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Link between Infertility, Overweight and Subclinical Hypothyroidism

Vikas Ratnaparkhe[1], Harsh Shah[2], Kavita Upadhyay[3]

[1]M.D Internal Medicine, Consultant Dept. Of Medicine, Dr. Hedgewar Hospital, Aurangabad
[2]D.N.B General Medicine (Dr. Hedgewar Hospital, Aurangabad)
[3]Resident D.N.B General Medicine, Dr. Hedgewar Hospital, Aurangabad

Corresponding Author: Kavita Upadhyay

ABSTRACT

Background: Subclinical hypothyroidism (SCH) is mild form of hypothyroidism. It is a biochemical condition associated with elevated serum TSH and normal free T4.
Reduced production of thyroid hormone is the hallmark of 'Hypothyroidism'. [1] Increased TSH level is the indicator of hypo-functioning of thyroid gland.
The prevalence of subclinical hypothyroidism in India ranges from 9% to 32 %. [2,3] SCH is a silent disorder, likely to be missed. It can progress to overt hypothyroidism and aggravation of co-morbid clinical conditions like obesity and infertility if not treated.
Objective: To assess the various clinical presentations associated with SCH especially in relation with BMI, Infertility and lifestyle related disorders.
Materials and Methods: This was a prospective study of 200 adult patients diagnosed with SCH from January 2016 - June 2017 at Dr. Hedgewar hospital, Aurangabad.
Results: In our study the 63% of patients were females belonging to rural area (126 out of 200). Most of the SCH patients (37.5%) were from third and fourth decade and incidentally this is the most fertile period in the life of female. In our study, Infertility was recorded in 15.74% out of a total of 127 females of fertile age group. 80% females had BMI > 23 which is in the range of overweight, pre-obese and obese. In our study rural female preponderance was observed as regards the associated co-morbidities. In 67.5% patients with BMI > 23% we could establish the link between Female sex, obesity, dyslipidemia, infertility and SCH which needs further evaluation.
56% patients were symptomatic. The symptoms were Fatigue -56 %, weight gain - 34%, constipation - 30.5% and cold intolerance - 26%. Hypertension was present in 20% of cases and diabetes was found in 15% cases. Dyslipidemia was seen in 7.4% cases. Therefore, Obese fertile Females must be screened for SCH. 74.5% patients were treated with low dose levothyroxine.
Conclusion: SCH is a silent disorder. Strong clinical suspicion of SCH in female patients presenting with infertility and obesity is required. The incidence of SCH was more in rural female population.
80% of infertile females had BMI greater than or equal to 23. Treatment with low dose levothyroxine results in normalization of biochemical parameters and prevents progression of co-morbidities.

Key Words: Sub-clinical hypothyroidism (SCH), Thyroid stimulating hormone (TSH) levothyroxine, obesity, infertility.

INTRODUCTION

Subclinical hypothyroidism (SCH) is mild form of hypothyroidism. It is a biochemical condition associated with elevated serum TSH and normal free T4.
Reduced production of thyroid hormone is the hallmark of 'Hypothyroidism'. [1] Increased TSH level is the indicator of hypo-functioning of thyroid gland.

The prevalence of subclinical hypothyroidism in India ranges from 9% to 32 %. [2,3] SCH is a silent disorder, likely to be missed. It can progress to overt hypothyroidism and aggravation of co-

morbid clinical conditions like obesity and infertility if not treated.

MATERIALS AND METHODS

The current work represents single institutional prospective observational study at Dr. Hedgewar Hospital, located in central Maharashtra. This study was conducted from January 2016 to June 2017 in patients visiting the OPD/IPD in General Medicine Department. Adult patients with raised thyroid stimulating hormone (TSH) levels and normal T3 and T4 levels were included in the study.

Inclusion criteria: Adult patients with raised thyroid stimulating hormone (TSH) levels >4.05 and with normal T3 and T4 levels were included in the study.

