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Original Research Article

Natural history of subclinical hypothyroidism in diabetes mellitus: a prospective observational study

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ABSTRACT

Background: The natural course of subclinical hypothyroidism (SCH) is variable. Several studies have shown that not all SCH progresses to overt hypothyroidism (OH). Little data are available regarding the natural course of SCH in diabetes mellitus (DM). We aimed to investigate the natural course of SCH in DM patients.
Methods: A total of 118 patients with SCH (52 with DM and 66 without DM) were enrolled in this prospective observational study. Anthropometric, thyroid hormone and Anti-thyroid peroxidase (TPO) antibody (Ab) level were measured at baseline. Thyroid hormone levels were also estimated at 6 month and 12 months.
Result: The majority of the patients, 76(61.86%), remained with SCH, 21(17.8%) progressed to OH and 24 (20.83%) reverted to normal. The rate of progression to OH (DM: 7.69% vs non-DM: 25.76%) was significantly lower in patients with diabetes than in those without. Multivariate logistic regression analysis showed that the risk factors for progression to OH were the glycemic status and thyroid autoantibody.
Conclusion: The present study suggests that patient with SCH have variable disease courses. Glycemic status and autoimmunity are the two most powerful predictors of OH. DM protects the progression to OH whereas thyroid autoantibody increases the risk of progression to OH. We recommend a more aggressive follow up for thyroid autoantibody positive and non-diabetic patients.

Keywords: Diabetes mellitus, Overt hypothyroidism, Subclinical hypothyroidism, Thyroid autoimmunity

INTRODUCTION

The prevalence of thyroid disorder (TD), especially subclinical hypothyroidism (SCH) is high in patients with diabetes mellitus (DM).[1-4] In type 1 DM this is due to autoimmunity, however in type 2 DM association between the two is complex.[1,2] In type 2 DM this association is due to the complex interplay among genetic, hormonal and biochemical factors.[1,2] A prospective longitudinal follow up study shows that higher thyroid stimulating hormone (TSH) level and lower free thyroxine (FT4) levels were associated with an increased risk of DM and progression from pre-diabetes to DM in the Korean population.[5] TSH increases blood sugar level by suppressing insulin secretion and increasing hepatic glucose production by increasing the expression of glucose 6 phosphate and phosphoenolpyruvate carboxikinase activity.[6,7] Low levels of thyroid hormone (T3) also regulates glucose homeostasis by suppressing beta cell function8. This shows that high TSH and low T3 levels are a risk factors for the development of DM. In addition, SCH amplifies the cardiovascular disease (CVD) and micro-vascular

complications in diabetic patients.[9] On the other hand, diabetes also affects the thyroid function such as, nocturnal peak of TSH is blunted, TSH response to TRH is impaired and T4 to T3 conversion is impaired.[10] This shows that TD and DM have multifaceted relationship between them.

Majority of TD in DM are SCH and various guidelines recommend levothyroxine (L-T4) when TSH is persistently >10 mIU/l.[11,12] When TSH is <10 mIU/l guidelines suggest L-T4 therapy only when the risk of progression to OH (overt hypothyroidism) is high.[11,12] There are only two studies in diabetic patients, which access the rate of progression of SCH to OH. Gray et al, have shown that rate of progression is 5% in diabetic patients with positive anti thyroid peroxidase (TPO) patients.[13] Here they compare between SCH with DM vs euthyroid patient with DM.

In Fremantle study rate progression to OH was nil in female SCH patients with DM.[14] In this study only female patients were enrolled. There is no study till now that have been performed in diabetic patients with SCH and compared it with non-diabetic patients with SCH regarding rate of rate of progression to OH. Furthermore, India thyroid patients differ than caucasians.[15-17] Hence, we aimed this study to investigate the natural course of SCH in patients with DM from India and compare it with non-diabetic patients with SCH.

METHODS

Study type

This prospective observational study enrolled 126 patients who were diagnosed with spontaneous SCH at the Endocrine Clinic and Hospital or were referred to this clinic from 2018 to 2023. All patients were ambulatory and not admitted for any serious medical condition. All patients were representative of the general population. This study was conducted in a non-iodine deficient area. 8 patients were excluded from the study because they were lost to follow up or had become pregnant. The diagnostic criteria for diagnosis of SCH were TSH value between >4.2 to <10 µIU/ml with normal total triiodothyronine (TT3) and total thyroxine (TT4) on two occasion (12 weeks apart). OH was defined as having TSH >10 µIU/ml (with normal or low TT4) or TSH<10 µIU/ml with low TT4.

