

Study of Evaluating Spontaneous Course of SCH and the Risk Factors which Enhances the Occurrence of Overt Hypothyroidism (OH)

Rupam Kumari

Assistant professor, Department of General Medicine, Rama Medical College Hospital and Research Centre, Hapur, Uttar Pradesh, India

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Corresponding Author: Dr. Rupam Kumari

Conflict of interest: Nil

Abstract

Aim: The aim of the study was to determine the spontaneous course of SCH and to identify the risk factors, which enhances the occurrence of overt hypothyroidism (OH).

Methods: This was a prospective observational study conducted at Department of General Medicine, Rama Medical College Hospital and Research Centre, Hapur, Uttar Pradesh, India from March 2022 to Feb 2023. A total of 100 patients were recruited in this study.

Results: Mean \pm SD age, BMI and WC were 44.46 \pm 12.48 years, 25.35 \pm 4.76 kg/m² and 93.17 \pm 10.75 CM, respectively. There was no significant age, BMI and WC difference between male and females' group. Central obesity was present in 85%, 83.34% and 85.71% all, males and females respectively and there was no significant difference between males and females. Diabetes mellitus (DM) was present in 32%, 53.34% and 22.85% all, males and females respectively. Anti-TPO antibody was present in 35%, 16.66% and 42.85% all, males and females respectively. Prevalence of DM was significantly more in males as compared to females. TSH <6 was present in 40%, 53.34% and 34.28% all, males and females respectively. Prevalence of autoimmunity was similar in two groups. Mean \pm SD value of total T3, total T4 and TSH at baseline were 114.56 \pm 24.06 ng/dl, 7.63 \pm 1.43micro gm/dl and 6.56 \pm 1.68 IU/L respectively. There was no significant difference of TT3, TT4 and TSH between males and females' group.

Conclusion: In a cohort of 50 patients followed for one year only the presence of anti-TPO antibody was predictive of OH. The initial risk stratification can identify patients with SCH at greatest risk for progression to OH in which treatment is mandatory.

Keywords: SCH, OH, Progression, Anti-TPO antibody

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Introduction

Among various endocrine problems, thyroid disorders are the most common worldwide. It has been reported that in India alone, about 42 million people suffer from thyroid disorders.[1] Worldwide, iodine deficiency is the most common cause of hypothyroidism.[2] Subclinical hypothyroidism (SCH) is a common endocrine disorder in India and worldwide.[3] It is defined as an elevated serum thyrotropin (TSH) level with normal total thyroxine or free thyroxine (T4) level and without clinical features of hypothyroidism. SCH is often detected incidentally as patients exhibit few or no signs of thyroid dysfunction. There is a paucity of studies evaluating the natural history of SCH from India.[4] Patients with SCH are often asymptomatic but 1/3rd of patients may have symptoms that are suggestive of thyroid hormone deficiency such as dry skin, fatigue, poor memory, muscle cramps, puffy eyes, cold intolerance and hoarseness of voice.[5] This syndrome is most often seen in patients with early

Hashimoto's disease and is a common phenomenon, occurring in 7 to 10 % of older women.[6,7]

Huber et al evaluated spontaneous history of SCH in 154 female patients over a 10 year period; 57% of patients continued to have mild thyroid failure, 34% of patients progressed to OH and 9% of patients reverted to normal TSH level.[8] In Wickham study TSH >6 (IU/l) was predictive of progression to OH with odds ratio of 14 (95% CI, 9-24) as compared to TSH <6 IU/L.[9] Other predictors of progression are presence of antithyroid antibodies, female gender, low-normal FT4, lithium therapy, history of radioiodine ablation for Graves' disease and history of external radiation therapy for non-thyroid malignancies. Due to high prevalence of this disease and associated complications, it is important to determine the spontaneous course of the disease. The early detection of patients who might progress to OH or regress would be important in this scenario. Clinicians often consider TSH abnormal when its

value exceeds the upper reference range of the laboratory, which may result in unnecessary long term thyroxine replacement.

SCH is known to be associated with dyslipidemia, abortion, miscarriage, endothelial dysfunction, coronary artery disease, peripheral vascular disease, aortic atherosclerosis, myocardial infarction, and others. [10,11]

The aim of the study was to determine the spontaneous course of SCH and to identify the risk factors, which enhances the occurrence of overt hypothyroidism (OH).

Methods

This was a prospective observational study conducted at Department of General Medicine, Rama Medical College Hospital and Research Centre, Hapur, Uttar Pradesh, India from March 2022 to Feb 2023. A total of 100 patients were recruited in this study.

