

Original Research Article

Clinical Spectrum of Subclinical Hypothyroidism and its Management- A Prospective Observational Study

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Abstract: Hypothyroidism is a common problem; it causes symptoms that reduce the functional status and quality of life. Subclinical hypothyroidism (SCH) describes a situation in which thyroid function is only mildly decreased, where the blood level of thyroxine remains within the normal range, but the TSH level in the blood is raised, which indicates mild thyroid failure or impending thyroid failure. Various causes are responsible for this type of medical scenario but the most common cause is chronic autoimmune thyroiditis followed by iodine deficiency, radiation therapy to head and neck region, use of drugs like lithium, amiodarone and unexplainable causes. Prevalence of SCH amounts to approximately 5-10%, being more frequent in women and with increasing prevalence with advancing age. Early diagnosis & treatment of subclinical hypothyroidism may prevent the onset of overt hypothyroidism and its associated effects. Our aim was to study the clinical spectrum of subclinical hypothyroidism and its management. All cases are diagnosed to have subclinical hypothyroidism with TSH > 4.0 μIU/ml and normal T3, T4 Levels. This study was conducted over a period of one year; total subjects included were 155 and included patients with ages 18- 77 years. Weight gain is the dominant symptom in majority. Goiter was noted in 19 subjects. The patients with subclinical hypothyroidism with TSH level above 10 mIU/L should be managed with low dose thyroxine with proper follow up in order to minimize thyroid deficient related symptoms and signs.

Keywords: Subclinical Hypothyroidism, Thyroid Stimulating Hormone, Goiter, Thyroxine, Auto-Immune Thyroiditis

INTRODUCTION

Hypothyroidism is a common problem; it causes symptoms that reduce the functional status and quality of life. The term subclinical hypothyroidism was first introduced in early 1970's coincident with introduction of serum Thyroid Stimulating Hormone (TSH) measurements. This term eventually replaced other terminologies like preclinical myxoedema, compensated euthyroidism, preclinical hypothyroidism and decreased thyroid reserve [1]. Sub clinical hypothyroidism can be best defined as a high serum TSH concentration and normal serum total/ free thyroxine (T4), tri-iodothyronine (T3) concentrations associated with few or no symptoms/signs of hypothyroidism [2]. However few authorities consider

that patient should not have any classical signs/symptoms of hypothyroidism to label him/her as having sub clinical hypothyroidism. Hence, subclinical hypothyroidism is essentially a laboratory diagnosis. It is referred to as a state of mild thyroid failure [3]. The importance of studying subclinical hypothyroidism is that it is much more common than overt hypothyroidism [4], and hence early diagnosis & treatment may prevent the onset of overt hypothyroidism and its associated effects. Subclinical hypothyroidism may be associated with increased risk of coronary artery disease (CAD), peripheral vascular disease, and various biochemical abnormalities, including increased LDL-C levels, increased total cholesterol and serum triglyceride values [5].

AIM OF THE STUDY

To study the clinical spectrum of subclinical hypothyroidism and its management

MATERIALS AND METHODS

This prospective observational study included subjects/patients who visited our department for a general health check up or for symptoms of hypothyroidism and this study was conducted in Nizam’s institute of medical sciences (NIMS), Multi-specialty, Tertiary Care referral centre at Hyderabad. All cases are diagnosed to have subclinical hypothyroidism with TSH > 4.0µIU/ml and normal T3, T4 Levels. This study was conducted over a period of one year and total subjects included were 155. The study was started after getting approval from the Institute Ethics Committee. Patient’s informed consent taken, a detailed history and clinical examination is done with a special reference to certain parameters like body mass index, blood pressure & thyroid swelling. Along with routine laboratory investigations, fasting thyroid sample is drawn. Anti thyroid antibodies and fasting lipid profile are done in all patients with abnormal thyroid profile suggestive of subclinical hypothyroidism. High Resolution Ultrasound (HRUS) neck and Fine Needle Aspiration Cytology (FNAC) of goiter are done in patients with subclinical hypothyroidism and thyromegaly. Other additional investigations were done wherever indicated.

INCLUSION CRITERIA

All patients above the age of 18 years with elevated TSH levels (> 4.0µIU/ml) and normal total T3/T4 levels detected on screening with or without symptoms of hypothyroidism.

EXCLUSION CRITERIA

1) Patients with TSH value more than 20 µIU/ml.

