ORIGINAL ARTICLE

FREQUENCY OF CONVERSION TO OVERT HYPOTHYROIDISM IN PATIENTS WITH AND WITHOUT SUBCLINICAL HYPOTHYROIDISM

Muhammad Shahzad Anwer, Rizwan Hashim, Farooq Ahmed Khan, Aamir Ijaz

Department of Chemical Pathology and Endocrinology, Armed Forces Institute of Pathology, Rawalpindi

Background: Sub-clinical hypothyroidism (SCO) poses diagnostic and management difficulties for pathologists and clinicians. Cases of SCO are now diagnosed with increasing frequencies worldwide mainly because of availability of more sensitive methods for serum TSH, total T_3 and free T_4 assays. The rate of progression of SCO to overt hypothyroidism varies in different populations. Sub-clinical hypothyroidism has been suggested as a risk factor for hypothyroid complications. There is a need to identify and treat patients with SCO before they convert to overt hypothyroidism and develop complications. Objective was to compare the development of overt hypothyroidism in a cohort of patients of sub-clinical hypothyroidism and in subjects with normal thyroid function tests. **Methods**: It was Cohort study conducted at Department of Chemical Pathology and Endocrinology, Armed Forces Institute of Pathology, Rawalpindi. Hundred patients of SCO and almost equal number of age and sex-matched subjects with normal Thyroid function test (TFT) were enrolled as healthy controls. Sub-clinical hypothyroid patients and controls were followed for a period of one year on six monthly bases. The patients were examined for signs and symptoms of hypothyroidism and serum TSH, total T_3 and free T_4 were estimated. The clinical history, physical examination and thyroid function tests were recorded on the pre-designed Performa. **Results**: Fourteen (14%) out of 100 cases of the SCO patients developed overt hypothyroidism, SCO had 2.8 times more risk for conversion to overt hypothyroidism as compared to healthy controls. Moreover female gender and initial levels of serum TSH were the most important predictors for conversion of SCO to overt hypothyroidism. **Conclusion**: The frequency of conversion to overt hypothyroidism in SCO patients approaches 14% and was more commonly observed in female patients.

Keywords: Subclinical hypothyroidism, thyroid stimulating hormone, thyroid function tests, overt hypothyroidism

INTRODUCTION

Sub-clinical hypothyroidism (SCO) is defined as an elevated serum thyroid stimulating hormone (TSH) concentration with normal serum thyroxine (T_4) and serum tri-iodothyronine (T_3) concentration.[1–5] Patients with SCO often have no symptoms or only have non-specific complaints.[3,6,7] Sub-clinical hypothyroidism is caused by same etiological factors as those of overt hypothyroidism.[6,8]

More and more cases of SCO are now recognized worldwide because of use of more sensitive methods for serum TSH, total T_3 and Free T_4 assays. The prevalence of SCO ranges from 1–20%[9] and is twice often in women as in men. By the age of 15 years, prevalence of disorder is about 17% in women and 7% in men.[10] In iodine deficiency regions it could be up to 4.2%.[11] Sub-clinical hypothyroidism affects about 10 million people in USA.[8] In a study carried out in Quetta (Pakistan) almost every fourth patient reporting for thyroid function tests was diagnosed to be suffering from Sub-clinical thyroid disease (SCTD).[12]

Sub-clinical hypothyroidism has been suggested as a risk factor for hypothyroid complications. There is a need to identify and treat patients with SCO before they convert to overt hypothyroidism and develop complications.[3,6] SCO is associated with adverse levels of serum cholesterol (increased LDL-cholesterol and reduced HDL-cholesterol), atherosclerosis and depression.[6,8]

Rate of progression of SCO to overt disease varies from one population to the other. It depends on factors like presence of autoimmunity and iodine intake in diet. A 20 years follow up (Whickham survey) reported 4.3% per year conversion of SCO to overt disease, moreover the rate of conversion was 2.6% if raised serum TSH levels was present alone, and 2.1% if anti-thyroid antibodies alone were positive,[9,13] in studies from UK 17.8%[14] and in studies carried out in Spain 26.2%[15] SCO used to convert to overt hypothyroidism.

