
BENEATH THE SURFACE: UNDERSTANDING SUBCLINICAL HYPERTHYROIDISM

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ABSTRACT

Subclinical hyperthyroidism (SH) is a condition characterized by low thyroid-stimulating hormone (TSH) levels and normal levels of free thyroxine (T₄) and triiodothyronine (T₃). Its prevalence increases with age and is more common in iodine-deficient populations. The causes of subclinical hyperthyroidism can be divided into exogenous and endogenous factors. Exogenous subclinical hyperthyroidism results from the use of suppressive doses of thyroid hormones for various medical conditions, while endogenous subclinical hyperthyroidism may arise from underlying thyroid disorders like Grave's Disease, toxic multi-nodular goiter, and thyroiditis. Other factors, such as central hypothyroidism, pregnancy, non-thyroidal illnesses, and specific medications, can also lead to low TSH levels with normal T₄ and T₃. The prevalence of exogenous subclinical hyperthyroidism may vary depending on the chosen TSH cutoff levels. The prevalence is influenced by factors such as dietary iodine intake, with higher prevalence observed in populations with iodine deficiency. This review provides insights into the various causes and prevalence rates of exogenous subclinical hyperthyroidism, offering a comprehensive understanding of this condition.

Keywords: subclinical hyperthyroidism, thyroid-stimulating hormone, iodine deficiency, thyroid disorders, thyroid hormone therapy.

1. Introduction

Subclinical hyperthyroidism (SH) is diagnosed when serum TSH is below normal reference range with serum free thyroxine (T₄) and triiodothyronine (T₃) levels within the normal reference range. The frequency of subclinical hyperthyroidism increases with age and also seems to be higher in iodine-deficient populations (Cooper, 2012). The etiology of subclinical hyperthyroidism can be divided into two categories: exogenous vs. endogenous (Cooper, 2012). Exogenous SH is caused by the ingestion of suppressive doses of thyroid hormones as treatment for thyroid cancer, goiter or hypothyroidism (Biondi, 2005). Common causes of ESCH include toxic multi-nodular goiter, Grave's Disease, solitary autonomously functioning thyroid nodules, and thyroiditis (Bahn, 2011). In addition, low TSH levels with normal T₄ and T₃ can be seen in some subjects with central hypothyroidism, pregnancy, non-thyroidal illness or those who are taking medications such as corticosteroids, phenytoin and dopamine (Bahn, 2011). The prevalence of ESCH may vary depending on TSH cutoff levels used to define it. In the Third National Health and Nutrition Exam Survey (NHANES III) the prevalence was 0.7% using a

cutoff of 0.1mIU/L and 3.2% using a TSH cutoff of 0.4mIU/L. Prevalence also varies inversely with the population's iodine intake, being more common when dietary iodine is relatively deficient, reflecting higher prevalence of toxic nodules and toxic multinodular goiter in these populations.

Some prospective studies have shown that TSH may normalize in 50% of subjects with ESCH whereas overt hyperthyroidism may develop in 5% per year (Biondi, 2005). A panel of experts in 2005 classified patients with subclinical hyperthyroidism in two categories: those with mildly low but still detectable serum TSH (levels between 0.1-0.4mIU/L) and those with an undetectable serum TSH (level below 0.1mIU/L). The progression to overt hyperthyroidism was less common in patients with mildly low TSH as compared to patients with undetectable TSH (Andersen, 2000; Biondi, 2005).

Subclinical hyperthyroidism has been associated with cardiovascular and skeletal effects and impaired quality of life in some studies (Garib, 2014; Laulund, 2014; Mark, 2015; Wirth 2014). The data to guide clinical decisions regarding the treatment of patients with ESCH is limited. In some subjects with ESCH, TFT levels are normal when repeated weeks or months later so that further evaluation may not be cost effective in subjects with normalization of TFTs. Studies evaluating the long-term benefits of correcting ESCH are limited, particularly studies with clinically important endpoints such as cardiovascular disease and fracture. According to ATA/AACE 2011 management guidelines, treatment for ESCH should be considered in individuals ≥ 65 years of age and in patients with cardiac disease or symptoms of hyperthyroidism for TSH $>0.1\text{mIU/L}$ but below the lower limit of normal. When TSH is persistently $<0.1\text{mIU/L}$, treatment of ESCH should be considered in subjects older than 65 years of age, in post-menopausal women who are not on estrogens or bisphosphonates, and in subjects with cardiac risk factors, heart disease or osteoporosis and with symptoms of hyperthyroidism (Bahn, 2011).

2. Materials and Method

2.1. Design

This study was a single site observational retrospective chart review of subjects with ESCH seen in the Ambulatory Care Clinics at the James A. Haley VA Hospital (JAHVA), Tampa, Florida, between July 1, 2002, and June 30, 2012. Chart reviews were done using the automatic data mining tool within the computerized patient record system (CPRS) at JAHVA. ESCH is a biochemical diagnosis defined as a TSH level $< 0.46\text{uIU/ml}$ ($0.464.7\text{uIU/ml}$) with normal Thyroxine (T₄) measured as Total and/or Free T₄ and triiodothyronine (T₃) levels measured as Total and/or Free T₃ levels. This study was approved by the JAHVA Research & Development (R&D) Committee and by the University of South Florida Institutional Review Board (USF IRB) (Pro.0012341).