Inclusion criteria was patients with age >18 years with recent diagnosis of spontaneous SCH (Normal total T4 and TSH >4.2 IU/L-<10 IU/L) were enrolled in the study. Pregnant women, patients with radio-iodine therapy and patients with previous history of thyroxine therapy were excluded from this study. No patients were on any drug, which alters the thyroid hormone profile. Diagnosis of SCH was based on raised TSH (>4.2 IU/L) but <10 IU/L and normal total T3 (TT3) and T4(TT4). A total 58 SCH patients were enrolled in the present study. Data

regarding age, sex, body mass index (BMI), waist circumference (WC), blood glucose (BG), anti-TPO antibody were collected from patients on a predefined format on each visit. Weight was measured by a weighing machine with accuracy of 0.1 kg. Height was measured by a stadiometer with accuracy of 0.1 cm. BMI was calculated by weight (kg) divided by square of height (meter). Two visits were planned at six-month interval for one year. Thyroid test was repeated after one month to exclude the normal fluctuation at each visit thyroid profile was tested and demographic profile were recorded. At the follow up examination, we defined patients with OH as those with TSH ≥10 IU/L.

Ethics Statement

All SCH patients provided written informed consent and agreed to participate in this study.

Statistical Analysis

All recorded data were summarized using descriptive analysis. Mean and standard deviation were used to describe continuous variables. Frequency and percentage were used to describe categorical variables. The differences between sex groups for baseline variables were done by independent sample t-test (two tailed). A p<0.05 was considered as statistically significant. Chi square test was used for categorical variables. Statistical analysis was performed using SPSS version 26.

Results

Table 1: Baseline demographic profile of study population

Parameters	All, N (%)	Male, N (%)	Female, N (%)	P value
N	100	30	70	
Age (years)	44.46±12.48	47.73±12.18	41.19±12.38	<0.051
BMI (kg/m ²)	25.35±4.76	25.25±3.33	26.14±5.25	<0.07
WC	93.17±10.75	96.84±5.65	93.37±12.58	<0.24
Central Obesity				
Present	85 (85)	25 (83.34)	60 (85.71)	<0.91
Absent	15 (15)	5 (16.66)	10 (14.29)	
Diabetes Mellitus				
Present	32 (32)	16 (53.34)	16 (22.85)	<0.01
Absent	68 (68)	14 (46.66)	54 (77.15)	
Anti TPO				
Present	35 (35)	5 (16.66)	30 (42.85)	<0.11
Absent	65 (65)	25 (83.34)	40 (57.15)	
Total T3	114.56±24.06	116.64±24.06	115.05±24.32	<0.74
Total T4	7.63±1.43	7.43±1.24	7.87±1.46	<0.22
TSH	6.56±1.68	6.64±1.58	6.56±1.64	<0.52
TSH				
<6	40 (40)	16 (53.34)	24 (34.28)	<0.52
>6	60 (60)	14 (46.66)	46 (65.72)	

Mean \pm SD age, BMI and WC were 44.46 \pm 12.48 years, 25.35 \pm 4.76 kg/m² and 93.17 \pm 10.75 CM, respectively. There was no significant age, BMI, and WC difference between male and females' group. Central obesity was present in 85%, 83.34% and 85.71% all, males and females respectively and there was no significant difference between males and females. Diabetes mellitus (DM) was present in 32%, 53.34% and 22.85% all, males, and females respectively. Anti-TPO antibody was present in 35%, 16.66% and 42.85% all, males, and females

respectively. Prevalence of DM was significantly more in males as compared to females. TSH <6 was present in 40%, 53.34% and 34.28% all, males and females respectively. Prevalence of autoimmunity was similar in two groups. Mean \pm SD value of total T3, total T4 and TSH at baseline were 114.56 \pm 24.06 ng/dl, 7.63 \pm 1.43micro gm/dl and 6.56 \pm 1.68 IU/L respectively. There was no significant difference of TT3, TT4 and TSH between males and females' group.

