Original Article

Natural History and Comorbidities of Subjects with Subclinical Hyperthyroidism: Analysis at a Tertiary Hospital Setting

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Abstract

Introduction: Subclinical hyperthyroidism (SH, grade 1, thyrotropin (TSH) ≥0.1 mU/L and grade 2, TSH <0.1 mU/L) is a common disorder with increased prevalence in older subjects. There is evidence for increased morbidities in SH, such as atrial fibrillation and osteoporosis. We aim to study the natural history and comorbidities of SH from patients referred to a tertiary endocrine clinic in Singapore as they are currently unknown. **Materials and Methods:** Retrospective evaluation of SH subjects for natural progression and comorbidities. **Results:** One hundred and thirteen SH subjects (male/female: 24/89, mean age: 67.2 years, grade 1/grade 2: 60/53) were identified from the endocrine clinic. The aetiology of SH include 52 multinodular goitre, 15 Graves' disease, 7 toxic adenoma and 39 unclassified. A minority of SH patients (5.3 %) progressed to overt hyperthyroidism while 13% remitted to euthyroid state (1 to 3 years with a mean follow-up of 18 months) in the total cohort. Most of the patients remained in SH state during follow-up (50/60 in grade 1 SH and 42/53 in grade SH). However, no single predictive factor could be identified for progression or remission of SH. The prevalence of morbidities in SH subjects include ischaemic heart disease (16.8%), heart failure (8.9%), tachyarrhythmias (13.3%), any cardiovascular disease (28%), cerebrovascular disease (28%), osteoporosis (28%), and any fracture (15.9%). **Conclusion:** Most of SH cases in our cohort remain in subclinical state with very few progressing to overt hyperthyroidism. Significant proportion of SH subjects have vascular disease, but this association needs to be confirmed in prospective controlled studies.

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Key words: Cardiovascular risk, Progression, Remission

Introduction

Subclinical hyperthyroidism (SH) is characterised by low serum concentration of thyrotropin (TSH) in the presence of normal serum thyroid hormones and the absence of obvious symptoms of hyperthyroidism. The reported prevalence of SH is variable (depending on the area, iodine intake, inclusion of exogenous SH), more common in women than in men (ratio of female:male is 1.5: 1) and its incidence increases with advancing age.[1] In the recent Cardiovascular Health Study (CHS) of 3233 American community-dwelling individuals aged 65 years or older, the prevalence of SH (TSH 0.10 to 0.44 mU/L) was 1.5%.[2] The prevalence of thyroid autonomy is inversely correlated with the population's iodine intake.[3] Singapore has been classified as an iodine-sufficient country by the World Health Organization (WHO) and International Council for the Control of Iodine Deficiency Disorders (ICCIDD).[4] However the exact prevalence of SH in Singapore is currently not known.

The current management of SH is not consistent among endocrinologists and most of the patients are just monitored with regular thyroid function tests. Most of the reported studies including the recent ones showed that most SH patients remain in this clinical state for a longer duration with very few progressing to overt hyperthyroidism.[5-7] Furthermore, it has been suggested that patients with grade 1

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SH (serum TSH between 0.1 and 0.4 mU/L) rarely progress to overt hyperthyroidism as opposed to grade 2 SH (serum TSH <0.1 mU/L).[5]

SH is associated with increased cardiovascular morbidity, increased prevalence of supraventricular arrhythmias, and atrial fibrillation.[2,8,9] A few but not all studies have shown increased vascular mortality in SH subjects.[10,11]

The natural history and comorbidities of SH in the local Singapore population are unknown and hence we wished to evaluate the natural history of SH and prevalence of cardiac abnormalities (atrial fibrillation/other arrhythmias/cardiac failure/ischaemic heart disease), and other comorbidities such as reduced bone mineral density and fracture rates.

Materials and Methods

Potential SH patients were identified initially from the records of the laboratory medicine service at Tan Tock Seng Hospital (TTSH), Singapore, from October 2005 to January 2010, after local ethics committee approval was obtained. Serum thyroid stimulating hormone (TSH), free thyroxine (FT4) and free triiodothyronine (FT3) were performed on 2 Beckman Coulter DxI-800 immunoassay analysers using manufacturer-supplied reagents and calibrators. Locally derived 95% reference intervals for each of the assays were FT4 8 to 21 pmol/L, FT3 4.3 to 8.3 pmol/L and TSH 0.34 to 5.6 mU/L.