2.2. Selection

Inclusion criteria were male and female subjects between 18 and 100 years of age with TSH $<0.46\text{uIU/ml}$ and normal T₄ and T₃ serum levels. Excluded subjects included those hospitalized or taking thyroid hormones, glucocorticoid and/or phenytoin as these medications are known to decrease TSH levels. A total of 95 subjects met study criteria and their charts were reviewed.

2.3. Data Collection

We collected data using the automatic data mining tool within CPRS at the JAHVA. We retrieved TSH, T₄ and T₃ levels; data for I-123 radioiodine uptake/scans, bone density (DEXA) scans and thyroid

antibodies, if obtained, was also extracted. Charts were reviewed for the 12-month period following initial diagnosis of ESCH to re-assess levels of TSH, T₄, T₃ and the medical evaluation completed.

2.4. Clinical Endpoints

The primary endpoint is to assess the medical evaluation completed in subjects with ESCH. Secondary endpoint is to assess the clinical progression observed in subjects with ESCH. The goal, based on our findings, is to educate Primary Care Providers in the recognition, evaluation and management of ESCH.

2.5. Statistical Analysis

Descriptive statistics were used to calculate the mean, interquartile range, and standard deviation for the continuous variables and frequency and percent for categorical variables. Data were analyzed using SAS 9.2 (SAS Institute, Cary, NC). Pie diagrams were used to show the results graphically.

3. Results

Ninety-five total subjects were included in the study, 74 (78%) males and 23 (22%) females.

In Figure 1, at the end of one year, out of the ninety-five subjects with ESCH 47 (51%) had normal TFT, 42 (45%) subjects had persistent ESCH and 4 (4%) subjects developed overt hyperthyroidism.

Figure 1.

In Figure 2, at the end of one year only 32 (33%) of the subjects had completed an I-123 radioiodine thyroid uptake and scan.

Figure 2.

In Figure 3, at the end one year only 9 (10%) of the subjects had completed biochemical evaluation for thyroid antibodies.

Figure 3.

4. Discussion

ESCH is a well-known condition to many Endocrinologists but Primary Care Physicians are less familiar with this entity and the evaluation and management that ESCH may require. Since many subjects with low TSH are initially managed by Primary Care Physicians (PCPs) it is very important that PCPs recognize these biochemical abnormalities early and take appropriate action by either referring to an Endocrinologist or by completing the necessary tests. It was noted that less than 50% of the subjects in our study with ESCH who were managed by PCPs received the recommended evaluations.

It has been recommended that subjects with persistent ESCH be followed periodically with TFTs and that further evaluation via I-123 thyroid uptake and scan, thyroid antibodies, and bone DEXA scans should be considered to assess the cause, severity, risk of complications and need for treatment (Nanada, 2004; Surks, 2014).

In this research project, our study group collected data until December 2012. When analyzing the data our investigators noted that several subjects with persistent ESCH were not receiving the recommended clinical and biochemical evaluations and for this reason our Endocrinology Section organized a 4-hour symposium with the objective of educating Primary Care Physicians in the diagnosis, evaluation and management of subclinical thyroid disease, including ESCH. Following this symposium, all Endocrinology providers have noted major improvements in the early recognition, diagnosis, evaluation and management of subjects with ESCH by our Primary Care Physicians while managing

patients in clinic or via E-Consult (Electronic Endocrinology Consultation). Currently patients with low TSH have been evaluated clinically and T4 and T3 levels have been ordered, TFTs have been monitored and further evaluation with I-123 thyroid uptake and scan, thyroid antibodies, and bone DEXA scans have been ordered for subjects with persistent ESCH. E-Consults have greatly facilitated communication between Endocrinologists and PCPs in our institution thereby providing an opportunity for our Endocrinologists to offer guidance for timely and cost-effective evaluations of subjects with ESCH.

There are some limitations to this study. The sample size was small, 95 subjects, as several subjects were excluded because T4/T3 levels were not checked, but this limitation substantiates the fact that our study demonstrated that ESCH was under-recognized and that early recognition of this entity by PCPs is extremely important. Male subjects outnumbered female subjects as a proportionately larger population of Veterans are male.

5. Conclusion

Following a retrospective review of 95 subjects with ESCH which covered a one year period, at the end of that year 51% had normal TFTs, 45% had persistent ESCH, and 4% had overt hyperthyroidism. It was noted that less than 50% of the subjects with ESCH received further work-up (or tests) other than TFTs.

6. Clinical Significance

Subjects with persistent ESCH should be followed periodically with TFTs and further evaluation may be required to assess cause, severity, risk of complications and need for treatment. The education of Primary Care Providers in the recognition, evaluation and management of ESCH is of great importance. E-Consults are valuable tools as they can be used to provide timely guidance in the evaluation and management of ESCH.

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