Treatment of SCO is currently one of the most controversial topics in medicine. Some physicians are in favour of initiation of treatment before conversion to overt hypothyroidism so as to prevent complications associated with overt hypothyroidism.[16,17] While people against initiation of treatment without abnormal thyroid hormones fear of an over-correction in these patients. There is also no consensus about the level of TSH at which treatment should be started.[16,17]

There is not much local data, available on the subject under discussion and no previous local study has directly documented the conversion to overt hypothyroidism in SCO patients in our population. Keeping in view the sparse data and the complications of the condition, there is a need to address the disease pattern in our setup. Hence, a study had been carried out

to compare the frequency of conversion to overt hypothyroidism in patients with and without SCO. This should give an insight into the disease status in this area.

Keeping in view the unique iodine intake and autoimmune status of our patients there is a dire need of a longitudinal study for follow up of SCO patients. Such a study can be of immense help in formulating treatment guidelines in patients with SCO.

MATERIAL AND METHODS

This cohort study was conducted in the Department of Chemical Pathology and Endocrinology, Armed Forces Institute of Pathology, Rawalpindi. A total of hundred (100) cases of SCO between the ages of 20–70 years for TFT and almost equal number of age and sex-matched subjects from general population with normal TFT reported at Armed Forces Institute of Pathology (AFIP) for routine investigations were included as healthy controls. All patients on treatment for hypothyroidism or having known hypothyroidism, chronic renal failure and all patients who have underwent surgical operation for thyroid disease or pharmacological iodine exposure (less than one year duration), patients taking non thyroid drugs, i.e., metoclopramide and domperidone and patients having pituitary dysfunction or recovery from non-thyroidal illness were excluded from the study.

After interview, history and physical examination, blood sampling for thyroid profile was done, 5ml of blood was collected for serum thyroid profile in plain tube, thyroid profile analysis included serum TSH, free T_4 and total T_3 levels were done. The tubes were properly labelled and sent for analysis within 15 minutes. The patients were instructed to report back after 6 and 12 months for repeat sampling, the laboratory request forms with specified dates of the next visit were handed over to each patient.

Hormonal analysis (TSH, T_4 and T_3) was done by Chemiluminescence Immunoassay technique using Immulite 2000, an automated, random access, immunoassay analyzer.

Data were recorded and analysed using SPSS-11. Frequency and percentage was calculated for qualitative data like gender and conversion/ development of overt hypothyroidism. Mean and standard deviation (SD) was calculated for numerical data like age and TFT. A Chi-square test was done to compare frequency of conversion/development to overt hypothyroidism in patients with SCO and controls. Relative risk (RR) of developing overt hypothyroidism was also calculated: RR =Incidence in exposed (cases)/Incidence in non exposed (controls). TFTs were compared in subjects with and without SCO by using student *t*-test/Mann-Whitney U Test (for non normal data). A p value of ≤ 0.05 was considered significant.

RESULTS

A total of 100 patients of SCO were studied along with equal number of controls. The mean age of the SCO patients was 43.4±11.7 years and controls was 41.6±12.4 ($p>0.05$). Mean serum TFT concentrations of patients with SCO and control group are shown in Table-1. There was insignificant difference ($p>0.05$) noted in serum T_3 levels at the start of study and that of serum T_4 levels at the beginning of the study and after six months of follow up between the SCO cases and the healthy controls while rest of the cases and controls showed significant difference ($p<0.05$).

Alternate hypothesis was true in case of this study. Sub-clinical hypothyroidism had 2.8 times more risk for conversion to overt hypothyroidism as compared to healthy controls with significant differences ($p=0.03$).