Endogenous SH patients were identified from the initial list of patients who had low serum TSH and normal thyroid hormones (both FT4 and FT3). Patients on antithyroid drugs or levothyroxine and those who had low serum TSH due to non-thyroid illnesses were excluded. All patients on antithyroid drugs such as carbimazole or propylthiouracil given for overt hyperthyroidism or SH and those on levothyroxine supplement for hypothyroidism (obtained from TTSH pharmacy department or from medical records) were excluded. The medical records were then reviewed for natural progression of SH (by serial measurements of thyroid function after initial diagnosis of SH). The associated comorbidities, presence of ischaemic heart disease, atrial fibrillation, cerebrovascular disease, cardiac failure, reduced bone mineral density (BMD), and fracture was also reviewed from the medical records.

Statistical Analysis

This was done using statistical software STATA 11, (Texas, USA). The difference between groups was analysed using Student's t-test or Mann-Whitney U test (for not normally distributed data). Logistic regression analysis was done for factors predicting progression or remission of SH; factors evaluated include aetiology of SH, age at diagnosis, age > or <65 years, gender, TSH, FT4 and FT3 levels, grade of SH,

and size of the goitre. Similar factors were studied for the prediction of comorbidities such as presence of ischaemic heart disease, atrial fibrillation, cerebrovascular disease, any vascular disease and reduced BMD. A *P* value of <0.05 is defined for significant results between comparisons and for regression analyses.

Results

A total of 113 SH subjects (24 males and 89 females), mean age at diagnosis, ± SD 67.2 ± 17.7 years) were identified from the initial list of 6660 patients with biochemical SH. We have excluded patients with biochemical SH due to exogenous use of levothyroxine, those recovering from overt hyperthyroidism and those with transient SH state from non-thyroid illnesses. The prevalence of 3 common ethnicities in the total cohort is as follows: 98 (87%) Chinese, 6 (5%) Malay and 9 (8%) Indians. The aetiology of SH include 52 multinodular goitre (MNG), 15 Graves' disease (GD), 7 toxic adenoma (TA) and 39 unclassified. Sixty (53%) patients had grade 1 SH, whereas 53 (47%) had grade 2 SH at diagnosis. Clinical parameters in both grades of SH are summarised in Table 1.

Only 6 patients (5.3%) progressed to overt hyperthyroidism, while 15 remitted to euthyroid state on follow-up (1 to 3 years with a mean follow-up period of 18 months, 53 patients up to 2 years and 18 patients followed up to 3 years after diagnosis) in the whole study cohort. Figure 1 illustrates these progression/remission in both grades of SH. As this is a retrospective evaluation of patients followed by different clinicians, the follow-up was not uniform and some of the patients were lost to follow-up after a certain period. The progression to overt hyperthyroidism, remission to euthyroid state and persistence of SH in each grades of SH at 1 year, 2 years and 3 years is illustrated in Table 1. However, no single predictive factor (including initial TSH/FT4/FT3 levels, grade of SH, size of the goitre, diagnosis of SH and TSH receptor antibody levels) could be identified for progression (Table 2) or remission of SH.

The prevalence of morbidities in SH subjects include ischaemic heart disease (16.8%), heart failure (8.9%), tachyarrhythmia (13.3%), any cardiovascular disease (28%), cerebrovascular disease (28%), osteoporosis (28%), and any fracture (15.9%).

Subjects with FT4 >15 pmol/L predicted increased prevalence of any cardiovascular disease in logistic regression analysis, but became insignificant after adjusting for age.

Discussion

The natural history of patients with SH in Singapore appears to be similar to other clinical studies reported from

Table 1. Clinical Parameters in 2 Different Grades of Subclinical Hyperthyroidism

Characteristics	Grade 1 SH (n = 60)	Grade 2 SH (n = 53)	P value
Age (year)	68 ± 6.3	66 ± 19.3	0.3
Sex female (%)	45 (75%)	44 (83%)	0.2
Age >65 years (%)	38 (63%)	33 (62%)	0.4
TSH (mU/L)	0.21 ± 0.06	0.04 ± 0.02	<0.001
FT4 (pmol/L)	13.9 ± 2.6	15.4 ± 2.3	0.0008
FT3 (pmol/L)	4.8 ±0.6	4.9 ± 1.9	0.4
Diagnosis of SH (%)			
MNG	30 (50%)	22 (42%)	
GD	6 (10%)	9 (17%)	
TA	2 (3%)	5 (9%)	
Unclassified	22 (37%)	17 (32%)	
Progression to overt hyperthyroidism at 1, 2 and 3 years	0/60, 1/28, 1/7*	4/53, 4/25, 4/11*	
Remission to euthyroid state at 1, 2 and 3 years	7/60, 2/28, 0/7*	4/53, 4/25, 3/11*	
Persistence of SH at 1, 2 and 3years	53/60, 25/28, 6/7*	44/53, 18/25, 6/11*	