- 2) Patients with overt hypothyroidism (primary /secondary) and on treatment with Thyroxine OR with hypothyroidism while on anti thyroid drugs.
- 3) Patients on treatment with anti lipidemic drugs.
- 4) Patients with acute medical illness admitted in ICU.

Sample collection and procedure - Fasting blood sample was collected. Fasting blood sugars and complete blood counts were done. Immulite kit (Chemiluminescence Immuno Assay-CLIA) was used for thyroid hormone estimation [6, 7]. mT4 estimation was done by solid phase competitive chemiluminescence enzyme immune assay. Reagent wedge contains monoclonal murine anti T4 coated beads and 7.5ml alkaline phosphatase conjugated to T4 and it is centrifuged. Automated Immulite analyzer provided the results. T3 estimation It is done by solid phase competitive chemiluminescence enzyme immune assay. 25µml of serum is must for the procedure. 7.5ml alkaline phosphatase was conjugated to T3. The sample is then centrifuged. Automated Immulite analyzer provided the results. TSH estimation -It is a third generation TSH assay. It’s a solid phase; two site chemiluminescenceimmunometric assay. 6.5ml alkaline phosphatase was conjugated to a polyclonal anti-TSH buffer. The sample is centrifuged and fed into the system which will provide the results.

RESULTS

In this study, a total of 155 subjects with subclinical hypothyroidism were included. This study included patients with ages 18- 77 years and age groups were made according to the need of the study (Table 1). Mean age of patients with subclinical hypothyroidism in our study was 43.90±2.23 years. 114 females (73.55 %) and 41 males (26.45%)(fig-1). Female to Male ratio is 2.8:1.

Table 1: Age distribution

Age	Number	Percentage
18-30	32	20.65
31-40	34	21.94
41-50	42	27.10
51-60	30	19.35
61-70	11	7.10
>70	6	3.87

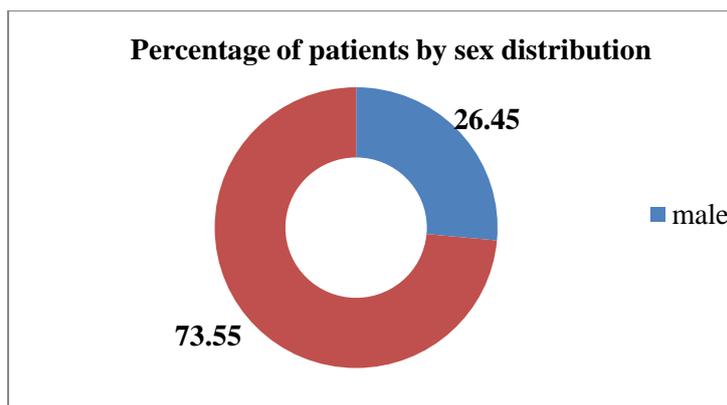


Fig-1: sex distribution

Clinical presentation of the subjects/ patients - 122 patients (78.70%) out of 155 were symptomatic on first visit. 48 patients (30.96%) presented with weight gain as the predominant symptom. 33 patients (21.29%) initially presented with non specific body pains. 23 patients (14.83%) presented with loss of appetite. 19 patients (12.25%) presented with neck swelling as the predominant symptom. 18 patients (11.61%) complained of constipation. Another 18 patients (11.61%) presented with tingling sensation of feet. 16 patients (10.32%) presented with hair fall. Swelling of feet was the main presenting complaint in 14 patients (9.03%). Menstrual irregularities were observed in 11 patients (7.09 %). Dry skin was found in 6 patients

(3.87%). Increased somnolence was the main presenting complaint in 5 patients (3.22%). 2 patients (1.29%) presented with poor memory. Dyspnoea was the presenting symptom in 2 patients (1.29%). Swelling of face was complained by another 2 patients (1.29%). One patient was presented with cold intolerance. Hoarse voice was observed in 1 patient. No patient presented with decreased concentration and impaired hearing. 33 patients (21.29%) who came to OP for general health check up were incidentally detected to have subclinical hypothyroidism. Family history of thyroid disease was present in 8 cases (5.16%). One pregnant woman came to OP for evaluation of anemia also found to have subclinical hypothyroidism (table 2).

