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Original Research Article

A study of subclinical hypothyroidism treated with alternate day fixed dose thyroxine therapy

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ABSTRACT

Background: Subclinical hypothyroidism (SCH) is a biochemical diagnosis wherein free T4 is within normal range while serum TSH value >5mIU/L. We aimed to study effects of alternate day fixed dose thyroxine therapy on this subset of patients with a 3month follow up of various clinical and biochemical parameters.
Methods: It was an interventional trial. Fifty consecutive consenting participants with SCH aged 18-45 years were started on alternate day 50µg thyroxine and were observed for 3 months for changes in body mass index, blood pressure, serum cholesterol, serum triglyceride, serum TSH, T3 and T4 levels.
Results: Forty four out of fifty participants had initial TSH levels between 5-10 µU/mL and at the end of 3 months, 58% of these (n=29/44) shown improved thyroid profile as their TSH fell to the target 2-4 µU/mL. Seven participants' (n=7,14%) turned into iatrogenic hyperthyroidism as their T3 and T4 levels rose above normal and TSH levels fell to below 1 µU/mL. Another 7 participants (n=7,14%) showed increased T3 and T4 levels (n=3, n=4 respectively) above normal range with TSH still within normal range. One patient (n=1,2%) had persistently raised TSH levels. Out of 6 participants (n=6,12%) who had initial TSH>10 µU/mL, 3 participants achieved normal TSH with alternate day therapy (n=3,6%) while 3 participants did not achieve euthyroid status (n=3,6%). Authors observed decrease in cholesterol levels (initial=183.18±52.96 mg/dL, final=170.04±42.13 mg/dL, $p<0.05$). It lead to reduction in weight (initial BMI=24.11±5.69, final=23.33±5.30, $p<0.05$).
Conclusions: Authors found that treatment of SCH with alternative day thyroxine therapy is effective in normalizing TSH values. Its dose needs to be titrated according to TSH levels to avoid side effects. It decreased cost of therapy resulting in good compliance in noncompliant patients and reduced pill burden helped the patients in adhering to the therapy.

Keywords: Endocrinology, Alternate day, Hypothyroidism, Subclinical, Thyroxine

INTRODUCTION

Subclinical hypothyroidism (SCH) is a biochemical diagnosis of an underactive thyroid, where free T4 is within normal range while serum TSH value is above normal range (>5µIU/mL) sustained for >3 months. Other causes of a raised TSH, a past history of thyroid disease and patients on Thyroid hormone treatment need to be excluded. This condition occurs in 3% to 8% of the general population. It is more common in women, and its prevalence increases with age. Elevated TSH levels are due to increased secretion of TSH from pituitary indicating that the gland has reduced functional status but is still able to maintain serum thyroid levels within the normal range. The most important implication of SCH is high likelihood of progression to clinical hypothyroidism.[1] Despite being a public health problem, consensus regarding use of thyroxine to treat SCH is

lacking.[2] Therefore we studied this subset of patients for the effects of alternate day fixed dose thyroxine therapy with 3 month follow up of various clinical and biochemical parameters.

METHODS

Present study was conducted in the OPD of Department of Medicine (after getting approval from the institutional review board) on 50 consecutive consenting participants with SCH from February 2015 to September 2015. It was a prospective, interventional study. It was a pilot study based on applied research.

Study population included all the patients attending the outpatient department. Sample size was 50.

Inclusion criteria

- Participants between age 16-45 year coming to our OPD with symptoms of hypothyroidism and S.TSH >5 mIU/L with normal S. T3 and S. T4.
- Participants opting for alternate day thyroxine replacement.
- Participants providing valid informed consent for participation.

Exclusion criteria

- Participants / guardians not providing consent.
- Vulnerable patients Prisoners and orphans, Patients with mental illness
- Participants having any other chronic illnesses.
- Pregnant females.