Exclusion criteria: Recovery from critical non thyroidal illness, Previous radioiodine therapy, Thyroid surgery, External radiation therapy, Patients with thyroid disease taking medications for it.

Adult patients visiting Hedgewar Hospital were labelled as having subclinical hypothyroidism, [4] if their TSH was > 4.05 mIU/ml (Normal range: 0.17-4.05mIU/ml) and FT4 was in the normal range(0.89-1.7ng/dL)

TSH and FT4 were done by ECLIA (Electro Chemiluminescence Assay) in the fasting state.

Assay	Abbreviation	Lower Limit	Upper Limit
Serum Thyroid Stimulating Hormone	TSH	0.17 mIU/L	4.05 mIU/L
Serum Free Thyroxine	FT4	0.89	1.7ng/dl
Serum Free Triiodothyronine	FT3	1.6	3.8pg/ml

Demographic data included age, sex, geographical distribution and Body Mass Index for subjects were classified according to WHO guidelines.

Clinical presentations of patients were recorded and analyzed. Body mass index was calculated from the recorded height and weight. Details about the past history, family history, previous illness, any reports were ever available were also noted, the treatment given and the follow up period of the patient were also traced. Tailor made treatment for the patients having TSH levels between 10µIU/ml and 4.25µIU/ml was started. All patients on treatment were advised 6 weekly follow up. Levothyroxine therapy was titrated.

Treatment algorithm for SCH: [11]

Indications for initiation of low dose levothyroxine therapy: [5,6]

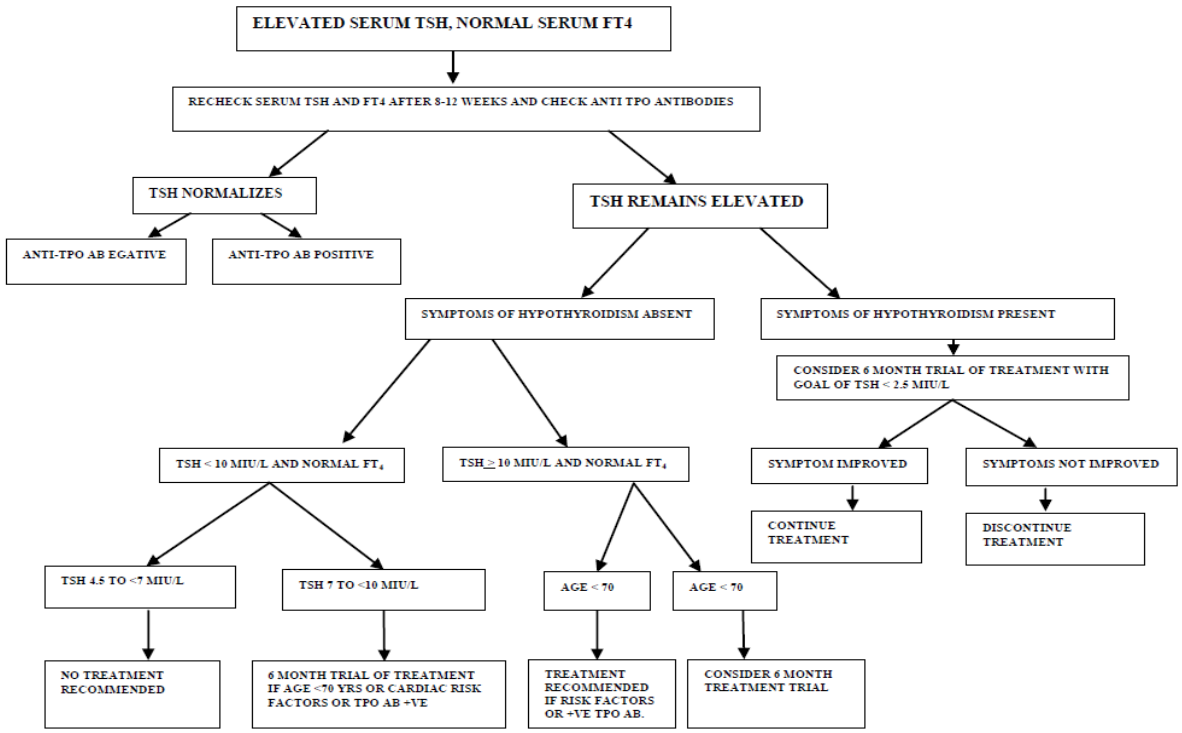
Dyslipidemia, Goiter, Pregnancy, TSH >10mIUml, Symptomatic, Infertility

