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Original Research Article

Risk of progression to overt hypothyroidism in Indian patients with subclinical hypothyroidism: a prospective observational study

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ABSTRACT

Background: Subclinical hypothyroidism (SCH) is a common endocrine disorder but spontaneous course of SCH in India is lacking. The aim of the study is to determine the spontaneous course of SCH and to identify the risk factors, which enhances the occurrence of overt hypothyroidism (OH).
Method: This is a real world prospective observational study. 58 SCH were followed up six monthly for one year to determine the course of SCH.
Results: After one year of follow up 11 (18.97%) patients progressed to OH. 37 (63.79%) remained in subclinical hypothyroid category. In 10 (17.29%) patients TSH (thyrotropin) normalized. Rate of progression (odds ratio: 4.58; 95% CI: 1.14, 18.28) was significantly more in anti-thyroid peroxidase (TPO) positive group as compared to anti-TPO negative group.
Conclusions: This first data from India clearly shows that SCH has a variable course. Rate of progression to OH is high (18.97%) in Indian SCH patients. In a cohort of 58 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

INTRODUCTION

Subclinical hypothyroidism (SCH) is a common endocrine disorder in India and worldwide.[1-5] It is defined as an elevated serum thyrotropin (TSH) level with normal total thyroxine or free thyroxine (T4) level.[6] The prevalence of SCH in general population ranges from 4-10% and is higher in older population.[1,5,7] 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.[8,9] SCH is known to be associated with dyslipidemia, abortion, miscarriage, endothelial dysfunction, coronary artery disease, peripheral vascular disease, aortic atherosclerosis, myocardial infarction and others.[10-13] SCH also represents early stage of thyroid disease that commonly progresses to OH. Various studies have been reported the rate of progression to OH ranges from 3-18% per year.[14-18] 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.[18] 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.[19] 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.

The prevalence of SCH from this part of India is high.[1,3,4] 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. Here we investigated the rate of progression to OH in SCH patients from Uttar Pradesh of India. Our second aim was to identify the risk factors for progression to OH, which would have implications for follow up and proper management of patients with SCH.

METHODS

This is a prospective observational study conducted between 2018 to 2022 at endocrine clinic and hospital, Varanasi-India. 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. Protocol was approved by ethics committee for research, Opal hospital, Varanasi, India dated 6/1/2018. Study also conducted using good clinical practice following declaration of Helsinki.

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

A total of 58 patients were recruited in this study. Among them 19 were males and 39 were females. Baseline characteristics of all patients were summarized in Table 1. Mean ± SD age, BMI and WC were 42.23±12.79 years, 26.49±4.82 kg/m^2 and 94.12±19.81 CM, respectively. There was no significant age, BMI and WC difference between male and females' group. Central obesity was present in 84.48%, 84.21% and 84.62% all, males and females respectively and there was no significant difference between males and females. Diabetes mellitus (DM) was present in 31.04%, 52.63% and 20.51% all, males and females respectively. Anti-TPO antibody was present in 34.48%, 21.05% and 41.03% all, males and females respectively. Prevalence of DM was significantly more in males as compared to females. Prevalence of autoimmunity was similar in two groups. Mean ± SD value of total T3, total T4 and TSH at baseline were 115.66±24.09 ng/dl, 7.83±1.41 micro gm/dl and 6.61±1.64 IU/L respectively. There was no significant difference of TT3, TT4 and TSH between males and females' group.

At one-year follow up examination 11 (18.97%) patients progressed to OH (defined as TSH ≥10 IU/L). The 37 (63.79%) patients remained in SCH category. In 10 (17.24%) patients TSH normalized. In anti-TPO positive group rate of progression to OH was 35% while in negative group it was 10.53%. 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 (Table 2).

Table 1: Baseline demographic profile of study population.

