SUBCLINICAL HYPERTHYROIDISM-A COHORT STUDY

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ABSTRACT

Objective: To compare the development of overt hyperthyroidism in a cohort of patients of subclinical hyperthyroidism (SCR) and in subjects with normal thyroid function tests

Study Design: A cohort study.

Place and Duration of study: The study was conducted in the department of Chemical Pathology and Endocrinology, Armed Forces Institute of Pathology, Rawalpindi from Sept 2006 to Sept 2007.

Patients and Methods: Fifty patients of SCR and almost equal number of age and sex-matched subjects with normal Thyroid function test (TFT) were included in the study as controls. Subclinical hyperthyroid patients and controls were followed for a period of one year on a six monthly basis. The patients were examined for signs and symptoms of hyperthyroidism and serum TSH, total T3 and free T4 were estimated. The clinical history, physical examination and TFT results were recorded. Five ml of blood was collected for serum thyroid profile in plain tube. Hormonal analysis (TSH, T4 and T3) was done for the patients and the controls enrolled in the study. The TFTs was analyzed using Chemiluminescence Immunoassay technique on Immulite 2000 an automated, random access, immunoassay analyzer.

Results: Six (12%) out of 50 cases of the SCR patients and 2 (4%) out of 50 controls developed overt hyperthyroidism. SCR had no significant risk for conversion to overt hyperthyroidism as compared to healthy controls in this study. In addition to initial levels of serum TSH were one of important predictor for conversion of SCR to overt hyperthyroidism.

Conclusion: Patients with SCR have no significant risk but showed an increase in frequency of conversion to overt hyperthyroidism (12% in this study) as compared to controls.

Keywords: Subclinical hyperthyroidism, Thyroid Stimulating Hormone, Thyroid Function Tests, Overt hyperthyroidism.

INTRODUCTION

Subclinical hyperthyroidism (SCR) is defined as serum thyroid stimulating hormone (TSH) below the reference range with serum free thyroxine (T4) and total tri-iodothyronine (T3) levels within the reference range[1-2]. SCR poses diagnostic and management problems for pathologists and clinicians[3]. Patients with SCR often have no symptoms or only have non-specific complaints[1,4,5]. SCR is caused by same etiological factors as those of overt hyperthyroidism[6]. SCR may be caused by exogenous or endogenous factors[6].

More cases of the SCR are now recognized worldwide because of the use of more sensitive methods for serum TSH, total T3 and free T4 assays. The frequency of SCR ranged from 0.6% to 16%[4]. In a study carried out in Quetta (Pakistan) almost every fourth patient reporting for thyroid function tests was diagnosed as subclinical thyroid disease (SCTD) [7]. SCR has been suggested as a risk factor for hyperthyroid complications. There is a need to identify and treat patients with SCR before they convert to overt hyperthyroidism and develop complications[1, 4]. Patients of the SCR are at increased risk for developing complications like atrial fibrillation, osteoporosis and neuropsychiatric disorders[1, 4].

Rate of progression of SCR to overt hyperthyroidism varies in various populations and is less common in patients with low TSH than in patients with undetectable TSH. It

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depends on factors like the presence of autoimmunity and iodine intake in the diet. In cases of the SCR, the rate of conversion has been reported from 1.5%[8] in the UK to 8.8%[9] in US while another European study has reported 5% rate of conversion in SCR[10].

Treatment of SCR is currently one of the most controversial topics in medicine. Some physicians are in favor of initiation of treatment before conversion to overt hyperthyroidism and prevent complications associated with overt hyperthyroidism[11-12]. While people against initiation of treatment without abnormal thyroid hormones fear of over-correction in these patients. Keeping in view the sparse data and the complications of the condition, a study had been carried out to compare the frequency of conversion to overt hyperthyroidism in patients with and without SCR. This should give an insight into the disease status in this area.

PATIENTS AND METHODS

This cohort study was conducted in the Department of Chemical Pathology and Endocrinology, Armed Forces Institute of Pathology (AFIP), Rawalpindi from Sep 2006 to Sep 2007. Fifty cases of SCR between the ages of 20-70 years for TFT and almost equal number of age and sex-matched subjects from the general population with normal TFT who reported at AFIP for routine investigations were included as controls. All patients on treatment for hyperthyroidism or having known hyperthyroidism, patients taking non thyroid drugs i.e. steroids, dopamine and patients having pituitary dysfunction or nonthyroidal illness were not included in the study. Normal thyroid function test (TFT) (reference ranges): include TSH = 0.45-4.5 mIU/L, free T4=08-24 pmol/L and total T3=1.1-2.7 nmoI/L[5,11].

After taking a history and physical examination, 5 ml blood was collected for serum thyroid profile in plain tube. The thyroid profile analysis included serum TSH, free T4 and total T3. Serum was separated and analyzed by utilizing Chemiluminescence Immunoassay technique on Immulite 2000, an automated, random access, immunoassay analyzer. The patients and the healthy controls were instructed to report back after 06 and 12th month for repeat sampling, the laboratory request forms with specified dates of the next visit were handed over to each patient.