DM was defined by doing fasting blood glucose amongst the study patients, and if it was > =126 it was defined as DM (normal range : <100, impaired fasting glucose: 100-125 and DM: >=126.). [7]

Hypertension has been defined as an average of 2 seated blood pressure readings which demonstrates systolic blood pressure >=140 mmHg or diastolic blood pressure >= 90 mmHg or previous diagnosis of hypertension and/or patient is on antihypertensive medications. [8]

Dyslipidemia is defined as total cholesterol :>= 240mg/dL OR LDL cholesterol >130 mg/dL OR triglyceride levels >= 150 mg/dL OR HDL cholesterol < 40 mg/dL in men and < 50 mg/dL in females OR previous h/o dyslipidemia and / or currently being treated with lipid lowering agents. [9]

Infertility is defined as the inability to conceive after 12 unsuccessful fertility focused menstrual cylces. [10]

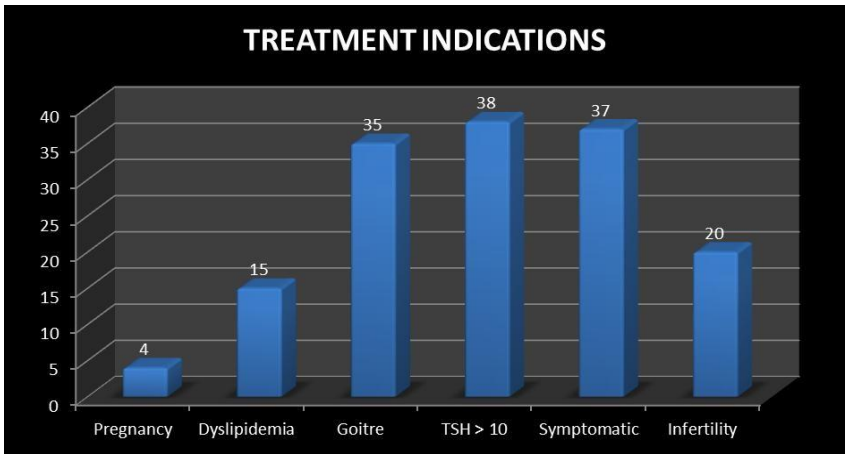


RESULTS

In our study the incidence of SCH was more in rural female population (63%) 126 out of 200 cases. The most affected age group was of third and fourth decade (35-44 years) 37.5%, incidentally this is the fertile age group for females. In our study, 20 (15.74%) females were infertile out of a total of 127 fertile females.16 out of these 20 (80%) females had BMI > 23. There was rural female preponderance as regards the co-morbidity Diabetes Mellitus and obesity associated with SCH. 67.5% patients had BMI >23%. Patients with dyslipidemia having obesity in 3rd & 4th decades having female sex show significant co-relation with SCH. Out of 200 patients 112 (56%) patients were symptomatic. Fatigue was the most common symptom (56 %) followed by weight gain (34%), constipation (30.5%) and cold intolerance (26%). Hypertension was present in 20% of cases and diabetes was found in 15% cases. Dyslipidemia was seen in 7.4% cases Therefore Obese fertile Females must be screened for SCH. 149 patients out of 200 (74.5%) were initiated on low dose levothyroxine.

