Treatment of Primary Hypothyroidism: Towards an Indian Consensus

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ABSTRACT

Primary hypothyroidism is a common illness. The treatment of choice is levothyroxine. However, no formal guidelines exist on several special situations that arise during the treatment of hypothyroidism. This article focuses on data collected by the Indian Thyroid Society, which sent questionnaires to various endocrinologists from all over the country in order to find out how hypothyroidism is commonly managed by them. The answers provide interesting insights into current therapeutic trends, and also help to frame simple and practical guidelines for special clinical dilemmas that arise during therapy.

INTRODUCTION

Primary hypothyroidism is very common, occurring in about 1% of the population.[1] The incidence rises with age. About 6% of women and 2.5% of men older than 60 years have serum TSH levels which are higher than twice the upper limit of normal.[2] The most common causes of primary hypothyroidism are iodine deficiency and autoimmune thyroid disease. The diagnosis of primary hypothyroidism is based on a low level of thyroid hormones in association with a high TSH level. Thyroid hormone actions are very important, and even the correction of mild thyroid dysfunction can have a positive impact on health. In many cases, hypothyroidism is suspected early,[3] but sometimes it is diagnosed only when obvious symptoms and signs occur, e.g. goiter, weight gain, cold intolerance, or constipation. The treatment of choice is levothyroxine (LT_4), which is one of the most widely prescribed drugs.[4] This report summarizes the findings of a consensus study conducted by the Indian Thyroid Society, and pertains to certain issues in the therapy of hypothyroidism that are still controversial, and of interest to the physician.

The Indian Thyroid Society conducted this study during January to March 2004, and information was obtained from replies to questionnaires, which had been sent to 55 selected endocrinologists from all over the country. The results are discussed not as a comprehensive treatise on the therapy of hypothyroidism, but in a practical format. Here, the opinions of the majority were included as the consensus results.

SCREENING

Screening for thyroid diseases is controversial.[5-8] While it has been shown that screening can detect hypothyroidism in certain high-risk groups, it is not known whether therapy improves outcomes in screen-detected subjects. It seems reasonable to screen for hypothyroidism because: firstly, the prevalence of primary hypothyroidism in the general population is high. Secondly, signs and symptoms of thyroid hypofunction are too nonspecific to always ensure a clinical diagnosis. Finally, TSH is a very effective method to screen, and hypothyroidism is easily treated. Serum free thyroxine (FT_4) estimations are needed for screening only when there is a suspicion of pituitary or hypothalamic disease, when TSH levels are often unreliable. The study questionnaire asked the physicians to list out their priorities for screening, i.e. in which special situations would they screen for hypothyroidism?

Responses: Single serum TSH estimation is the best way to screen. Routine screening of all subjects is not necessary. However screening could be considered in certain special situations (see Table 1) as well as in the presence of clinical signs and symptoms of hypothyroidism.

Comment: Recent evidence-based recommendations, in addition, recommend that screening be done also in the elderly, postpartum women, radiation exposure (>20mGy) and Down syndrome.[5] Other situations where screening might be useful include sleep apnea, hyperprolactinemia and recurrent abortions,

Table 1: Indications for Screening

Dyslipidemia
Menstrual irregularity
Infertility
Unexplained hyponatremia
Type 1 diabetes
Carpal tunnel syndrome
Depression
Short stature

Table 2 : Subclinical Hypothyroidism : Indications for Therapy

Positive anti-thyroid antibodies
Goiter
Dyslipidemia
Depression
Infertility
Pregnancy
Obesity
Carpal tunnel syndrome
Unexplained hyponatremia
Menstrual irregularities
Short stature

though these are not well-proven indications. The American Thyroid Association (ATA) recommends universal screening of all individuals at 35 years of age and every 5 years thereafter.[6] In the United States, a cost-effectiveness study found TSH screening comparable to other well-accepted public health strategies like screening for hypertension, hypercholesterolemia and breast cancer. [7] Such studies are needed in the Indian context too.

DIAGNOSIS

Once the TSH is found to be elevated, is it necessary to order further tests to diagnose and treat primary hypothyroidism?

Responses

The majority stated that both TSH and a free T_4 measurement are together required at the time of diagnosis of hypothyroidism.

Comment

While TSH is a useful screening tool, the actual diagnosis of primary hypothyroidism must be made on the basis of a high TSH in association with a low T_4.[8] This is because an initial FT_4 estimation can help in assessing response to therapy. Also, the presence of subclinical hypothyroidism (a normal FT_4 and a high TSH; see below) may necessitate a slightly different approach. In addition to these two tests, anti-thyroid peroxidase (anti-TPO) antibody may be measured if autoimmune thyroid disease is suspected.