Parameters		All, N (%)	Male, N (%)	Female, N (%)	P value
Number		58	19	39	
Age (years)		42.33±12.79	46.84±12.02	40.13±12.79	<0.057
BMI (kg/m^2)		26.49±4.82	25.12±3.44	27.15±5.28	<0.08
WC		94.12±10.81	95.89±5.71	93.25±12.55	<0.27
Central obesity	Present	49 (84.48)	16 (84.21)	33 (84.62)	<0.96
	Absent	9 (15.52)	3 (15.79)	6 (15.38)	

Continued.

Parameters		All, N (%)	Male, N (%)	Female, N (%)	P value
DM	Present	18 (31.04)	10 (52.63)	8 (20.51)	<0.01
	Absent	40 (68.96)	9 (47.37)	31 (79.49)	
Anti-TPO	Present	20 (34.48)	4 (21.05)	16 (41.03)	<0.13
	Absent	38 (65.52)	15 (78.59)	23 (58.97)	
Total T3		115.66±24.09	116.89±24.08	115.05±24.39	<0.78
Total T4		7.83±1.41	7.53±1.21	7.97±1.49	<0.23
TSH		6.61±1.64	6.79±1.56	6.52±1.69	<0.54

Table 2: Predictors of progression in study population.

Parameters		Progressor, n (%)	Non-progressor, n (%)	Odds ratio (95% CI)	P value
Sex	Male	4 (21.05)	15 (78.95)	1.22 (0.308, 4.8)	<0.77
	Female	7 (17.95)	32 (72.05)		
Glycemic status	DM (Present)	2 (11.11)	16 (88.89)	0.43 (0.08, 2.2)	<0.306
	DM (Absent)	9 (22.5)	31 (77.5)		
Anti-TPO	Present	7 (35)	13 (65)	4.58 (1.14, 18.28)	<0.02
	Absent	4 (10.53)	34 (89.47)		
Central obesity	Present	9 (18.37)	40 (81.67)	0.789 (0.139, 4.44)	<0.789
	Absent	2 (22.22)	7 (77.78)		
TSH	<6	6 (24)	19 (76)	1.768 (0.47, 6.63)	<0.394
	>6	5 (15.15)	28 (84.85)		

DISCUSSION

SCH is a common endocrine syndrome affecting 8-19.3% of Indian population.[1,3,4] As there is scarce data available from India describing spontaneous course of SCH over a long period, we studied a cohort of 58 patients with SCH in a prospective real-world study for one year. We also analyzed possible prognostic factors for progression to OH. This is to our best knowledge, the first study from India evaluating the spontaneous course of SCH. It is generally seen that not all patients with SCH progress to OH. Many patients remained SCH during one year period and even in some cases there is normalization of TSH. In our study 18.97% of patients progressed to OH while in 63.79% of patient's remains SCH during follow up period. There was normalization of TSH in 17.24% of patients. Other have also reported a high rate of progression to OH.[14,15,21] In our study presence of thyroid antibody (Anti-TPO) was predictive of increased risk of progression to OH. Odds ratio for progression to OH in anti-TPO antibody positive group was 4.58 (95% CI; 1.14, 18.28). Sex, glycemic status, central obesity and baseline TSH (>6) were not predictive of progression to OH. In our study rate of progression to OH was more than the study by Huber et al.[18] 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. Since they can be euthyroid so they will not progress to OH. 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.[20] Smaller size and weight mean less thyroid hormone reserve and so more rapid progression to OH.

In this study anti-TPO (autoimmunity) positivity was 34.4%, which was much lower than that in the Spanish study (76%).[21] 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 more mild thyroid failure in Indian patients than westerns. A similar low positive rate (20.5%) Anti-TPO antibody was reported by Kasigi et al.[22] In study by Huber et al (TSH>6) and Imaizumi et al (TSH>8) base line TSH was predictive of progression to OH.[17,18] 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 (11.11%) were numerically less than non-diabetic patients (22.5%) 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.[23]

The limitation of this study is that thyroid status was based on a single blood test and it is known that there is variation in reproducibility of TSH value.[24] However the strength of

the present study is that it is the first such study from India with adequate sample size.

CONCLUSION

This first data from India clearly shows that SCH has a variable course. Rate of progression to OH is high (18.97%) in Indian SCH patients. In a cohort of 58 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.

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