Distribution of Patients started with low dose levothyroxine therapy at our institute:

INDICATIONS	FREQUENCY
PREGNANCY	4
DYSLIPDEMIA	15
GOITER	35
TSH > 10MIU/ML	38
SYMPTOMATIC	37
INFERTILITY	20
TOTAL	149

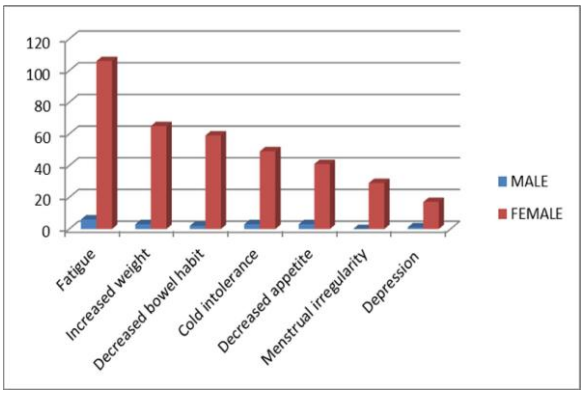


Distribution of symptoms of subclinical hypothyroidism according to gender:

Out of 200 patients 112 (56%) patients were symptomatic. Fatigue was the most common symptom (56 %) followed by weight gain (34%), constipation (30.5%) and cold intolerance(26%).Menstrual irregularities were found in 22% women followed by infertility in 10.5 %. Reduced appetite was seen in 44 (22%) patients, Depression was seen in 18 (9%) patients.

A significant number of patients had BMI > 23 (67.5%)(11). Hypertension was present in 20% of cases and diabetes was found in 15% cases. Dyslipidemia was seen in 7.4% cases. 149 patients out of 200 (74.5%) were initiated on low dose levothyroxine.

Symptoms	Male	Female	Total	P - Value
Fatigue	6	106	112	0.666
Increased weight	3	65	68	0.497
Decreased bowel habit	2	59	61	0.283
Cold intolerance	3	49	52	0.935
Decreased appetite	3	41	44	0.796
Menstrual irregularity	0	29	29	-
Depression	1	17	18	0.934



Distribution of TSH according to BMI [12]

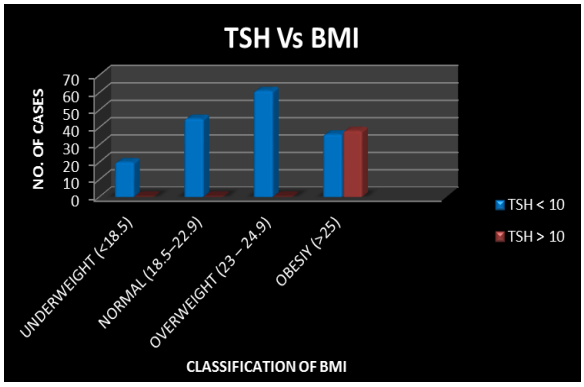
When put together the maximum cases were under the category of overweight-61 (30.5%), obese - 37% versus normal- 45 (22.5%) cases and underweight - 20 (10%).

In all 135/200 patients had BMI > 23 it means they were either over weight, obese. We found that this relationship is statistically significant [($p<0.05$) i.e. here it is 0.000]

TSH	≤ 10		> 10		TOTAL	
	COUNT	% OF TOTAL	COUNT	% OF TOTAL	COUNT	% OF TOTAL
UNDERWEIGHT (<18.5)	20	10.0	0	0.0	20	10.0
NORMAL (18.5–22.9)	45	22.5	0	0.0	45	22.5
OVERWEIGHT (23 – 24.9)	61	30.5	0	0.0	61	30.5
OBESIY (>25)	36	18	38	19	74	37
TOTAL	162	81.0	38	19.0	200	100

Chi-Square Test:

	VALUE	DF	P VALUE
PEARSON CHI-SQUARE	112.83	4	.000



In our study, a total of 149 cases out of 200 were treated.

The following indications were treated – Pregnancy-4, Dyslipidemia-15, Goiter-35, TSH > 10 – 38, Symptomatic-37 and Infertility – 20.Total treated cases:

In our study, 149(74.5%) cases were treated and 51(25.5%) cases were not treated.