The Normal reference range was as follows:

- T3: 0.8-2.0 ng/mL
- T4: 4.5-12.5 mic g/dL
- TSH: 0.5-5.0 mic IU/mL

We recorded:

1. Clinical parameters
- Blood Pressure
- Pulse rate
- Height(baseline)
- Weight

2. Biochemical parameters
- Fasting blood Sugar level
- Serum Urea
- Serum Creatinine
- Serum Total Cholesterol(Fasting)
- Serum Triglyceride(Fasting)

3. Thyroid Profile
- Serum TSH level
- Serum total T3 level
- Serum total T4 level

Method of testing as available for our hospital patients was chemiluminescence. Thyroxine was given at a fixed dose to all patients irrespective of TSH values i.e. 50microgram/alternate day. Patients were followed monthly for detailed clinical assessment till 3 months. While biochemical assessment was done at the end of third month. Compliance was checked as per the patient's history. In case of doubt, patients were motivated to bring their bottles containing tablets and the tablets were counted on follow up. If a dose was missed the patient was instructed to take the missed dose the next morning without affecting the schedule of next dose. Serum TSH value was the determinant for dose titration. Values between normal range of TSH were continued with same dose while TSH values below normal were down titrated and values above normal were up-titrated by 12.5µg at the end of three months.

RESULT

Clinical presentation

As per our study, more females presented to us with symptomatic SCH (43/50) i.e. 86% as compared to males.

This echoes an established fact in literature, also confirmed in various studies like NHANES, Colorado prevalence study and 'the eight city study in india' that females are more prone to thyroid disorders.[3-5]

Table 1: Common symptoms of SCH (Sub clinical hypothyroidism) seen in the study.

Symptom	No. of participants
Weight gain	22
Hair fall	9
Irregular menses	9
Easy fatiguablity	8
Neck swelling	7
Body ache	7
Cold intolerance	5
Dry and coarse skin	4
Peripheral edema	4
Dyspnea on exertion	2
Female infertility	2
Acne	1
Depressed mood	1
Decrease sleep and concentration	1

Weight gain was the single most common presenting complaint. Other complaints were commonly related to the metabolic profile like easy fatigability, cold intolerance, body ache and dyspnoea on exertion, complaints involving skin and cutaneous system including increased hair fall, dry and coarse skin, peripheral edema, neck swelling, acne and gynaecological problems of irregular menses and primary infertility and cognitive disturbances like depressed mood and reduced sleep and concentration (Table 1).

Effects on thyroid profile

Out of the 50 participants studied, 44 participants (n=44/50, 88%) were having their initial TSH between 5 to 10 µU/mL. As seen in table 2, out of these 44, 29 participants (n=29/44, 65.9%) when given alternate day thyroxine replacement showed a decline in their TSH level to the target range that is between 2-4 µU/mL. As per the recent guidelines issued by the thyroid associations, the TSH should be the determinant in decicding the therapy of thyroid disorders.[6-8] Seven participants (n=7/44, 15.9%) showed complete change in thyroid profile as their T3, T4 levels rose above normal and TSH levels fell to below 1 µU/mL. These participants were thought to be developing iatrogenic hyperthyroidism. Some participants developed increase in their T3 (n=3/44, 6.8%) and T4 levels (n=4/44, 9.1%) respectively, so they needed dose reduction for thyroxine replacement. One patient (n=1/44, 2.2%) had persistently raised TSH levels.

Table 2: Thyroid profile before and after 3 months of alternate day thyroxine therapy.

No. of patient (s)	%	Initial values			After 3 months		
		TSH	T3	T4	TSH	T3	T4
29	58	5-10	Normal	Normal	2-5	Normal	Normal
7	14	5-10	Normal	Normal	<1	Increased	Increased
3	6	5-10	Normal	Normal	2-5	Increased	Normal
4	8	5-10	Normal	Normal	2-5	Normal	Increased
3	6	>10	Normal	Normal	2-5	Normal	Normal
3	6	>10	Normal	Normal	>5	Normal	Normal
1	2	5-10	Normal	Normal	>5	Normal	Normal

Normal reference range was as follows: T3: 0.8-2.0 ng/mL, T4 :4.5-12.5 mic g/dL, TSH: 0.5-5.0 mic IU/mL

Out of the 6 participants (n=6/50, 12%) who had TSH more than 10 µU/mL, 3 participants (n=3/6, 50%) achieved normal TSH with alternate day therapy while 3 participants (n=3/6, 50%) failed to achieve normal TSH with the given therapy. There is significant difference between initial TSH and final TSH level (p= 0.0001) (Table 2). This is also seen in other studies incorporating weekly and alternate day strategies to combat non compliance and to reduce costs in the treatment of sub clinical hypothyroidism.[9-12]