THERAPY: THE IMPORTANCE OF DIFFERENT DOSE STRENGTHS

The issues here are: should there be a standard dose or should it be individualized to special situations? Should one start with the full dose or should one escalate slowly?

Responses

The majority of responders stated that they would start with a full dose for young healthy individuals without any cardiac problems. According to the responders, the desirable initiating dose in healthy adults was 1.7 µg/kg/day. For the elderly, or in subjects with heart disease, one should start with 12.5to 25 µg/day and increase the dose by 12.5 µg every 6 weeks. In the elderly, the final dose required may be less than 1 µg/kg/day. The majority of specialists stated that it was important to have pills of different strengths, as this would afford flexibility in dosing, and precise titration of biochemical parameters. This would also be important in cases of very severe and longstanding hypothyroidism, where specialists preferred to treat the disease a little differently by starting with a lower dose of 25 to 50 µg/d and escalating the dose gradually.

Comment

Levothyroxine preparations have a narrow therapeutic index, and precise titration of the dose is frequently necessary. Also, there is an increasing need for more precise therapy in special situations and the need for maintaining the FT_4 in the normal range by accurate titration of dose. The use of smaller strength tablets of thyroxine is obviously important. It is better to prescribe an accurate-dose pill, rather than the inaccurate option of asking the patient to break a pill into two. In a randomized study, the use of restricted strength tablets did not alter cost-effectiveness and also resulted in very complex treatment regimens.[9] This could adversely affect compliance. It is important to note that several drugs can interfere with levothyroxine absorption. This includes cholestyramine, ferrous sulfate, sucralfate and aluminum hydroxide.[10] Other agents like the antitubercular drug rifampicin and anticonvulsants can accelerate the metabolism of l-thyroxine; hence dose adjustments may be needed in these situations.[11, 12] Subjects with chronic thyroiditis or total thyroidectomy may need higher l-thyroxine doses as compared to subjects with Grave's disease who have undergone I-131 therapy or surgery; in the latter situation, some residual functional thyroid tissue might be present. To address the controversial issue of "perfect" thyroid hormone replacement, a recent study has compared the use of a combination of tri-iodothyronine and levothyroxine (i.e. T_3+T_4) vs. isolated levothyroxine therapy; the results show no definite advantage of the combination therapy. In fact this study showed that such treatment increases the risk of subclinical hypothyroidism, due to fluctuations in the steady-state free T_3 serum concentrations.[13] Both T_4 and T_3 preparations are commonly available, and in the body, T_4 needs to be converted into T_3 for tissue action. Though the issue of combination therapy is still controversial, for the present, levothyroxine alone is the treatment of choice.

SUBCLINICAL HYPOTHYROIDISM

When the FT_4 is normal and the TSH is high, this state is termed subclinical hypothyroidism. As a rule, there must be no history of thyroid dysfunction or therapy. Clinical evidence of thyroid dysfunction is often scant or lacking. In this situation, if the TSH is more than 10 mU/L, thyroxine therapy is indicated. In cases where the TSH is above normal (usually this means above 5 mU/L) but below 10 mU/L, a variety of criteria indicate the need to therapy.

Responses

Majority of the respondents would not universally institute LT_4 therapy in subclinical hypothyroidism in all cases, regardless of the clinical scenario. Rather, it was endorsed that the treatment of subclinical hypothyroidism be restricted to specific clinical situations (see Table 2).

Comment

There are three principal reasons for starting therapy in subclinical hypothyroidism:[14] firstly, to avert the symptoms of eventual

thyroid failure. Secondly, to reverse the effects of mild thyroid deficiency on many organ systems and relieve subtle signs and symptoms caused by thyroxine deficiency, thus improving the patient's quality of life; this is controversial.[15] Finally, as in Table 2, therapy is indicated in specific scenarios.[14,15] The dose required for treating subclinical hypothyroidism may be only about 50 to 75 µg/day.[16]

FOLLOW-UP MONITORING

In general, follow up will depend on the accessibility to health care, economic status, response to therapy and the presence of special situations like pregnancy.

Response

The same two tests, i.e. FT_4 and TSH were the preferred duo as far as monitoring response to therapy was concerned. The patient is to be maintained on the initial dose for the first 6 weeks and then retested. TSH must be maintained within the normal levels for the particular laboratory, which means usually that the values are between 0.5 to 5 mU/L. If repeat testing shows an elevated TSH level, then the dosage is to be increased by 12.5-25µg; if the TSH is low, then the dose reduced by 12.5-25 µg. After normalization, most specialists would retest thyroid functions after 3-6 months, and then yearly. In addition, freeT_4 must be within the normal range. Wherever needed, i.e. during an intercurrent illness, a repeat testing would be ordered.