Inclusion criteria

The inclusion criteria of this study were individuals aged >18 who met the criteria for SCH.

Exclusion criteria

Exclusion criteria were pregnancy, renal failure, adrenal insufficiency, history of neck irradiation, cirrhosis, history of thyroidectomy and patients taking drugs which affects thyroid function such as L-T4, anti-thyroid drug (ATD), Lithium, amiodarone and dopamine antagonist. All patients were investigated for Anti TPO Ab at time of enrolling. 24 (46.15%) diabetic and 10 (15.15%) non-diabetic patients were hypertensive and were on combination antihypertensive medications. 36 (69.23%) diabetic and 2 (3.03%) non-diabetic patients were suffering from dyslipidemia and were on anti dyslipidemic therapy. All diabetic patients were on metformin therapy.

Follow up investigation were performed at 6-month intervals for one year. We have chosen one year because the majority of patients progressed to OH in 1 year in many trials and there was a lack of adequate funds to follow up for more years.[18-20] At the end of one year we classified patients in to 3 subgroups based on thyroid function tests. OH group (progresser) means TSH >10 µIU/ml with low or normal TT4 or TSH <10 µIU/ml with low TT4.

Persistent SCH (persister) mean TSH between 4.2 to 10 µIU/ml with normal TT4 and normal thyroid function group (regresser) means TSH <4.2 µIU/ml with normal TT4. Thyroid function test and Anti-TPO Ab levels were measured using venous blood samples from a local laboratory. Serum TT3 (reference range: 60-200 ng/dl), TT4 (range: 4.5-12 µg/dl) and TSH (reference range: 0-4.2 µIU/ml) levels were measured using chemi luminescence immuno assay. Anti-TPO Ab (reference value: positive >34 IU/ml) was measured using chemi luminescence immuno assay.

Ethical approval

All patients were informed about the study and need of follow up for disease management. Written informed consent was obtained from all patients. The Ethical Committee of the Opal Hospital approved the study protocol.

Statistical analysis

We used SPSS software for data analysis. Mean and standard deviation were used for continuous variables and for categorical variable frequency and percentage was used. We used one-way ANOVA, Chi Square, t-test (two tail) and binary logistic regression test as statistical analysis method. For statistical significance a p-value of <0.05 was considered as cut off value.

RESULTS

Baseline characteristics of study population

The baseline characteristics of all patients are summarized in Table 1. A total of 118 (52 diabetic and 66 non diabetic) patients were included in this study with mean age (years), BMI (kg/m2) and waist circumference (WC) (cm) being 49.62, 26.73 and 95.88 respectively. The male to female ratio was 1:1.41. Generalized obesity (BMI>25), BMI>30 and central obesity were observed in 65.3%, 16% and 80.5% of the patients, respectively. Anti-TPO Ab was

positive in 33.1% of the patients. The mean±SD total T3, Total T4 and TSH value were 112.53±21.33, 7.95±1.51 and 6.2±2.32 respectively. As compared to non-diabetics, diabetic patients were non significantly older. Prevalence of male patients was significantly more in diabetic patients as compared to non-diabetics.

Natural course of SCH

Majority of the patients 73 (61.86%) remains SCH during one year follow up. 21 (17.8%) patients progressed to OH and 24 (20.34%) revert back to normal (euthyroid). In diabetic patients 4 (7.69%) progressed to OH, 36 (69.23%) remained SCH and 12 (23.08%) became euthyroid during follow up. In non-diabetic patients[17] (25.76% progressed to OH, 37 (56.06% remained SCH and 12 (18.18% revert back to normal (Table 2 and 3). Rate of progression to OH was significantly less in diabetic patients as compared to non-diabetics patients. In diabetic patients 13 (25%) patients were positive for Anti-TOP Ab. In this group, 2 (15.38%) progressed to OH, 2 (15.38%) became euthyroid and 9 (69.23%) remained SCH. In diabetic patients 39 (75%) were negative for Anti-TPO Ab and in this group, 2 (5.13%) progressed to OH, 10 (25.68%) became euthyroid and 27 (69.23%) remained SCH.