Data recorded and analyzed by using Statistical Package for Social Sciences (SPSS) version 15. Frequency and percentage were calculated for quantative variables like gender and conversion / development of overt hyperthyroidism. Mean and standard deviation (SD) were calculated from quantative variables like age and TFT. The chi - square test was used to compare frequency of conversion / development to overt hyperthyroidism in patients with SCR and controls. Relative risk (RR) of developing overt hyperthyroidism was calculated as: **RR** = Incidence in exposed (i.e. cases) / Incidence in non exposed (i.e. controls). TFT was compared with subjects with and without SCR by using student's t-test/Mann-Whitney U Test (for abnormal data). A *p*-value of less than 0.05 was considered significant.

RESULTS

Fifty patients of SCR were studied along with an equal number of controls. The mean age of the SCR patients was 39 ± 10.6 years and controls were 38.3 ± 10.6 years ($p>0.05$). Mean serum TFT concentrations of patients with SCR and control group is shown in table 1. There was an insignificant difference ($p > 0.05$) noted in serum T3 and T4 levels at the start and 06 months of follow up between the cases and the healthy controls, while the rest of them showed significant difference ($p < 0.05$). There were 39 (78%) females in case group and 44 (88%) in controls ($p>0.05$).

In case group, out of 50 cases 6 (12%) patients converted to overt hyperthyroidism while in controls only 02 (4%) converted to overt hyperthyroidism ($p = 0.269$). SCR had no significant risk for conversion to overt

hyperthyroidism as compared to general population.

Mean of the initial serum TSH levels of overt hyperthyroidism was 0.24 ± 0.08 mIU/l and mean serum TSH levels at the time when they converted to overt hyperthyroidism was 0.05 ± 0.03 mIU/l as shown in figure 1 (p=0. 01). While in control group, mean of the initial serum TSH levels of overt hyperthyroidism was 0.88 ± 0.07 mIU/l however mean serum TSH levels when they converted to overt hyperthyroidism was 0.07 ± 0.007 mIU/l (p=0. 01).

There were 39 female and 11 male patients of SCR. Out of 39 female patients 5 (12.8%) converted to overt hyperthyroidism and out of 11 male patients 1 (9%) converted to overt hyperthyroidism (p = 0.737). In the control group, there were 44 females and 06 males. Two 2 healthy controls out of 50 converted to overt hyperthyroidism, among these one was male and the other one was a female who converted to overt hyperthyroidism (p = 0.091).

DISCUSSION

The conversion of overt hyperthyroidism in patients with SCR has been highlighted by a number of international studies, although the pattern and type of the findings were found to be variable[6-12].

But to date, no local data are available on the frequency of conversion to overt hyperthyroidism in SCR patients.

The frequency of progression to overt hyperthyroidism noted in this study was in agreement with the findings in other studies where up to 30% patients progressed to overt hyperthyroidism[13]. This variability could be due to the difference in ethnic origin, age and sex ratio in the populations under study.

Thyroid gland was slightly palpable in 2 patients out of 6 who converted to overt hyperthyroidism at the end of study. However goiter was absent and thyrotoxicosis resembling Grave's disease was not observed in any of these patients. Hyperthyroidism in these patients was mild and most probably could have been due to autoimmune mediated (early Grave's disease)

Table-1: Comparison of serum TFT concentrations in cases and controls at different times.

Investigations (serum)	Time			*p*-value
		Cases-SCR (n=50)	Controls (n=50)	
T3 levels	Start of study	1.88 ± 0.39	1.93 ± 0.31	.256
	06 months of study	1.87 ± 0.50	2.00 ± 0.33	.071
	12 months of study	2.71 ± 2.70	2.02 ± (.31)	.001
T4 levels	Start of study	17.10 ± 2.65	17.69 ± 2.20	.153
	06 months of study	17.82 ± 2.54	17.84 ± 2.55	.390
	12 months of study	21.30 ± 3.57	18.45 ± 3.38	.001
TSH levels	Start of study	0.28 ± 0.07	1.62 ± 0.72	.001
	06 months of study	0.22 ± 0.09	1.62 ± 0.80	.001
	12 months of study	0.18 ± 0.11	1.59 ± 1.03	.001

Values were expressed as mean ± SD

which occurs between 20 to 50 years of life[14]. Moreover, radioactive iodine uptake scans and thyroid stimulating immunoglobulins (TSI) are required for reaching a definitive diagnosis[4,15,16]. patients with subclinical Graves' disease developed overt hyperthyroidism, whereas none of the 9 patients with multinodular goiter progressed to overt disease.