INDICATIONS	FREQUENCY
PREGNANCY	4
DYSLIPIDEMIA	15
GOITER	35
TSH > 10	38
SYMPTOMATIC	37
INFERTILITY	20
TOTAL	149

Sex Distribution:

Distribution of patients as per Sex :

SEX	FREQUENCY	PERCENTAGE
MALE	12	6.0
FEMALE	188	94.0
TOTAL	200	100.0

In our study, female population 188 (94%) was dominant than male population 12 (6%).

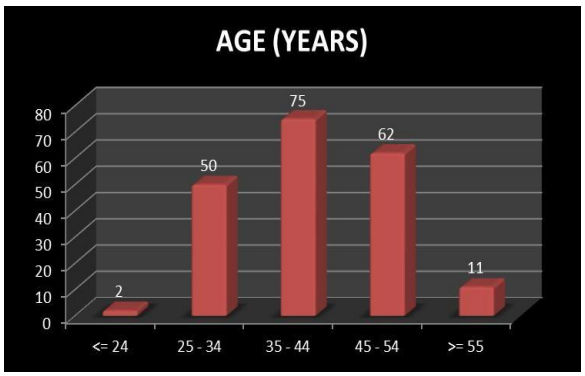
Geographical Distribution:

Rural population was predominant in our study 67 %.

RESIDENCE	FREQUENCY	PERCENTAGE
RURAL	134	67.0
URBAN	66	33.0
TOTAL	200	100.0

Distribution of patients as per Age-Group (Years)

Age (Years)	Frequency	Percentage
<= 24	2	1.0
25 - 34	50	25.0
35 - 44	75	37.5
45 - 54	62	31.0
>= 55	11	5.5
Total	200	100.0

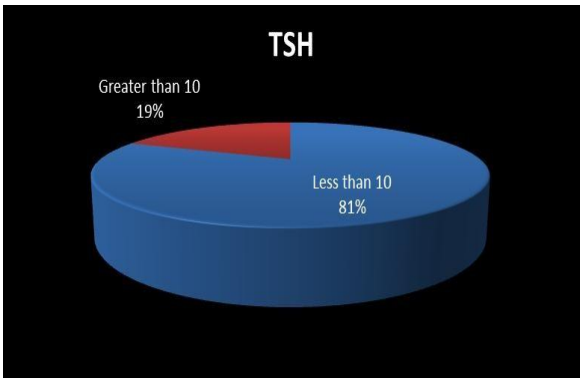


In our study, the most common age group affected was 35-44 yr – 75(37.5%) cases, followed by 45-54 yr-62 (31%),then 25-34 yr-50 (25%) cases, then >=55 yr – 11(5.5%) and the least affected group was <=24 yr – 2 (1%) cases

TSH (Thyroid Stimulating Hormone)

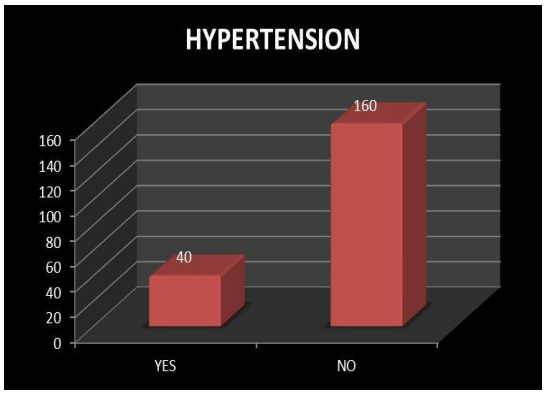
TSH	Frequency	Percentage
< =10	162	81.0
> 10	38	19.0
Total	200	100.0

In our study, 162(81%) cases had TSH <=10 and remaining 38 (19%) cases had TSH > 10.