In non-diabetic 26 (39.4%) were positive for Anti-TPO Ab and 40 (60.6%) were negative for Anti-TPO Ab. In Anti-TPO Ab positive non-diabetic group, 10 (38.46%) progressed to OH, 3 (11.54%) regressed to euthyroid and 13 (50%) remained SCH. While in Anti-TPO Ab negative non-diabetic group, 7 (17.5%) progressed to OH, 9 (22.5%) regressed to euthyroid and 24 (60%) remained SCH.

Table 1: Baseline characteristics of patients.

Factors		All	Diabetic	Non diabetic	P value
Number (%)		118 (100%)	52 (44.1%)	66 (55.9%)	
Age (years)		49.62±13.36	50.15±11.05	49.61±13.60	0.45
Gender	Male	49 (41.5%)	27 (51.9%)	22 (33.3%)	0.042*
	Female	69 (58.5%)	25 (48.1%)	44 (66.7%)	
Body mass index		26.73±4.87	27.03±4.44	26.50±5.20	0.563
Waist-circumference		95.88±11.68	97.60±10.74	94.53±12.28	0.158
General obesity (BMI>25)	Present	77 (65.3%)	36 (69.2%)	41 (62.1%)	0.421
	Absent	41 (34.7%)	16 (30.8%)	25 (37.9%)	
General obesity (BMI>30)	Present	19 (16.1%)	8 (15.4%)	11 (16.7%)	0.857
	Absent	99 (83.9%)	44 (84.6%)	55 (83.3%)	
Central obesity	Present	95 (80.5%)	44 (84.6%)	51 (77.3%)	0.317
	Absent	23 (19.5%)	8 (15.4%)	15 (22.7%)	
Anti TPO	Yes	39 (33.1%)	13 (25.0%)	26 (39.4%)	0.099
	No	79 (66.9%)	39 (75.0%)	40 (60.6%)	
T3 baseline		112.53±21.33	113.23±23.05	111.99±20.04	0.755
T4 baseline		7.95±1.51	8.18±1.54	7.77±1.47	0.141
TSH baseline		6.20 (2.32)	5.80 (2.07)	6.45 (2.87)	0.307
T3 final		116.79±23.60	122.00±25.72	112.68±21.08	0.033*
T4 final		7.84±1.56	8.18±1.47	7.57±1.58	0.033*
TSH final		6.72±2.90	6.00±2.38	7.29±3.16	0.013*

*Statistically significant.

Table 2: Natural history of SCH patients at the end of trial.

Parameter	Regressor (Euthyroid)	Persister (SCH)	Progressors (OH)
All	24 (20.34%)	73 (61.86%)	21 (17.78%)
Diabetic	12 (23.08%)	36 (69.23%)	4 (7.69%)
Non-diabetic	12 (18.18%)	37 (56.06%)	17 (25.76%)

P value<0.05

Table 3: Functional status of patients at the end of trial.

Variables		Normal and SCH	Overt hypothyroidism	P value
Number (%)		97 (82.2%)	21 (17.8%)	
Age (years)		49.63±13.22	48.97±14.33	0.748
Gender	Male	39 (40.2%)	10 (47.6%)	0.532

Continued.

Variables		Normal and SCH	Overt hypothyroidism	P value
Number (%)		97 (82.2%)	21 (17.8%)	
	Female	58 (59.8%)	11 (52.4%)	
Body mass index		26.87±5.07	26.10±3.81	0.513
Waist-circumference		95.67±11.75	96.87±11.57	0.670
General obesity (BMI>25)	Present	65 (67.0%)	12 (57.1%)	0.389
	Absent	32 (33.0%)	9 (42.9%)	
General obesity (BMI>30)	Present	16 (16.5%)	3 (14.3%)	1.000
	Absent	81 (83.5%)	18 (85.7%)	
Central obesity	Present	80 (82.5%)	15 (71.4%)	0.241
	Absent	17 (17.5%)	6 (28.6%)	
Diabetes mellitus	Present	48 (49.5%)	4 (19.0%)	0.01*
	Absent	49 (50.5%)	17 (81.0%)	
Anti TPO	Yes	27 (27.8%)	12 (57.1%)	0.010*
	No	70 (72.2%)	9 (42.9%)	
T3 baseline		112.73±22.02	111.62±18.27	0.830
T4 baseline		7.95±1.46	7.95±1.78	0.996
TSH baseline		6.17 (2.23)	6.70 (3.02)	0.670
T3 final		116.82±21.78	116.64±31.30	0.975
T4 final		7.98±1.53	7.21±1.57	0.040*
TSH final		5.66±1.80	11.63±1.73	<0.0001*

*Statistically significant.