TSH: Thyrotropin, FT4: Free thyroxine, FT3: Free triiodothyronine, SH: Subclinical hyperthyroidism, MNG: Multinodular goitre, GD: Graves' disease, TA: Toxic adenoma
The values were provided in mean ± SD and P value of <0.05.
*Number of patients at different thyroid status/total number of patients followed at that time period.
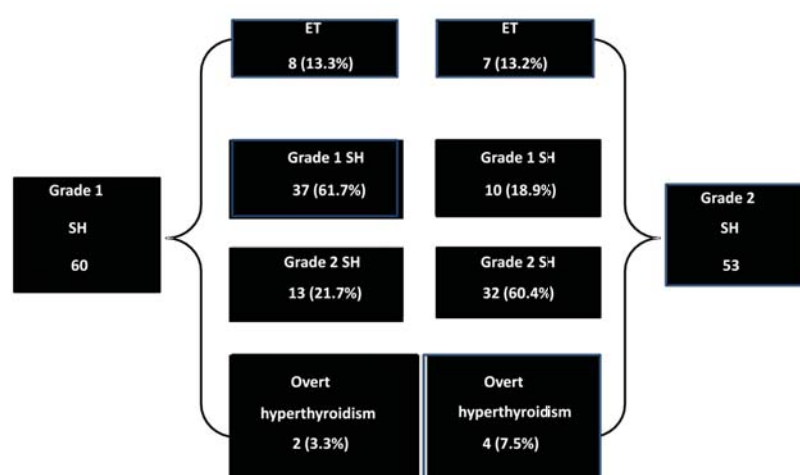

Fig. 1. Natural progression of SH in two grades of SH over 1 to 3 years period.
SH: Subclinical hyperthyroidism, ET: Euthyroid state

different geographical areas and iodine status. Furthermore, like previous published studies, we could not find any factors which could predict the progression of SH to overt hyperthyroidism or reversal to euthyroid state. We also found significant comorbidities in our SH patients such as cardiac problems (ischaemic heart disease, heart failure and atrial fibrillation), and cerebrovascular disease even though this could be an overestimate as this was evaluated in a tertiary care setting.

The progression of SH to overt hyperthyroidism was 5.3% in our SH cohort, which is rather similar to another retrospective study conducted in New Zealand.[12] Progression to overt hyperthyroidism was seen in 8% at 1 year, 16% at 2 years, 21% at 3 years and 26% at 5 years in that study evaluating 96 consecutive SH patients. The rate of progression to overt hyperthyroidism may have been higher in our study, if we had followed our cohort for a longer period. However, in an another large study from Dundee, UK (2024 SH patients), the rate of progression to overt hyperthyroidism was much lower (0.5 % to 0.7%) when followed up to 7 years after diagnosis of SH.[7] The reason for the vast difference in the rate of progression could be due to the fact that both our study and the New Zealand study assessed SH patients at a secondary care setting with more

Table 2. Predictors for Progression of Subclinical Hyperthyroidism to Overt Hyperthyroidism over 1 to 3 Years Period

Factors	Odds ratio	Standard Error	*P* value	95% CI
Age at diagnosis	1.02	0.03	0.41	0.97 – 1.08
Age >65 years	3.1	3.5	0.3	0.35 – 27.53
Diagnosis of SH				
MNG	7.85	9.91	0.10	0.66 – 93.36
Graves' disease	8.50	12.57	0.15	0.47 – 154.17
Toxic adenoma	2.76	3.43	0.42	0.24 – 31.55
Initial TSH	0.42	0.37	0.3	0.07 – 2.41
Initial FT4	2.03	1.80	0.42	0.35 – 11.60
Initial FT3	0.97	0.66	0.97	0.26 – 3.68
TSH receptor antibody	2.04	1.86	0.44	0.33 – 12.3

SH: Subclinical hyperthyroidism, MNG: Multinodular goitre, TSH: Thyrotropin, FT4: Free thyroxine, FT3: Free triiodothyronine

frequent monitoring of thyroid function tests, whereas the Scottish study was done at a primary setting with possible less frequent monitoring. Furthermore, relative low iodine status in Scotland could also have contributed to the very low rate of progression in that study.

The majority of our SH patients remained in the SH state after follow-up period; 50 out of 60 grade 1 SH and 42 out of 53 grade 2 SH remained in SH state, which is similar to the Scottish study at 2 years after diagnosis. However, in that study, with a longer follow-up period, the less number of patients remained in SH state (67.5% at 5 years and 63% at 7 years).[7] We did not follow longer than 3 years to compare our results to that Scottish study.

