthetic thyroxine is quite safe and well tolerated by most of the patients and can be continued for prolonged periods without a need to bring about many changes in dosage. This review article looks into the practical aspects of management of hypothyroidism.

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Hypothyroidism is one of the most prevalent endocrine disorder. The manifestations of the condition can vary from subtle to overt. Most of the manifestations respond well to appropriate replacement of thyroxine.

Pharmacology of Thyroxine :

Thyroxine is available in India in the form of tablets (four to five pharmaceutical brands) of varying strengths from 25 to 200 ug with 100 ug is the most widely used and easily available strength. Tri-iodothyronine (T3) tablets are not available in most of the cities and no parenteral preparation has been marketed in India. Thyroxine tablet seems to be stable if stored properly at room temperature with long shelf life but may lose potency if exposed to moisture, light or air. About 60-80% of the administered dose is absorbed relatively slowly (in comparison to tri-iodothyronine, which is rapidly absorbed), primarily from proximal small intestine, jejunum. Presence of food has been found to be associated with 30-40% reduction in thyroxine absorption. Ideally, thyroxine should be taken on empty stomach in morning as a single dose and any caloric intake should be avoided for next 30 minutes. Although half life of thyroxine is about 7 days, it is better to take the tablet at the same time every day, to improve compliance.

Initiation of Treatment :

The goal of treatment of a patient suffering from hypothyroidism is to achieve euthyroid state and normalize thyroid function. The initial starting dose of thyroxine depends on patient's age, presence of coronary artery disease and arrhythmias. Thyroxine can be started with full replacement dose (1.6-1.7 ug/kg body weight) in case of a healthy young or middle aged individual with no history of coronary artery disease[1]. In case of elderly persons and patients with history of coronary artery disease, replacement should be started with lower dose. The starting dose may be 25-50 ug/day with increment of not more than 12.5-25 ug. Patients should be clearly explained about possibility of aggravation of symptoms of coronary artery disease, especially chest pain. In case if patient develops chest pain on starting or increasing the dose, it may be decreased up to 50% and cardiac evaluation should be done before increasing the dose further.

Monitoring of Therapy :

Monitoring of adequacy of thyroxine therapy can easily be done by measurement of serum TSH levels. Samples for serum TSH can be collected at any time of the day, irrespective of food intake (fasting is not required) but morning samples are better. Patient should be instructed to take morning replacement dose only after sample collection. The first re-evaluation visit after commencement of treatment should not be before 6-8 weeks. Doses of thyroxine can be increased or decreased based on serum TSH levels. The target serum TSH level for primary hypothyroidism is between 1-3 mU/L. Suppression of serum TSH less than 0.1 mU/L should be avoided as it is associated with higher risk of side effects especially of atrial fibrillation in elderly and increased bone loss in postmenopausal women. Dose changes of 25 ug/day are usually adequate for most of the patients. If serum TSH levels are still high, dose may be increased by 25 ug/day. After 6 months of therapy, the dose should be reassessed as restoration of euthyroidism increases the metabolic clearance of thyroxine.

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The dose which was adequate during early phase of therapy may not be adequate when patient is euthyroid because of increased clearance of thyroxine. Once serum TSH comes in target range, monitoring may be less frequent (once in 3 months) for first year and if dose of thyroxine is stable for one year, monitoring frequency may be done once in 6 months or may be once in a year. Adequacy of thyroxine therapy can never be judged on the basis of improvement in clinical symptoms. No change in dose should be done on the basis of persistence of symptoms or disappearance of symptoms.

Central Hypothyroidism :

The most common cause of central hypothyroidism is pituitary adenoma[2]. Isolated secondary hypothyroidism is very rare. Central hypothyroidism is suspected when serum T4 level is low with normal or inappropriately elevated serum TSH level (inappropriate to decreased level of serum T4). Once central hypothyroidism is suspected, it is most important to evaluate other hormones of pituitary, especially pituitary-adrenal axis. The most critical step before starting thyroxine is to rule out hypoadrenalism[3]. Patient with both hypothyroidism and hypoadrenalism may have symptoms of hypothyroidism only but may develop symptoms of hypoadrenalism once thyroxine is started as metabolic clearance of cortisol is reduced in case of hypothyroidism and at times, may lead to acute adrenal crisis. The initiation of thyroxine therapy is similar to primary hypothyroidism but monitoring of therapy is done with serum T4 levels (total or free), not with serum TSH levels. The target level of serum T4 is middle to upper normal range. Pituitary imaging is also required in these cases to rule out any surgically treatable lesion.

Serum Total T4 or Serum free T4 : Which is Better ?