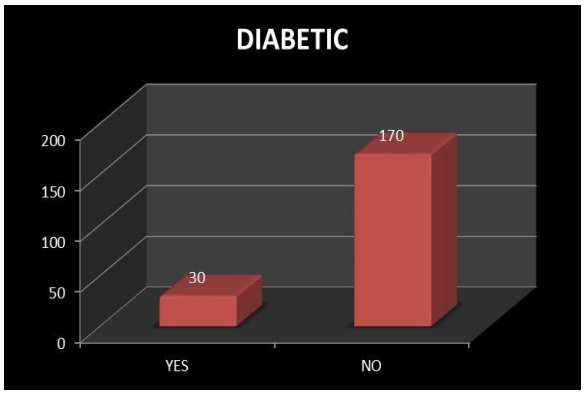


Hypertension and Diabetes Mellitus:

Incidence of Hypertension was 20% and Diabetes Mellitus was 15% in our study.



Number of cases of Hypertension



Number of cases of diabetes mellitus (DM)

30 patients out of 200 were diabetic: Males – 2, Females -28.

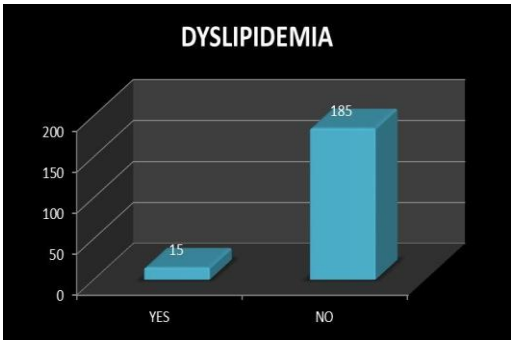
Out of them 20 were from rural area, 13 of them had BMI> 23.

3 females were infertile. Diabetes is linked with raised BMI with poor correlation.

DYSLIPIDEMIA:

In our study, 15 (7.5%) cases had dyslipidemia out of a total of 200 cases.

Dyslipidemia	Frequency	Percentage
Yes	15	7.5
No	185	92.5
Total	200	100.0



INFERTILITY

In our study, 20 (15.74%) females were infertile out of a total of 119 (18-44 years) females of fertile age group.

16 out of these 20 (80%) females had BMI > 23.

Number of cases with Infertility:

Infertility	Frequency	Percentage
Yes	20	15.74
No	147	84.26
Total	127	100.0

DISCUSSION

Western studies have shown a prevalence of SCH 3%-8%. [1] Whereas Indian studies have shown a prevalence of SCH ranging from 9% to32%. [2,3] The prevalence of SCH increases with age. It is more prevalent in female. After the sixth decade of life, the prevalence in men approaches that of women, with a combined prevalence of 10%. SCH aggravates the co-morbid conditions like obesity, infertility, dyslipidemia.

Most of the patients with SCH (80%) have a serum TSH of less than 10 mIU/L. These patients have high likelihood of progression to overt hypothyroidism. The therapeutic approach is to start levothyroxine therapy for the patients with persistent serum TSH levels more than 10.0 mIU/L and individualized therapy for those with a TSH levels less than 10.0 mIU/L.

Controversies exist with regard to the population screening for SCH. The effectiveness of treatment on progression to overt hypothyroidism and overall mortality has been demonstrated. Antithyroid antibodies can be detected in 80% of patients with SCH. [5,1]

Recovery from nonthyroidal illness, presence of antibodies interfering with the TSH assay, and certain cases of central hypothyroidism with biologically inactive TSH and thyroid hormone resistance, should be excluded before diagnosing it to be SCH. However, the most common cause of elevated TSH is autoimmune thyroid disease. Previous radioiodine therapy, thyroid surgery, and external radiation therapy can also result in mild thyroid failure. Transient SCH may occur after episodes of postpartum, silent, and granulomatous thyroiditis. [14,15]

The clinical importance of SCH, treatment for mildly elevated serum TSH level (<10 mIU/L) and the exact upper limit of normal for the serum TSH level are debatable. When the TSH level is above 10mIU/L, levothyroxine therapy is generally agreed to be appropriate. However, management of patients with a serum TSH level of less than 10 mIU/L is controversial. [16]