Comment

TSH normalization may take about 8 to 12 weeks. TSH is the most sensitive indicator of T_4 effect, as TSH level rises significantly in response to minor declines in T_4 which stimulate the TSH-producing cells in the pituitary. The majority of endocrinologists stress on exclusively measuring free T_4 (FT_4), thus raising the fundamental issue of doing away with total T_4 estimations.[17] Total T_4 estimations include protein-bound as well as free T_4 levels. Conditions that increase thyroid binding globulin (TBG) levels (e.g. pregnancy, oral contraceptives) can raise total T_4 levels, but the biologically active i.e. free T_4 levels remain unchanged. The reverse occurs when the TBG levels fall as in nephrotic syndrome and malabsorption: here the total T_4 levels fall but this does not alter the free T_4 levels. While interpreting thyroid function tests, it is important to remember that several non-thyroidal illnesses and drugs can alter free and total hormone levels. Monitoring can also prevent over-treatment with levothyroxine, which is associated with bone loss, atrial fibrillation and thyrotoxicosis.

PREGNANCY

In general, there is an increased need for thyroid hormones during pregnancy.[18] Also, patients with a previous history of unexplained infertility or frequent miscarriages must have a sensitive TSH measurement before and during pregnancy.[19]

Responses

Free T_4 (FT_4), rather than total T_4, is a better measure of thyroid status in pregnancy. In pregnancy, the preferred initiating dose did not alter. During pregnancy, the follow up is to be more intensive, i.e. every 4 to 6 weeks, to keep FT_4 within normal limits.

Comment

In pregnancy, given the increase in thyroid binding globulin, it is better to monitor with free T_4, rather than total T_4 levels. Due to increased demand, dosage of levothyroxine may need to be increased by about 30-50% during pregnancy, in order to keep the free T_4 within normal limits. Recent evidence suggests that the increased need for thyroxine may occur as early as in the 5th week of gestation, and thus hypothyroid women should increase the thyroxine intake by 25 to 50 µg as early as possible, at the time of the missed period itself.[18,19] There is now accumulating evidence to suggest that universal screening should be done to detect hypothyroidism before pregnancy. For the present the following three groups should be screened prior to pregnancy: women more than 35 years, those with a family history of thyroid disorders or those with coexisting autoimmune disorders.[19] After delivery, the pre-pregnancy dose can be resumed.

MOOD DISORDERS

Hypothyroidism has been associated with depression as well as rapid cycling bipolar illness, psychosis, anhedonia, memory impairment and slowness of speech or thinking.[20,21]

Responses

It is important to screen for as well as treat subclincal and overt hypothyroidism in these subjects.

Comment

In psychiatric illnesses with subclinical or overt hypothyroidism levothyroxine therapy should be instituted.[21,22] Lithium, a commonly prescribed drug in psychiatric practice, could precipitate this thyroid dysfunction.[23]

MENSTRUAL DISTURBANCES

Primary hypothyroidism is associated with almost every type of menstrual dysfunction, including amenorrhea, hypomenorrhoea, menorrhagia as well as metrorrhagia.

Responses

It is advisable to screen for hypothyroidism as well as treat subclincal hypothyroidism in these subjects.

Comment

Levothyroxine therapy could help to normalize TSH and correct the reproductive dysfunction.[24] In addition, hypothyroidism can lead to a high prolactin level, which in turn can cause amenorrhea, galactorrhea, and other menstrual abnormalities. Levothyroxine alone will suffice to correct these abnormalities in many, but not all cases.[25]

DYSLIPIDEMIA AND CARDIOVASCULAR RISK

More than 90% of subjects with primary hypothyroidism have increased levels of cholesterol and/or triglycerides.[26] On the other hand about 13% of all subjects with lipid abnormalities have thyroid disease.[27] The degree of dyslipidemia has generally correlated well with the severity of thyroid failure.

Responses

Dyslipidemics should be screened for hypothyroidism. Subclinical or overt hypothyroidism if associated with dyslipidemia, warrants levothyroxine therapy.

Comment

In addition to lipid modulation, both subclinical and overt hypothyroidism can reduce cardiac function. Both changes in systolic time intervals, as well as ST-T changes have been reported: these cardiac alterations are reversible with levothyroxine therapy.[28] Lipid abnormalities in subclinical hypothyroidism are reversible with levothyroxine therapy; treatment even improves carotid intima-media thickness, a marker of atherogenic risk.[29]

SUMMARY

The answers to this questionnaire helped to frame simple, clear-cut answers to some common clinical dilemmas. The results are based on the viewpoint of the majority of the responders, and individual opinions did vary. These consensus statements are only a guideline, and not a substitute for individualizing therapy based on clinical evaluation.

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