Measurement of serum total T4 and serum free T4 will provide similar information. The measurement of serum total T4 is much easier than that of serum free T4. Measurement of serum free T4 is cumbersome and difficult as this is an assay requiring high precision because we are measuring a hormone in very low concentration in blood. Measurement of serum free T4 is more useful than serum total T4 in conditions only where thyroxine binding globulin (TBG) levels are altered like in pregnancy, when TBG levels are increased[4]. This could be the case in cases of severe illness also where TBG levels are reduced. The congenital deficiency of TBG is a rare condition and its prevalence in India is very low (0.04%, 1 in 2500)[5]. In all non-stressed and non-pregnant individuals, measurement of serum total T4 is as good as serum free T4 and much easier.

What to Do if Patient Forgets to Take Tablet ?

The half life of thyroxine is about 7 days. If some one forgets to take the dose for one or two days in a month, it will not make much effect on serum TSH level. If it is not taken for more than a week in a month, serum TSH level may be affected. If a patient forgets to take the dose in the morning, he or she can take same dose whenever the patient (afternoon or evening) and avoid food intake for next half an hour. If one day dose is completely missed, double dose can be taken next day morning. If a patient forgets to take the medicine for two days, the patient can take triple dose on the next morning without any concern. In case of no dose for more than 3 days, dose should not be increased by three times to compensate for the missed doses.

Duration of Treatment :

Hypothyroidism in majority of patients is permanent, requiring life long therapy. In patients with transient hypothyroidism secondary to sub-acute and postpartum thyroiditis, therapy may be discontinued once hypothyroid phase is over. However, these patients are at higher risk for developing permanent hypothyroidism in future and should be followed up regularly. Once diagnosis of primary hypothyroidism is confirmed biochemically, requirement of life long therapy should be clearly explained to the patient before starting the treatment.

Response to Treatment :

The response to treatment in case of a severely hypothyroid patient is excellent. The increased diuresis is the initial response followed by increase in pulse rate, pulse pressure, appetite and general sense of well being. The changes in skin and hair may take few months to disappear. The serum T4 levels come to normal range within 4-6 weeks while normalization of serum TSH may require few more weeks while complete clinical resolution may require 3-6 months.

Conditions Affecting Requirement of Thyroxine :

Thyroid hormone requirement is altered in many conditions. Any disease of proximal intestine mucosa will affect the absorption of thyroxine like celiac disease and also after jejuno-ileal bypass surgery and small bowel resection. Impaired gastric acid secretion as in atrophic gastritis is also known to reduce absorption[6]. Thyroxine can be adsorbed to co-administered drugs like cholestyramine, sucralfate, aluminium hydroxide, calcium carbonate, ferrous sulfate, lovastatin or various resins, decreasing its absorption and thereby increasing requirement. Similarly,

increased requirement has also been found in patients taking medication which induces cytochrome P450 enzyme (CYP3A4) in liver like rifampicin, phenytoin, carbamazepine and sertaline. Estrogen, as used in hormone replacement therapy for postmenopausal women, is also known to increase requirement. Amiodarone increases thyroxine requirement by blocking the peripheral conversion of T4 to T3. So protein and soya flavones have been observed to interfere directly with thyroid hormone action[7]. Aging is associated with decreased requirement of thyroxine as clearance of thyroxine is reduced[8]. Similarly, androgen therapy in women (for carcinoma breast) is also known to reduce requirement of thyroxine (Table 1).

Table 1 — *Conditions that alter thyroxine requirements*

(A) Conditions associated with increased thyroxine requirements :
- Gastrointestinal disorders
  - Mucosal diseases of small bowel
  - Jejuno-ileal bypass surgery
  - Small bowel resection
  - Diabetic diarrhoea
  - Atrophic gastritis
- Pregnancy
- Interaction with drugs
- Drugs that interfere with absorption – cholestyramine, sucralfate, aluminium hydroxide, calcium carbonate, ferrous sulfate, lovastatin
- Drugs that increase the cytochrome P450 enzyme rifampicin, phenytoin, carbamazepine sertaline, estrogen
- Drugs that block conversion of T4 to T3 – Amiodarone

(B) Conditions associated with decreased thyroxine requirements :
- Aging – 65 years and older
- Androgen therapy in women

Adverse Effects of Thyroxine :

Thyroxine replacement is considered as very safe without much immediate side effects. Allergic reaction to dye used in manufacturing of tablets has been rarely reported. Most of the adverse effects of thyroxine therapy are effects of over replacement. Administration of excessive doses of thyroxine have been found to be associated with accelerated bone loss[9], especially in postmenopausal women[10], increase in cardiac wall thickness and contractility and increases the risk of atrial fibrillation in case of elderly patients.

Dosage in Patients Receiving Thyroxine Without Clear Diagnosis :

It is not uncommon in clinical practice to come across a situation where thyroxine was started on clinical presumption of diagnosis of hypothyroidism without prior thyroid function test or started even in cases of normal serum TSH levels or mild subclinical hypothyroidism. It is very crucial to decide about the future therapy. As primary hypothyroidism is a life long disease, every effort should be made to be certain of diagnosis. The initial serum TSH level report will be very informative, if available. Serum TSH levels more than 20 mU/L at any time during therapy is consistent with diagnosis of primary hypothyroidism. If thyroxine was started with normal or mildly elevated serum TSH levels, the dose of thyroxine may be decreased to half and reassessed after 4-6 weeks. If serum TSH is still normal, thyroxine can be stopped altogether and reassessment after 4-6 weeks will clear the diagnosis. If decreasing thyroxine dose to half increases serum TSH more than 10 mU/L, then the patient should be treated as a case of hypothyroidism.