Some evidence indicates that levothyroxine replacement improves some parameters of lipid profiles and left ventricular function. [17] The American Thyroid Association recommends screening for SCH beginning at age 35 years and every 5 years thereafter as it is associated with metabolic risk factors such as hyperlipidemia, obesity, and infertility. [18]

The American College of Physicians acknowledges that treatment for subclinical thyroid dysfunction is controversial but suggests that screening to detect thyroid dysfunction may be indicated in women older than 50 years. Because of potential implications of SCH for adverse outcome of pregnancy and neuropsychiatric development of the fetus, aggressive case finding in pregnant women or in women

anticipating pregnancy has been suggested. [1]

Most patients with sub-clinical hypothyroidism present with vague and non- specific symptoms. Some studies state that clinical signs and symptoms cannot predict thyroid status. [10] Widespread iodine deficiency and the lack of screening programs make the situation complex in India. A significant proportion of patients with subclinical hypothyroidism may progress to overt hypothyroidism. Identifying subclinical hypothyroidism in a population with high prevalence thyroid disorders may prove beneficial. [3] The concomitant presence of subclinical hypothyroidism and thyroid antibodies multiplies the risk of developing clinical hypothyroidism in future. [3] Various studies have attempted to study the effect of subclinical hypothyroidism on metabolic and chronic illnesses. Controversies exist with regard to its clinical significance, the variability of normal TSH levels with age, cardiovascular mortality and the effect of thyroid hormone replacement. [11] An association has also been suggested between elevated total serum cholesterol levels and subclinical hypothyroidism. [12] The mild hyperlipidemia present in patients with subclinical hypothyroidism may also increase the risk of atherosclerosis. A recent review suggested that TSH levels greater than 10mIU/l is associated with a higher risk of coronary heart disease and mortality. [13] Increased rate of residual myocardial ischemia is also seen in patients with clinical hypothyroidism. [14] In the neuromuscular system subclinical hypothyroidism may cause peripheral neuropathies [15,16] muscular weakness and low exercise tolerance. [17] Reviews have also stated a significant prevalence of subclinical hypothyroidism among patients with bipolar mood disorders. [18]

A meta-analysis demonstrated that high TSH levels may also be related to cognitive impairment in young individuals.

Treatment of subclinical hypothyroidism may relieve clinical symptoms, improve lipid profiles and lower the risk of atherosclerosis. [14] In spite of a predicted high prevalence, clinical studies evaluating the patient presentation of subclinical hypothyroidism among Indians are few. This study attempts to assess the various clinical presentations associated with SCH especially in relation with BMI, Infertility, and lifestyle related disorders.

CONCLUSION

Subclinical hypothyroidism is a biochemical diagnosis with subtle symptoms. is also associated with conditions like dyslipidemia, pregnancy, infertility, goiter and some symptoms where it should be treated as treating it will be beneficial.

1. We studied was 200 cases of subclinical hypothyroidism. Out of 200 patients 112 (56%) patients were symptomatic. There was Female preponderance 188 Vs. 12
2. The most affected age group was of third and fourth decade (35-44 years),75 cases out of 200 (37.5%). The least affected group was of age less than 24 years.
3. Rural population was predominant (67%). The cause of this is not known.
4. 67.5% patients BMI > 23%.
5. In 19% cases TSH was more than 10 mIU/ml with normal FT_3 and FT_4 values.
6. There was rural female preponderance as regards the co-morbidity Diabetes Mellitus and obesity associated with SCH.
7. Patients with dyslipidemia having obesity in 3rd & 4th decades having female sex show significant co-relation with SCH.
8. In our study, 20 (15.74%) females were infertile out of a total of 127 fertile females. 16 out of these 20 (80%) females had BMI >23. There is no geographical bias for infertility of the pt.
9. Therefore Obese Females in fertile age group must be screened for SCH.

10. 74.5% (149 patients out of 200) were initiated on low dose levothyroxine.

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