In cases group (SCO), out of 100 cases 14 patients converted to overt hypothyroidism and 86 patients remained in state of SCO with raised serum TSH levels. Comparison of the frequency of conversion to overt hypothyroidism as compared to controls is shown in Figure-1. Comparison of mean serum TSH levels of SCO who converted ($n=14$) and those who did not converted ($n=86$) to overt hypothyroidism at various time intervals when followed up for 12 months is shown in Figure-2. Mean initial serum TSH levels of overt hypothyroidism ($n=14$) was 8.5±1.30 mIU/l and when they converted to overt hypothyroidism was 17.7±5.61 mIU/l ($p=0.01$). While in control group, mean initial serum TSH levels of overt hypothyroidism was 3.3±0.65 mIU/l. However mean serum TSH levels when they converted to overt hypothyroidism was 13.2±4.24 mIU/l ($p=0.01$).

There were 83 female and 17 male patients of SCO. Out of 83 female patients 13 (15.7%) converted to overt hypothyroidism and out of 17 male patients 1 (5.9%) converted to overt hypothyroidism. In control group, there were 84 females and 16 males. 5 controls out of the total 100 healthy controls converted to overt hypothyroidism. One was male and 4 were females among those who converted to overt hypothyroidism. No statistically significant difference ($p>0.05$) was noted for gender between cases and controls.

Clinical features were mostly vague and included malaise, weight gain; constipation, depression and intolerance to cold were the most common presenting features of SCO. Patients and controls who converted to overt hypothyroidism presented with common clinical features (Table-2). In control group, controls who converted to overt hypothyroidism presented mostly with malaise (60%).

Two female patients did not report at 6 month for follow up and one male patient did not report at 12 month interval for follow up but he did not convert to overt hypothyroidism when he was evaluated at 6 month scheduled follow up.

At the end of the study 1 patients who converted to overt hypothyroidism had serum TSH level <10 mIU/l, 3 patients had TSH >20 mIU/l, and the rest of 10 patients had their serum TSH level <20 mIU/l but

>10 mIU/l. Six patients of SCO who did not convert to overt hypothyroidism had their serum TSH levels >10 mIU/L at the end of the study. While in control group, out of 5 healthy controls who were converted to overt hypothyroidism, 3 had serum TSH levels between 10 and 20 mIU/L and 2 had serum TSH levels <10 mIU/L but >4.5 mIU/L and rest of 95 controls remained euthyroid till 12 months.

Patients who converted to overt hypothyroidism presented with clinical features of hypothyroidism were advised to start the treatment in consultation with the medical specialist according to the guidelines of a panel of 13 experts.[7] Apart from conversion to overt hypothyroidism 6 patients had serum TSH levels >10.0 mIU/L so they were advised to continue for regular follow up visits.

The demographic data of SCO showed the mean age of 43.4±11.7 years. Moreover female gender and initial levels of serum TSH were the most important predictors for conversion of SCO to overt hypothyroidism. The mean age of patients who were seen to convert to overt hypothyroid disease was 48±7.8 years.

Table-1: Mean serum TFT concentrations of patients with sub-clinical hypothyroidism and controls

Test	Duration	Mean±SD		*p*
		CASES-SCO	CONTROLS	
T_3 levels	At the start of study	1.78±(0.33)	1.87±(0.29)	0.112
	At 6 months of study	1.66±(0.38)	1.85±(0.32)	0.067
	At 12 months of study	1.50±(0.39)	1.87±(0.34)	0.189
T_4 levels	Start of study	14.38±(2.43)	17.01±(2.86)	0.140
	At 6 months of study	13.45±(2.44)	16.80±(3.17)	0.056
	At 12 months of study	11.87±(3.11)	16.90±(3.72)	0.208
TSH levels	At Start of study	6.08±(1.43)	1.72±(0.77)	0.001
	6 months of study	6.97±(1.67)	2.00±(1.47)	0.001
	12 months of study	8.97±(4.57)	2.38±(2.77)	0.001