Patients with Persistent Hypothyroid Symptoms Despite Normalization of Thyroid Function Test :

In some patients with severe hypothyroidism, symptoms of hypothyroidism may persist even when serum TSH has been normalized. Clinical improvement may lag behind biochemical improvement by few months. Reassurance of patient is the most helpful tool in such cases. Excessive thyroxine dose may be one of the causes. This may also happen when monitoring is done with serum T4 and not with serum TSH. If symptoms persist for few more months even after normalization of serum TSH, other causes of these symptoms should be ruled out.

Persistently High Serum TSH Levels :

Persistence of high serum TSH even after adequate duration of treatment is also not uncommon. Poor compliance to treatment is the most common cause. Failure to take thyroxine more than a week in a month may result in high serum TSH. Interference by another co-administered drug (as discussed) should also be suspected. Changing of pharmaceutical brand may also result in elevated serum TSH as bio-availability of all brands may not be the same. If high serum TSH persists even after 3-6 months of regular therapy of adequate doses, possibility of malabsorption should also be ruled out, especially celiac disease[11]. In rare cases, thyroid hormone resistance may be the cause.

Subclinical Hypothyroidism :

One of the most common clinical conditions, in practice, is mild elevation of serum TSH (5-15 mU/L) with normal serum T4 levels[12]. This condition is also known as mild hypothyroidism, early thyroid failure or preclinical hypothyroidism. It represents either early onset of hypothyroidism or variation in thyroid hormone parameters. In the most carefully controlled studies, one or another of the parameter has returned to normal in about 25-50% of patients. The most important decision in these patients to start thyroxine depends upon the likelihood of develop-

ment of overt hypothyroidism. The factors which predispose to development of overt hypothyroidism are progressive increase in levels of serum TSH (over 3-6 months), presence of goiter, high levels of thyroid peroxidase (TPO) antibodies[13] and family history of hypothyroidism. Patients with subclinical hypothyroidism receiving amiodarone or lithium are also at high risk of developing hypothyroidism. Once decision of starting thyroxine has been taken, the initial dose is usually 25-50 ug/day. The target range of serum TSH and frequency of serum TSH estimation is similar to primary hypothyroidism.

References

1 Jonklaas J, Bianco AC, Bauer AJ — Guidelines for the treatment of hypothyroidism: Prepared by the american thyroid association task force on thyroid hormone replacement. *Thyroid* 2014; **2412:** 1670-751

2 Grunenwald S, Caron P — Central hypothyroidism in adults: better understanding for better care. *Pituitary* 2015; **1:** 169-75.

3 Kim JW, Kim ES, Kim W — A case of Dyke-Davidoff-Masson syndrome associated with central hypothyroidism and secondary adrenal insufficiency. *Hormones (Athens)* 2013; **12:** 461-65.

4 Midgley JE, Hoermann R — Measurement of total rather than free thyroxine in pregnancy: the diagnostic implications. *Thyroid* 2013; **3:** 259-61.

5 Desai MP — Congenital hypothyroidism: Screening dilemma. *Indian J Endocrinol Metab* 2012; **16:** S153–S155.

6 Checchi S, Montanaro A, Pasqui L — L-thyroxine requirement in patients with autoimmune hypothyroidism and parietal cell antibodies. *J Clin Endocrinol Metab* 2008; **93:** 465-9.

7 Bell DS, Ovalle F — Use of soy protein supplement and resultant need for increased dose of levothyroxine. *Endocr Pract* 2001; **7:** 193-4.

8 Hays MT, Nielsen KR — Human thyroxine absorption: age effects and methodological analyses. *Thyroid* 1994; **4:** 55-64.

9 Ross DS, Neer RM, Ridgway EC, Daniels GH — Subclinical hyperthyroidism and reduced bone density as a possible result of prolonged suppression of the pituitary-thyroid axis with L-thyroxine. *Am J Med* 1987; **82:** 1167-70.

10 Affinito P, Sorrentino C, Farace MJ — Effects of thyroxine therapy on bone metabolism in postmenopausal women with hypothyroidism. *Acta Obstet Gynecol Scand* 1996; **75:** 843-48.

11 Collins D, Wilcox R, Nathan M, Zubarik R —Celiac disease and hypothyroidism. *Am J Med* 2012; **125:** 278-82.

12 Helfand M — Screening for subclinical thyroid dysfunction in nonpregnant adults: a summary of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med* 2004; **140:** 128-41.

13 Biondi B, Cooper DS — The clinical significance of subclinical thyroid dysfunction. *Endocr Rev* 2008; **29:** 76-131.