Effects on metabolic profile

Body weight: Mean initial BMI was seen as 24.11±5.69 which came down to 23.33±5.30 (p<0.0005) after three months. Mean initial body weight was seen as 59.780 kgs±12.39 which came down to 57.76±11.73 after three months of thyroxine replacement. This was also seen in study by Knudsen underscoring the importance of correction of thyroid profile to control weight and improving body mass index.[13]

Lipid profile

Total 14 participants (n=14/50) had initial fasting serum total cholesterol more than 200 mg%. The initial mean total cholesterol was 183.18±52.96 mg/dL while the final total cholesterol was 170.04±42.13 mg/dl after 3 months of our therapy. There is significant difference in total cholesterol levels at different time points (p value = 0.002). This was also observed by several other studies in participants with subclinical hypothyroidism that thyroxine replacement can lead to improvement in lipid profile like the study done by Monzani F et al.[14] Meier C et al also in his Basel Thyroid Study proved that TSH guided thyroxine replacement therapy reduces cholesterol levels and clinical symptoms in subclinical hypothyroidism.[15]

Fasting hypertriglyceridemia more than 150mg% was seen in 24 of the participants. Initially fasting serum triglyceride level was 168.14mg% which after treatment decreased to 153.56mg%, but it was not statistically significant (p>0.05). Similarly, little correlation between thyroid and triglycerides was seen in other studies.[16-17]

Blood pressure

Mean diastolic blood pressure of the participants was 77.20±10.70 initially which came to 75.76±8.77 after 3 months of therapy. Initially 5 participants out of 50 had increased diastolic Blood pressure (n=5/50). Thirteen participants (n=13/50) also had raised systolic blood pressure. After therapy no patient was noted to have hypertension but this was not statistically significant (p>0.05). This is in contrast to Razvi et al, who in their study found beneficial effects of thyroxine replacement in subclinical hypothyroidism on cardiovascular risk profile along with improvement in hemodynamic status, cardiac function and other lifestyle measures.[18] In the end, this research work may be considered as a pilot study of fixed dose intermittent thyroxine replacement therapy in subclinical hypothyroidism. Present study results favour such a protocol. However, for regulatory purposes and for

its wider use in the clinical practice, this requires confirmation with more multicentric randomized controlled trials and meta-analyses.

DISCUSSION

Hypothyroidism may be either subclinical or overt. As per the definition, subclinical hypothyroidism is characterized by a serum TSH above the upper reference limit in combination with a normal free thyroxine (TSH >5mIU/L, Normal T4).

We selected SCH for our study because many of these patients are neglected because of the prevalent ignorance regarding this condition despite the fact that ignoring SCH can lead to overt hypothyroidism. It is said that a "rule of thirds" operates in the Indian thyroid epidemiology. Two-thirds of those with iodine deficiency convert to SCH and two thirds with SCH convert to OH.[1] Thyroid disorders are one of the most important public health problems. Also, there is paucity of clarity amongst the physicians regarding evidence based recommendations that whether this subset should be treated or not.2 Moreover thyroid hormone being a highly protein bound hormone (>99.5%) and with a prolonged half life (t1/2=7days) could yield good results even on intermittent dosing. Patients of SCH as other thyroid deficiency states, when symptomatic, are given thyroxine replacement therapy but in low doses and often patients prefer intermittent dosing schedules (like using odd-even days) rather than daily dosing.

Intermittent dosing for thyroid disorders

As per a study done by Dayal D et al, to study the efficacy of an alternate day regimen to maintain euthyroidism in children with congenital hypothyroidism, it was described that the thyroid profiles remained within normal limits suggesting biochemical euthyroidism status with alternate day therapy.[9] In another study by Rangan S et al, author wrote 'non-compliance is the most common cause of lack of response to thyroxine treatment'.[10] In other words, decreased frequency of dosing of thyroid hormone is a topic of research worldwide.

CONCLUSION

Herein authors found that the treatment of SCH with alternative day thyroxine therapy is effective in normalizing TSH values. It is well tolerated but the dose needs to be titrated according to TSH. It decreased cost of therapy resulting in good compliance in noncompliant patients and also the reduced pill burden helped the patients in adhering to the therapy. It also leads to weight reduction and lowers serum cholesterol however it had no beneficial effect on hypertriglyceridemia.

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Ethical approval: The study was approved by the institutional ethics committee

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