Table 4: Binary logistic regression analysis for prediction of hypothyroidism.

Variable	Univariable		Multivariable	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Age (years)	1.006 (0.971-1.042)	0.746	-	-
Gender (Ref: Female)				
Male	1.352 (0.524-3.488)	0.533	-	-
Obesity with BMI>25 (Ref:Absent)				
Present	0.656 (0.251-1.718)	0.391	-	-
Obesity with BMI>30 (Ref:Absent)				
Present	0.844 (0.222-3.205)	0.803	-	-
Central obesity (Ref: Absent)				
Present	0.531 (0.180-1.567)	0.252	-	-
Diabetes mellitus (Ref: Present)				
Absent	4.163 (1.306-13.276)	0.016*	3.685 (1.132-11.994)	0.030*
TPO (Ref: Absent)				
Present	3.457 (1.308-9.134)	0.012*	3.038 (1.121-8.237)	0.029*
TSH baseline (Ref: ≤6)				
>6	1.203 (0.464-3.115)	0.704	-	-
TSH baseline (Ref: ≤8)				
>8	1.283 (0.418-3.941)	0.664	-	-

*Statistically significant.

Predictors for development of OH

Binary logistic regression analysis was performed to evaluate the risk factors for OH development (Table 4). In the univariate analysis, the risk of progression to OH was significantly greater in anti TPO Ab positive patients and non-diabetic patients. Odd ratio for progression to OH in positive anti TPO Ab patients was 3.457 (95% CI; 1.306-9.134), while in non-diabetic patients' odd ratio for progression to OH was 4.163 (95% CI; 1.306-13.276). In the multivariate analysis predictor of OH were also anti-TPO Ab positive and non-diabetic patients. Odd ratios for development of OH in anti-TPO Ab positive and non-diabetic patients were 3.038 (95% CI; 1.211-8.237) and 3.685 (95%CI; 1.132-11.994) respectively.

DISCUSSION

SCH is a common thyroid disorder observed in both the diabetic and non-diabetic population.[1-4] As there is scarce

data available regarding the risk of progression to OH in SCH diabetic patients, we conducted this real-world prospective study in 118 patients. We followed up for one year only because majority of SCH progressed to OH within 1 to 2 years. We also analyzed the various risk factors for progression to OH in this study. To best of our knowledge this is the first study, evaluating the natural history of SCH in diabetic patients while comparing it with SCH in non-diabetic patients. It has been seen that not all SCH patients progressed to OH. Many remains SCH while some revert back to euthyroid. In this present study 17.8% progressed to OH, 61.86% remains SCH and 20.34% revert back to euthyroid. In diabetic patients 7.69% progressed to OH, 69.23% remain SCH and 23.08% became normal. While in non-diabetic patients 25.76% progressed to OH, 56.06% remain SCH and 18.18% revert back to normal. This shows that diabetes has protective effect on progression to OH. In a study by Gray et al, 9/59 (15.25%) developed OH, 43/59 (72.88%) patients remain SCH and 7/59 (11.86%) revert back to normal during a follow up (mean 4.2 years) in diabetic with SCH (group 1) patients.[13] While in euthyroid diabetic (group 2) patients, none developed OH but 2/47 (4.26%) developed SCH during 4.2 years of follow up.

Gray et al concluded that in group 1, OH develop at a rate of 5% per annum in patients with thyroid microsomal antibody. While rate of progression to OH was 1% per annum in patients without antibody They again compared their data with Tunbridge et al, who observed that OH developed at a rate of 5% per annum in non-diabetic SCH cases with positive anti-microsomal antibody.[21] Thus Gray et al, concluded that DM has no bearing on the natural history of autoimmune thyroiditis. Our data is in contrast to Gray et al, data. We believe that DM has protective effect of natural course of SCH. Reason for discrepancies between our results as compared to Gray et al are many. First, definition for OH differs between two.