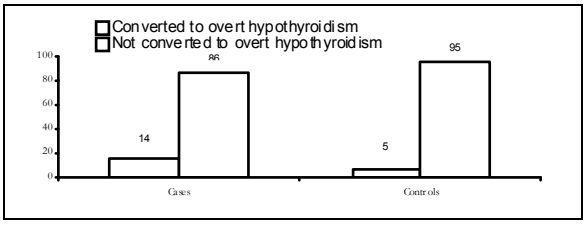

Figure-1: Conversion to overt hypothyroidism in patients of subclinical hypothyroidism and control group at 12 months follow up

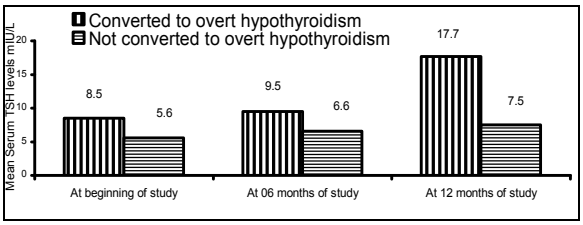

Figure-2: Mean serum TSH levels of sub-clinical hypothyroidism who converted and not converted to overt hypothyroidism at various time intervals when followed up for 12 months

Table-2: Frequency of clinical features in cases (n=14) and controls (n=5) that converted to overt hypothyroidism

Clinical features	Frequency (%)	
	Cases	Controls
Malaise	10 (77.8)	3(60)
Weight gain	8 (66.7)	1(20)
Constipation	8 (66.7)	1(20)
Depression	6 (33.3)	1(20)
Intolerance to cold	5 (22)	1(20)
Non pitting oedema	3 (11.1)	-
Puffiness of face/eyelids/leg swelling	2 (11.1)	-
Bradycardia	1 (11.1)	-

DISCUSSION

The conversion of overt hypothyroidism in patients with SCO has been highlighted by number of international studies, although the pattern and type of the findings have been found to be variable.[8,15,18–21] A local study (Quetta) highlighted the pattern of SCTD in hospital setting in 2001.[12]

But to date, no local data is available with regards to the frequency of conversion to overt hypothyroidism in SCO patients.

The frequency of progression to overt hypothyroidism noted in this study was in agreement with the findings in other studies where up to 20% patients progressed to overt hypothyroidism.[22] This variability could be due to the difference in ethnic origin, age and sex ratio in the populations under study.

The time of onset of overt hypothyroidism was 12 months in this study. Other studies had variable time duration.[6,14,18,23–26]

The other finding noted in this study was that the conversion from SCO to overt hypothyroidism was only 14%. The presence of risk factors like positive thyroid peroxidase (TPO) antibodies, initial high levels of serum TSH do have a significant relationship with progression to thyroid failure and the progression from euthyroidism to overt hypothyroidism might take years or may occur quickly.[6] Rosenthal *et al*.[23] found that one third (25%) of geriatric patients developed overt hypothyroidism and among these, 80% were those who had high-titre of anti-microsomal antibodies[23] during a 4 year of follow-up.

In the Whickham survey, an increased serum TSH level was predictive of progression to overt

hypothyroidism.[18] Old age, female sex, and TPO antibodies were also associated with an increased risk of progression to overt hypothyroidism and the annual rate of progression to overt hypothyroidism was 4.3% per year in women.[18]

In a prospective study carried out by Diez and Iglesias,[27] 107 subjects >55 years of age who had SCO and had no history of thyroid disease were followed up for 6–72 months[15] and out of these twenty-eight patients; 26.8% developed overt hypothyroidism. Moreover, majority of patients (82.1%) progressed to overt thyroid disease in the first month of follow up.

Huber *et al*[8] studied 82 patients with SCO over a mean period of 9.2 years and noted that 28% of patients developed overt hypothyroidism. They had evaluated only female patients (mean age of 50.7 year).