Table 2: Clinical Presentation-Symptoms

SYMPTOM	Number of Cases	Percentage
Weight gain	48	30.96
Generalized weakness	35	22.58
Body pains	33	21.29
Loss of appetite	23	14.83
Neck swelling	19	12.25
Constipation	18	11.61
Tingling sensation of feet	18	11.61
Hair fall	16	10.32
Swelling of feet	14	9.03
Menstrual disturbances	11	7.09
Dry skin	6	3.87
Increased somnolence	5	3.22
Poor memory	2	1.29
Swelling of face	2	1.29
Dyspnoea	2	1.29
Cold intolerance	1	0.64
Hoarse voice	1	0.64
Impaired hearing	0	0
Decreased concentration	0	0

Signs were observed only in 45 patients (29.00%). Goiter was seen in 19 patients (12.25%). 14 patients (9.03%) had pedal edema. Dry coarse skin was

observed in 6 patients (3.87%). Four patients (2.58%) showed delayed Deep Tendon Reflexes (DTR). Puffy face was seen in 2 patients (1.29%) (table 3).

Table 3: Clinical Presentation-Signs

SIGNS	NUMBER OF CASES	PERCENTAGE
Goiter	19	12.25
Pedal Edema	14	9.03
Dry Coarse Skin	6	3.87
Delayed DTR	4	2.58
Puffy Face	2	1.29

Goiter was observed in 19 patients (12.25%). Multinodular goiter was detected by HRUS in two patients (1.29%). Solitary adenoma was seen in one patient (0.64%). Diffuse thyroid swelling was seen in one patient (0.64%). Hashimoto's thyroiditis was observed in FNAC of thyroid in two patients (1.29%). Thyroid Peroxidase (TPO) antibodies were done in 105 patients and TPO positivity was found in 43 patients (40.95%). They were negative in 62 patients (59.04%).

Mean T3 level in patients with subclinical hypothyroidism was 2.53 nmol/lit. Mean T4 levels in patients was 7.59 µg/dl. Mean TSH level in patients was 8.11 µIU/ml.

Distribution of sub clinical hypothyroidism

118 Patients (76.12%) with subclinical hypothyroidism had TSH values ranging from 4.1- 9.9 µIU/ml. 37 patients (23.87%) had TSH value ≥ 10.0 µIU/ml (table 4).

Table 4: TSH Levels In Subclinical Cases

TSH (µIU/ml)	Number of Cases	Percentage
4.1-9.9	118	76.12
≥ 10	37	23.87
TOTAL	155	100

TPO antibodies were done in 105 patients of subclinical hypothyroidism. TPO positivity was found in 43 patients (40.95%). They were negative in 62 patients (59.04%).

DISCUSSION

Hypothyroidism as a clinical syndrome was described for the first time in London in 1870. It was named as myxoedema. In 1888, it was accepted widespread that cretinism, myxoedema and post-thyroidectomy changes all were a result of the loss of function of thyroid body. Kendall isolated thyroxine (thyroxyindole) for the first time in 1914. Harrington synthesized it for the first time in 1926. However, synthesis of thyroxine was done in large scale in 1949; later it became universally accepted therapy for hypothyroidism [8]. Subclinical hypothyroidism was a new clinical entity described in early 1970's after TSH estimation became routine. It represents a form of mild thyroid failure. Large epidemiological studies indicate that subclinical hypothyroidism is the most prevalent thyroid disease in the community [9]. Subclinical hypothyroidism can be defined as elevated TSH concentration in the presence of normal circulating total/free T3/T4 levels. It refers to a state of mild thyroid failure. In the progressive development of Thyroid disease, abnormal values for serum TSH generally occur before there is a diagnostic abnormality of serum T4, because of nonlinearity of the negative feedback relationship between serum T4 and release of TSH from the anterior pituitary. For a two-fold change in serum T4 up or down from the set point for that individual, the serum TSH will normally change up to

100-fold in the reverse direction. Thus, TSH may be recognizably abnormal months or years before there is a diagnostic change in the serum concentrations of T4 or T3 [10]. While considering the prevalence of thyroid dysfunction, a distinction needs to be made between so-called subclinical and overt abnormalities; a distinction that is based on laboratory rather than clinical criteria. The Whickham study, first reported in 1977 from iodine depleted region in Northern England, showed a prevalence of 1.4 -1.9% overt hypothyroidism in women, with progressive increase with age. According to the Indian study done by Deshmukh *et al.*, out of the 71 cases studied and followed up 17 % of the cases were turned out to be overt hypothyroidism [11]. Estimates of subclinical hypothyroidism were 4-5 fold higher compared to overt hypothyroidism, with about 10% of women over 50 showing an increase in serum TSH, again with progressive increase with age. The subsequent 20 year follow up [12] of this cohort showed an incidence of spontaneous hypothyroidism of about 3.5/1000 subjects/year in females and 0.6/1000/year in males.