According to Gray et al, hypothyroidism (OH) means persistent elevation of TSH with low serum T4. We defined OH when TSH is more than 10 (with or without low TT4) or TSH <10 with low TT4. Second, different duration of follow up (Gray: 4.2 years vs Present: 1 year). Third, comparisons of diabetic patients with SCH differ between two studies. Gray et al compare between diabetics with SCH to euthyroid diabetics. We compare between diabetics with SCH and non-diabetics with SCH. In another study (Fremantle Diabetic Study) in women with type 2 DM with SCH, Chubb et al found that none of diabetic's patient with SCH progressed to OH over 5 years follow up.[14] Reason for discrepancy between our study and Chubb et al can be many. First, they enrolled only female but we included both male and females. Second, average age (64.0±12.5 vs 49.62±13.36 years) and BMI (30.1±6.2 vs 26.73±4.87) was higher than ours.

We know that as age and BMI increases TSH rises and thus many may not be a true case of SCH and thus will not progresses. Third, rate of drop out was very high {(26/33) 78.79% in SCH group} in their study as compared to ours. In another study, Tudor et al concluded that incidence of treatable thyroid disease (OH and thyrotoxicosis) is low in diabetic patients (<0.5% per year).[22] But they followed up only euthyroid diabetic patients and not diabetic with SCH as we have done. Reason for lower rate of progression to OH in DM can be many. First, one of the complications of DM is weakened immune system.[23] DM suppresses both humoral and cellular immunity. So, thyroid autoimmunity is also weakened by DM and thus lower rate of progression to OH. Second: metformin is first line of therapy in DM and it is known to suppress the TSH level.[24,25] Metformin reduces TSH by various mechanism. Third: many diabetic patients are on statin therapy for prevention of CVD and this may alter the natural course of SCH. High cholesterol is a known risk factor for development of OH in SCH patients and statin by reducing cholesterol, prevents the progression of SCH to OH.[26] Besides this statin have also anti-inflammatory and immunomodulatory properties.[27] Fourth: many diabetic patients are hypertensive also and most are on combination antihypertensive therapy. Calcium channel blockers are known to suppress the TSH level and thus retard the progression to OH.[28]

Autoimmunity was present in 25%, 39.4% and 33.1% of diabetic, non-diabetic and all cases, respectively. In Gray et al study, anti-microsomal antibody was present in 65% of diabetics with SCH at time of recruitment. Reason for difference could be different iodine status and ethnicity. In Fremantle Diabetic Study, positivity rate for autoimmunity was 36.4%, which was similar to our study. This suggests that non-immune etiology is more responsible for mild thyroid failure in Indian patients. Present study confirms that autoimmunity is a risk factor for progression to OH in patients with SCH. Others have also found the same.[17,20] In the study by Imaizumi et al (TSH>8), Park et al (TSH>7.5), Rosario et al, (TSH>10) and Huber et al (TSH>6), baseline TSH was predictive of risk of progression to OH.[20,29,30,31] We did not find the same in our study. Reason for discrepancy could be due to different study design (non-diabetic vs diabetic), different ethnicity (Western and South East Asian vs Indian)- and different duration (long vs short) of follow up. Age and sex seem to have no role in rate of progression in our study. Others have also found the same.[18,20]

Limitations of present study are many like 2nd and 3rd thyroid function tests were based on single blood test and we know that there is variation in reproducibility of TSH. Secondly, small number of patients in both groups. Third limitation was that it was a single center study so there could be certain biases. Fourth was that authors did not capture data of statin and calcium channel blocker usage in this study as they may change the TSH value. Fifth, was the duration of follow up is short. However, this study has many strengths also. First, this is the first study which compare between diabetic with SCH and non-diabetic with SCH. Second, shorter follow up was due to shortage of fund and risk of progression is mostly seen during first

year of follow up. Third, dropout rate is low in present study.

CONCLUSION

The present study suggests that patients with SCH have a variable disease course. Glycaemic status and autoimmunity are the two most powerful predictor of OH progression. Our data suggest that DM protect the development of OH while autoimmunity increases the risk to development of OH. Age, sex, obesity and initial TSH value do not predict the outcome. We recommend more aggressive follow up in anti TPO Ab positive patients and non-diabetic patients.

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