Parle *et al*[15] studied 73 patients aged >60 years with SCO over 12 months follow-up and found that 17.8% developed overt hypothyroidism. Progression from mild to overt hypothyroidism could be related to the cause of thyroid hormone deficiency, the basal serum TSH levels, and the patient's age.[15]

In this study 13 (15.7%) out of 83 females having SCO converted to overt hypothyroidism compared to 17 male patients who had SCO and 1 (5.9%) of these converted to overt hypothyroidism when followed and these findings were in agreement with most of other studies.[15,17,28]

Studies carried out by various authors have implicated the presence of anti TPO antibodies, thyroid stimulating immuno-globulins (TSI) and female gender.[17,28] However, the autoantibody profile of the patient and healthy control group was not in the scope of this study.

In the entire population, the risk of hypothyroidism was higher in patients with serum TSH levels >6 mIU/liter and those who had positive anti-microsomal antibodies status.[8] Moreover finding of this study was that the baseline levels of mean TSH at beginning of a case of overt hypothyroidism was 8.55mIU/L and it was much elevated than the upper limit of the reference interval when compared to patients who did not convert to overt hypothyroidism (mean TSH =5.68±1.0) (Figure-2).

In addition, female gender and initial levels of TSH were the most pertinent predictors for the conversion of SCO to over hypothyroidism. Mean age of conversion to overt hypothyroid disease was 48± 7.8 years. The other important finding of this study was the mean age of SCO that was 43.4±11.7 years and age of conversion to overt hypothyroid disease was 48±7.8 years, these mean ages in different groups are slightly higher than the age limit of screening, i.e., >35 years recommended by American Thyroid Association (ATA).[17]

This study documents the frequency of conversion to overt hypothyroidism observed in patients of SCO (case group) in comparison to subjects without SCO (control group) on 06 monthly bases over a period of 12 months. This study demonstrated the risk of conversion to overt hypothyroidism increased in patients of SCO as compared to control group. The strong predictive factor of this type of thyroid disorder was female gender and initial levels of TSH at the beginning of study.

CONCLUSION

The present study signifies that patients with SCO have a trend towards conversion to overt hypothyroidism (14% in this study) and the same was observed more commonly in female patients. SCO had 2.8 times more risk for conversion to overt hypothyroidism as compared to the healthy controls in this study.

RECOMMENDATIONS

Longitudinal studies with large sample size are required to find the long term outcome of SCO patients along with its complications and all patients presenting with non specific complaints of hypothyroidism need to be screened for SCO initially with highly sensitive serum TSH assays. Moreover, SCO patients >35 years of age should be followed up for every 1 year.

REFERENCES

1. Ringel MD, Mazzaferri EL. Subclinical thyroid dysfunction–can there be a consensus about the consensus? J Clin Endocrinol Metab 2005;90:588–90.
2. Woeber KA. Subclinical thyroid dysfunction. Arch Intern Med 1997;157:1065–8.
3. Hashmi S. Subclinical hyperthyroidism. Med Today 2004;2:132–5.
4. Halfand M. US Preventive Services Task Force. Screening of subclinical thyroid dysfunction in non pregnant adults. A summary of the evidence for the US Preventive Services Task Force. Ann Intern Med 2004;140:128–41.
5. Col NF, Surks MI, Daniels GH. SCTD. Clinical applications. JAMA 2004;291:239–43.
6. Smallridge RC. Disclosing SCTD: An approach to mild laboratory abnormalities and vague or absent symptoms. Postgrad Med 2000;107:143–52.
7. Surks MI, Chopra IJ, Mariash CN, Nicoloff JT, Solomon DH. American Thyroid Association guidelines for use of laboratory tests in thyroid disorders. JAMA 1990;263:1529–32.
8. Huber G, Staub JJ, Meier C, Mitrache C, Gugliemetti M, Huber P *et al*. Prospective study of spontaneous course of SCO: prognostic value of thyrotropin, thyroid reserve, and thyroid antibodies. J Clin Endrocrinol Metab 2002;87:3221–6.
9. Cooper DS. Subclinical hypothyroidism. N Engl J Med 2001;345;260–5.
10. Hueston WJ, Pearson WS. Subclinical hypothyroidism and the risk of hypercholesterolemia. Ann Family Med 2004;2:351–5.
11. Jukie T, Labar E, Kusie Z. Subclinical hypothyroidism. Acta Clin Croat 2001;40:313–7.
12. Ijaz A, Marri MH, Qureshi AH, Qamar MA, Ali N. Pattern of SCTD. J Coll Physicians Surg Pak 2002;12:86–8.
13. Caraccio N, Ferrannini E, Monzani F. Lipoprotein profile in sub-clinical hypothyroidism: response to levothyroxine replacement, a randomized placebo-controlled study. J Clin Endocrinol Metab 2002;87:1533–8.