Present study was a prospective observational study conducted over a period of 12 months from January 2013 to January 2014 and enrolled subjects with age more than 18 years. We studied 155 subjects who attended general medicine OP in our tertiary care referral hospital. All cases had TSH > 4.0 µIU/ml with normal T3 and T4 levels. The mean age of subjects in our study was 43.9 \pm 2.23 years with range of 18 to 77. Majority of subjects were in the age group of 41- 50 yrs constituting 27.1%. Around 80% of patients were < 60

yrs age. Our study correlated with the studies conducted

by various authors as mentioned in the table 5.

Table 5: Mean Age Of The Patients

Study	Mean age(years)
Laway BA <i>et al</i> [13]	36.5± 10.1
Pradeep Sharma <i>et al</i> [14]	39.43±11.82
Krishnamurthy <i>et al</i> [15]	53.47±8.64
Sanjoy K Bhandopadyay <i>et al</i> [16]	38.56
Present study	43.9±2.23

Mean total T3level was 2.53±1.6nmol/lit. This is an expected finding because; peripheral de-iodination of T4 to T3 is unaffected in subclinical hypothyroidism. Mean total T3 level in our study is higher than those observed in other studies done by Krishnamurthy *et al* [15], Shrutimohanty *et al* [17] and Kuldip *et al* [18]. Study by Salmon Rizvi *et al* [19] has yielded similar results.

Mean total T4 levels among patients was 7.6±0.3µg/dl. This observation is comparable to Krishnamurthy *et al* [15]. Mean total T4 in our is lower than those observed in study by Shrutimohanty *et al* [17] and slightly higher than those observed in study by Kuldip *et al* [18]. Total T4 levels in cases were towards the lower limit of normal. This indicates that there is a trend towards impending thyroid failure if not intervened immediately.

Mean TSH values in patients was 8.11±0.5µIU/ml. This was comparable to other studies done by Kong *et al* [20], Kuldip *et al* [18], Pradeep Sharma *et al* [14] and Krishnamurthy *et al* [15].

MANAGEMENT

128 patients (82.58%) with subclinical hypothyroidism received treatment with 25 µgm of thyroxine at first visit. Dose of thyroxine was adjusted based on TSH value on follow up. 27 patients (17.42%) were not started on treatment as they did not have other risk factors.

All patients were asked to come for follow up after 6weeks and 12weeks with TSH report. Other associated co-morbid conditions were treated accordingly. The commonest indication for initiation treatment is presence of symptoms noted in 45 patients (35.15%). TSH value more than 10 is taken as an indication for treatment in 35 patients (27.34%). TPO positivity is for 23 patients (17.96%). Goiter is taken as an indication in 6 patients (4.68%). TSH more than 7 for more than 6 months is considered for initiation treatment in three patients (2.34%). These three subjects carried a report showing TSH>7, done on general checkup about 6 months earlier. Other subgroup indicates family history of hypothyroidism, persons with other autoimmune disorders, obesity, pregnancy and dyslipidemia. However in the algorithm describe no

subjects qualified for treatment with family history of hypothyroidism as the sole indication in the absence of other predefined parameters. 155 patients were enrolled in this study at 0 weeks. 122 patients (78.7%) were symptomatic at 0 weeks. 44 patients couldn't come for follow up at 6 weeks due to various reasons in spite of good effort from our side. Hence 111 patients attended for follow up at 6 weeks. 88 patients (79.27%) had symptoms even on treatment. 4 patients couldn't come for follow up at 12 weeks. Among 107 patients 48 patients (44.85%) were symptomatic on treatment. But the proportion of symptomatic patients was significantly decreased on subsequent follow up.

CONCLUSION

Subclinical hypothyroidism (SCH) is a condition with raised serum TSH levels above the upper normal limit with normal serum thyroxine concentration. Initiating levothyroxine replacement therapy is recommended for all patients with a TSH greater than 10 mIU/L, even if the free thyroxine concentration is within normal laboratory range. However, treatment of patients with a serum TSH level between 5 and 10 mIU/L remains controversial and levothyroxine therapy in this group should be individualized by taking into account patient preference, presence of symptoms, age, and associated medical conditions in order to improve the quality of life.

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