Table 2: Predictors of progression in study population

Parameters	Progressor n (%)	Non-progressor n (%)	Odds ratio (95% CI)	P value
Sex				
Male	5 (16.66)	25 (83.34)	1.22 (0.308, 4.8)	<0.77
Female	10 (14.28)	60 (85.72)		
Glycemic status				
Present	8 (25)	24 (75)	0.43 (0.08, 2.2)	<0.306
Absent	14 (20)	56 (80)		
Anti-TPO				
Present	10 (28.58)	25 (71.42)	4.58 (1.14, 18.28)	<0.02
Absent	10 (15.38)	55 (84.62)		
Central Obesity				
Present	15 (17.65)	70 (82.35)	0.789 (0.139, 4.44)	<0.789
Absent	5 (33.34)	10 (66.66)		
TSH				
<6	5 (25)	15 (75)	1.768 (0.47, 6.63)	<0.394
>6	5 (16.66)	25 (83.34)		

At one-year follow up examination 11 (18.97%) patients progressed to OH (defined as TSH \geq 10 IU/L). In anti-TPO positive group rate of progression to OH was 29.42% while in negative group it was 16.16%. Rate of progression was significantly higher in anti-TPO positive group as compared to negative ($p < 0.023$). Odds ratio for progression to OH in anti-TPO positive group was 4.58 (95% CI; 1.14, 18.28). Sex, glycemic status, central obesity and baseline TSH >6 was not associated with progression to OH.

Discussion

Globally, the leading cause of hypothyroidism in pregnancy is iodine deficiency, and in iodine sufficient areas, most common cause is autoimmune thyroiditis. Other common causes are radio-iodine therapy, thyroidectomy, congenital hypothyroidism, drug use (i.e., rifampicin and phenytoin) and any hypothalamic-pituitary disease. [12,13] Women with lower thyroid reserves preconceptually are often unable to cope with increased metabolic demands during pregnancy period and can enter into the hypothyroid state. Maternal thyroid hormone levels are critical to the fetus, especially in the first trimester due to inability to produce iodothyronines before ten weeks of gestation. This is the period when neurodevelopment of fetus can potentially be hampered due to deficiency of iodothyronines.[14]

Mean \pm SD age, BMI and WC were 44.46 \pm 12.48 years, 25.35 \pm 4.76 kg/m² and 93.17 \pm 10.75 CM, respectively. There was no significant age, BMI, and WC difference between male and females' group. Central obesity was present in 85%, 83.34% and 85.71% all, males, and females respectively and there was no significant difference between males and females. Diabetes mellitus (DM) was present in 32%, 53.34% and 22.85% all, males, and females, respectively. Anti-TPO antibody was present in 35%, 16.66% and 42.85% all, males, and females, respectively. Prevalence of DM was significantly more in males as compared to females. TSH <6 was present in 40%, 53.34% and 34.28% all, males, and females respectively. Prevalence of autoimmunity was similar in two groups. Mean \pm SD value of total T3, total T4 and TSH at baseline were 114.56 \pm 24.06 ng/dl, 7.63 \pm 1.43micro gm/dl and 6.56 \pm 1.68 IU/L respectively. There was no significant difference of TT3, TT4 and TSH between males and females' group. In our study rate of progression to OH was more than the study by Huber et al. [8] In their study at 10 year 28% developed OH over time, 68% remains in SCH state and few (4%) become normal. The reasons for difference could be different age of patients, different in methodology and different population. In our study mean age of patients was lower than Huber et al study. It is known that as age increases the mean value of TSH increases; so many

euthyroid patients can be miss-classified as SCH. That's why rate of progression will be lower in aged population cohort as compared to lower age cohort. Second reason for more progression to OH in Indian SCH patients could be due to smaller thyroid gland size and weight as compared to Caucasians.[15] Smaller size and weight mean less thyroid hormone reserve and so more rapid progression to OH.

At one-year follow up examination 11 (18.97%) patients progressed to OH (defined as TSH \geq 10 IU/L). In anti-TPO positive group rate of progression to OH was 29.42% while in negative group it was 16.16%. Rate of progression was significantly higher in anti-TPO positive group as compared to negative ($p < 0.023$). Odds ratio for progression to OH in anti-TPO positive group was 4.58 (95% CI; 1.14, 18.28). Sex, glycemic status, central obesity, and baseline TSH > 6 was not associated with progression to OH. In this study anti-TPO (autoimmunity) positivity was 34%, which was much lower than that in the Spanish study (76%).[16] This suggests that non-autoimmune etiologies might be responsible for mild thyroid failure in India. Iodine deficiency, endocrine disruptors and various goitrogens might be responsible for milder thyroid failure in Indian patients than westerns. A similar low positive rate (20.5%) Anti-TPO antibody was reported by Kasigi et al. [17] In study by Huber et al [8] (TSH > 6) and Imaizumi et al [18] (TSH > 8) base line TSH was predictive of progression to OH. We did not find such an association. The reason for difference is related to older age of SCH cohort in their study. Patients with TSH < 6 might be mis-classified as SCH in their study. In our study rate of progression to OH in diabetic patients were numerically less than non-diabetic patients but it was not statistically significant. Low rate of progression could be due to use of metformin in diabetic patients. Tudor et al also reported low rate of progression in diabetic patients.[19]

Conclusion

In a cohort of 50 patients followed for one year only the presence of anti-TPO antibody was predictive of OH. The initial risk stratification can identify patients with SCH at greatest risk for progression to OH in which treatment is mandatory.