14. Parle JV, Franklyn JA, Cross KW, Jones SC, Sheppard MC. Prevalence and follow up of abnormal thyrotrophin (TSH) concentrations in the elderly in the United Kindom. Clin Endorinol 1991;34:77–83.
15. Diez JJ, Iglesias P. Spontaneous subclinical hypothyroidism in patients older than 55 years: An analysis of natural course and risk factors for development of overt thyroid failure. J Clin Endrocrinol Metab 2004;89:4890–7.
16. Shrier DK, Burman KD. Subclinical hyperthyroidism: controversies in management. Am Fam Physician 2002;65:431–8.
17. Gharib H, Tuttle RM, Baskin HJ, Fish LH, Singer PA, McDermott MT. Subclinical thyroid dysfunction: a joint statement on management from the American association of clinical endocrinologists, the American Thyroid Association, and the Endocrine Society. J Clin Endocrinol Metab 2005;90:581–5.
18. Vanderpump MP, Tunbridge WM, French JM. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. Clin Endocrinol 1995;43:55–68.
19. Sawin CT, Geller A, Kaplan MM, Bacharach P, Wilson PW, Hershman JM. Low serum thyrotropin (thyroid-stimulating hormone) in older persons without hyperthyroidism. Arch Intern Med 1991;151:165–68.
20. Tenerz A, Forberg R, Jansson R. Is a more active attitude warranted in patients with subclinical thyrotoxicosis? J Intern Med 1990;228:229–33.
21. Woeber KA. Observations concerning the natural history of subclinical hyperthyroidism. Thyroid 2005;15:687–91.
22. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. Arch Intern Med 2000;160:526–34.
23. Rosenthal MJ, Hunt WC, Garry PJ, Goodwin JS. Thyroid failure in the elderly. Microsomal antibodies as discriminant for therapy. JAMA 1987;258:209–13.
24. Glinoer D, Riahi M, Grun JP, Kinthaert J. Risk of subclinical hypothyroidism in pregnant women with asymptomatic autoimmune thyroid disorders. J Clin Endocrinol Metab 1994;79:197–204.
25. Moore DC. Natural course of 'subclinical' hypothyroidism in childhood and adolescence. Arch Pediatr Adolesc Med 1996;150:293–7.
26. Stott DJ, McLellan AR, Finlayson J, Chu P & Alexander WD. Elderly patients with suppressed serum TSH but normal free thyroid hormone levels usually have mild thyroid overactivity and are at risk of developing overt hyperthyroidism. Q J Med 1991;78:77–84.
27. Diez JJ, Iglesias P, Burman KD. Spontaneous normalization of thyrotropin concentrations in patients with subclinical hypothyroidism. J Clin Endocrinol Metab 2005;90:4124–7.
28. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH *et al*. SCTD: scientific review and guidelines for diagnosis and management. JAMA 2004;291:228–38.

Address for Correspondence:

Muhammad Shahzad Anwer, Department of Chemical Pathology and Endocrinology, Armed Forces Institute of Pathology, Rawalpindi, Pakistan. **Cell:** +92-333-5219158
Email: path_shahzad@yahoo.com