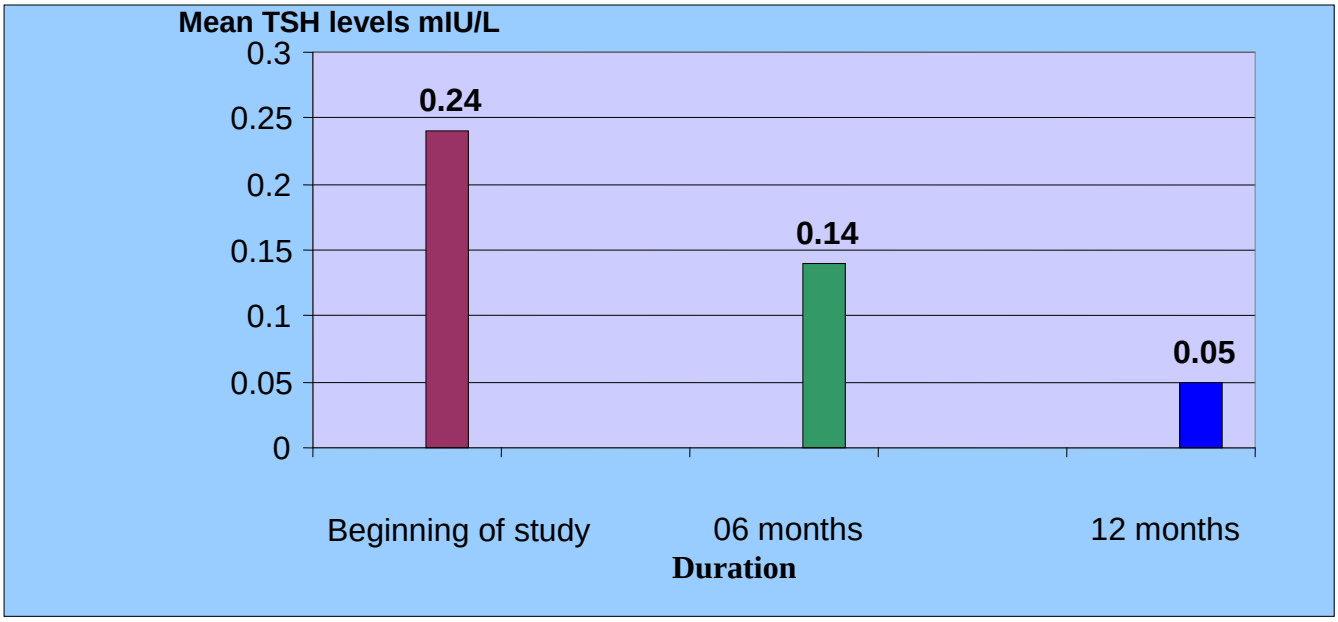

Figure-1: Mean serum TSH levels of subclinical hyperthyroidism who converted to overt hyperthyroidism (n=6).

However these investigations were beyond the scope of this study.

The time of onset of overt hyperthyroidism was 12 months in this study. While other studies have shown variable time duration[4, 12, 17].

The frequency with which SCR progresses to clinically overt disease remains uncertain and could depend on the initial serum TSH concentration and also on the cause of endogenous SCR. In patients of SCR who were >60 years of age Sawin et al[18] noted a 4.1% rate of progression to overt thyroid disease when they were followed for a period of 4 years.

Woeber[19] retrospectively examined 16 patients for a cumulative follow-up of 11–36 months and noted that in these patients the serum TSH levels reverted to normal in 5 of the 7 patients with subclinical Graves' disease and remained subnormal in all 9 patients with multinodular goiter. Only 1 (14.2%) of the 7

Tenerz et al[13] reported that 33 elderly patients with SCR were more likely to develop overt thyrotoxicosis (30% hyperthyroid, 23% remained with suppressed serum TSH levels, and 10% normalized the TSH levels during 2 years of follow-up[13].

Whereas in a study of 15 patients who were 60 years of age and had SCR and were monitored for 4–12 months, their serum TSH levels remained suppressed in 8, and there was progression to overt hyperthyroidism in only 2 (25%) out of 8 patients[20,21].

The progression to overt hyperthyroidism was less common in patients with relatively lower TSH levels than in patients who had undetectable TSH levels[15,22] moreover the baseline levels of mean serum TSH levels at the beginning of the study in cases of overt hyperthyroidism was 0.24 ± 0.08 mIU/*l* that was less than the lower limit of the reference interval

when compared to patients who did not convert to overt hyperthyroidism (mean TSH 0.28 ± 0.07).

This study documents important findings regarding the frequency of conversion to overt hyperthyroidism observed in patients of SCR (case group) in comparison to subjects without SCR (healthy control group) on a 06 monthly basis over a period of 12 months. This should give an insight into the disease status in our population.

CONCLUSION

The present study signifies that patients with SCR have no significant risk but showed an increase in frequency in conversion to overt hyperthyroidism (12% in this study) as compared to controls, and more commonly observed in female patients. This study signifies that longitudinal studies with large sample size are required to find the long term outcome of SCR patients.

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