References

1. Kochupillai N. Clinical endocrinology in India. *Current science*. 2000 Oct 25;79(8):1061-7.
2. Braverman LE, Cooper D. *Werner & Ingbar's the thyroid: a fundamental and clinical text*. Lippincott Williams & Wilkins; 2012 Jul 12.
3. Biondi B, Cooper DS. The clinical significance of subclinical thyroid dysfunction. *Endocrine reviews*. 2008 Feb 1;29(1):76-131.

4. Gopalakrishnan S, Chugh PK, Chhillar M. Goitrous autoimmune thyroiditis in a pediatric population: A longitudinal study. *Pediatrics*. 2008;122: e670-4.
5. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. *Archives of internal medicine*. 2000 Feb 28;160(4):526-34.
6. Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, Braverman LE. Serum TSH, T4, and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *The Journal of Clinical Endocrinology & Metabolism*. 2002 Feb 1;87(2):489-99.
7. Cooper DS. Subclinical hypothyroidism. *New England Journal of Medicine*. 2001 Jul 26;345(4):260-5.
8. Huber G, Staub JJ, Meier C, Mitrache C, Guglielmetti M, Huber P, Braverman LE. Prospective study of the spontaneous course of subclinical hypothyroidism: prognostic value of thyrotropin, thyroid reserve, and thyroid antibodies. *The Journal of Clinical Endocrinology & Metabolism*. 2002 Jul 1;87(7):3221-6.
9. Vanderpump MP, Tunbridge WM, French J, Appleton D, Bates D, Clark F, Evans JG, Hasan DM, Rodgers H, Tunbridge F, Young ET. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. *Clinical endocrinology*. 1995 Jul;43(1):55-68.
10. Tanis BC, Westendorp RG, Smelt AH. Effect of thyroid substitution on hypercholesterolaemia in patients with subclinical hypothyroidism: a reanalysis of intervention studies. *Clinical endocrinology*. 1996 Jun;44(6):643-9.
11. Hak AE, Pols HA, Visser TJ, Drexhage HA, Hofman A, Witteman JC. Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: the Rotterdam Study. *Annals of internal medicine*. 2000 Feb 15;132(4):270-8.
12. Cignini P, Cafà EV, Giorlandino C, Capriglione S, Spata A, Dugo N. Thyroid physiology and common diseases in pregnancy: review of literature. *Journal of prenatal medicine*. 2012 Oct;6(4):64.
13. Sahay RK, Nagesh VS. Hypothyroidism in pregnancy. *Indian journal of endocrinology and metabolism*. 2012 May;16(3):364.
14. Moog NK, Entringer S, Heim C, Wadhwa PD, Kathmann N, Buss C. Influence of maternal thyroid hormones during gestation on fetal brain development. *Neuroscience*. 2017 Feb 7; 342:68-100.
15. Harjeet A, Sahni D, Jit I, Aggarwal AK. Shape, measurements and weight of the thyroid gland

- in northwest Indians. Surgical and radiologic anatomy. 2004 Apr;26(2):91-5.
16. Díez JJ, Iglesias P. Spontaneous subclinical hypothyroidism in patients older than 55 years: an analysis of natural course and risk factors for the development of overt thyroid failure. *The Journal of Clinical Endocrinology & Metabolism*. 2004 Oct 1;89(10):4890-7.
 17. Kasagi K, Takahashi N, Inoue G, Honda T, Kawachi Y, Izumi Y. Thyroid function in Japanese adults as assessed by a general health checkup system in relation with thyroid-related antibodies and other clinical parameters. *Thyroid*. 2009 Sep 1;19(9):937-44.
 18. Imaizumi M, Sera N, Ueki I, Horie I, Ando T, Usa T et al. Risk for progression to overt hypothyroidism in an elderly Japanese population with subclinical hypothyroidism. *Thyroid*. 2011;21(11):1177-82.
 19. Tudor RM, Garrahy A, Woods CP. The prevalence and incidence of thyroid dysfunction in patients with diabetes- a longitudinal follow-up study. *Ir J Med Sci*. 2020;189(1):171-5.