In the natural history of SH, the reversal back to normal euthyroid state has also been reported in previous studies. In our study, 8 out of 60 grade 1 SH and 7 out of 53 grade 2 SH patients reverted to euthyroid state. This finding is also rather similar to the Scottish study, which reported euthyroid reversal in 17.2%, 31.5% and 35.6% at 2, 5 and 7 years respectively.[7] A higher number of grade 1 SH patients (38 out of 50) reverted to euthyroid state in another study from UK,[5] but this could be due to the lack of strict criteria for diagnosing the SH state and possibility of including patients with non-thyroid illnesses, whereas we have included SH patients confirmed with 2 thyroid function tests at least 6 weeks apart.

The association of cardiac disease in SH such as increased basal heart rate, reduced variability of heart rate, atrial fibrillation and increased left ventricular mass has been confirmed in few studies and reviewed by Biondi and Cooper.[9] The prevalence of atrial fibrillation in SH varies from 3.8%[13] to 12.7%.[8] The prevalence of tachyarrhythmia in our SH cohort was 13.3%, similar to 12.7% reported by Auer et al.[8] A few but not all studies have reported increased risk of heart disease in SH patients. A total of 16.8% of our

SH patients had ischaemic heart disease, the prevalence of which is rather similar to the Scottish study (16.2%)[13] even though the latter study is a population-based study whereas our study evaluated the prevalence of cardiac disease in a tertiary hospital setting. However, our estimation could be lower as we did not formally investigate them for the presence of ischaemic heart disease and collected information from the medical records and self-reporting in few patients.

We also found a significant proportion of cerebrovascular disease in our SH patients (28%). One Danish study also reported increased risk of stroke (hazard ratio of 3.39, CI, 1.15 to 10) in SH patients.[14] Another recent study done in Germany reported 11.5% prevalence of SH in patients admitted with ischaemic stroke. The same study also reported that patients with SH had a substantial functional disability and poor outcome at 3 months after stroke compared to euthyroid subjects.[15] However, the prevalence of SH was much lower (1.6%) in another South Korean study evaluating thyroid function in all consecutive ischaemic stroke patients.[16] The last 2 studies (German and South Korean) assessed the prevalence of SH in patients admitted with stroke, whereas we have studied the prevalence of cerebrovascular disease including mild transient ischaemic attacks in SH patients, which could be the reason for higher prevalence of cerebrovascular disease in our cohort. The association of increased prevalence of cerebrovascular disease could also explain higher prevalence of cognitive dysfunction and dementia in SH patients reported in few studies.[17] Hence, this association of cerebrovascular disease in SH needs to be confirmed in future prospective studies.

Our study is the first study evaluating a reasonable number of SH patients in a Singapore tertiary hospital representing all 3 common ethnicities and providing important clinical information in relation to natural history and comorbidities.

The disadvantages of our study include its retrospective nature, relatively shorter duration of follow-up of SH patients, assessment of comorbidities from medical records and hospital electronic system, which may have missed events that had happened in other hospitals elsewhere, and the possibility of overestimation of prevalence of associated comorbidities as this estimation was done in a tertiary hospital setting and hence cannot be generalised to the general Singapore population.

From the clinical perspective, our results confirm that most SH patients remain stable in SH state, but a significant number of patients have evidence of cardiovascular diseases such as ischaemic heart disease, atrial fibrillation and cerebrovascular disease as discussed above. Current joint guideline issued by American Thyroid Association and American Association of Clinical Endocrinologists (AACE/ATA) advocate treatment in selected SH patients depending on the age and serum TSH levels; treatment is suggested for those with TSH <0.1 mU/L if they are over 65 years of age, presence of heart disease, osteoporosis and the presence of hyperthyroid symptoms (almost all older grade 1 SH patients).[18] We also agree with the above recommendations and at the moment there is no conclusive evidence of treatment benefit in younger SH patients, particularly those with grade 2 SH. However, as significant comorbidities have been found even in grade 2 SH patients and in younger patients, further studies are warranted in this cohort, particularly the effectiveness of treatment of SH state in relation to the cardiovascular outcome.

Conclusion

In summary, most of SH cases in our cohort remain in subclinical state with very few progressing to overt hyperthyroidism. Although a significant proportion of our SH subjects have vascular disease including cerebrovascular disease, this association needs to be confirmed in population-based and prospective-controlled studies. There is also a need to evaluate whether intervention by treatment of SH improves the vascular outcome.

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