



Subclinical Hypothyroidism: Review of Concepts and Controversies

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Abstract:

Subclinical hypothyroidism is common in elderly people especially in women. The presence of subclinical hypothyroidism or thyroid antibodies increases the risk of developing overt hypothyroidism and the risk is even greater (about 5% a year) if both are present together. As the age progresses alterations are seen in thyroid gland structure and function. Some of these changes have favorable effects on longevity, whereas others are maladaptive and contribute to a decline in health and quality of life. Thyroid stimulating hormone concentrations above 2 mU/l are associated with an increased risk of hypothyroidism. The biochemical profile of subclinical hypothyroidism includes normal serum levels of thyroid hormones with mildly elevated serum thyroid stimulating hormone concentrations in the range of 4.5 to 10 mIU/L. Screening all acutely ill patients or the healthy general population for hypothyroidism is not recommended. An area of particular controversy is the diagnosis and management of subclinical hypothyroidism. Modest symptomatic benefits occur with thyroxine treatment in some patients with subclinical hypothyroidism, and lipid profiles may also improve. Monitored thyroxine treatment, maintaining normal thyroid stimulating hormone concentrations, has no adverse effects. In this article, the epidemiology of subclinical hypothyroidism is reviewed, some guidelines for screening, treatment and management of the subclinical thyroid dysfunction are discussed.

Introduction

Subclinical or “mild” thyroid disease is a common disorder, particularly in middle-aged and elderly individuals [1]. Greater sensitivity of assays and more frequent assessment of serum thyroid stimulating hormone (TSH) levels have resulted in more patients requiring interpretation of abnormal thyroid function test results. However, there is controversy in the definition, clinical importance, and necessity for prompt diagnosis and treatment of subclinical thyroid disease.

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medium, provided the original author and source are credited.

Subclinical hypothyroidism, also called mild hypothyroidism, is a term used for a condition in which there are small elevations in thyroid-stimulating hormone, yet normal circulating levels of thyroid hormones. This condition is more common in the elderly and is found twice as often in women as in men [2, 3]. While it is uncommon in younger persons, by the age of 65 years, the overall prevalence of the disorder is about 17% in women and 7% in men [4]. Despite recognition of this condition and the observation that a small percentage of these patients advance to overt hypothyroidism each year, controversy continues over whether elderly individuals should be screened for subclinical hypothyroidism [5, 6, 7]. Whereas the American Thyroid Association [8] has endorsed screening for this disorder, others, such as the US Preventive Services Task Force [9] have advised against routine screening. In addition, although the

American College of Physicians recognizes that screening women older than 50 years for hypothyroidism may have some value, they specifically note that the benefit of treating patients with subclinical hypothyroidism has not been evaluated [10]. The decision about whether to screen patients for this disorder is clouded by inconsistent evidence of any benefit from early treatment. A few trials have found that persons with subclinical hypothyroidism who are given L-thyroxine experience some improvements in their energy level and feelings of well-being [11, 12, 13]. Perhaps the most ambitious attempt to address the contentious issues of subclinical thyroid disease in a non-biased and systematic way was undertaken recently by The (American) Endocrine Society, the American Thyroid Association (ATA) and the American Association of Clinical Endocrinologists (AACE). These societies co-sponsored a Consensus Development Conference in 2002 and contracted an independent consulting firm to review and summarize existing published evidence [14]. The planning committee posed a series of clinically relevant questions related to the diagnosis and management of subclinical thyroid disease. Of those questions raised by committee five questions are most are mentioned here: they are

1. What is the definition of subclinical thyroid disease?
2. What is the epidemiology of subclinical thyroid disease?
3. What are the consequences of untreated subclinical thyroid disease, and how should it be evaluated?
4. What are the risks and benefits of treatment for subclinical thyroid disease?
5. Is screening for subclinical thyroid disease warranted?

Subclinical hypothyroidism is a more common entity than subclinical hyperthyroidism and as such this article will focus on subclinical hypothyroidism only. This is arguably also the area of most uncertainty.

Objectives

To understand the concept of subclinical thyroid disease, review its epidemiology, evaluation methods, and explore the risks and benefits of treatment and consequences of non treatment. In the past two decades a number of review articles addressing subclinical thyroid disease have been published. They have in turn focused on evolving issues regarding definition, diagnosis, and management of this common condition. It is important to note that the literature in this area is

still inadequate, and consensus statements may often be an expert panel opinion rather than strictly evidence based.

Whilst the American literature has been the most prolific in recent times in this area [8, 15, 16, 17, 18, 19] and articles have also been published by British and Australian groups [20]. Many of these focus on overt thyroid disease, rather than the more difficult area of subclinical thyroid disease. Previous review articles [16, 17, 21, 22, 23] and position statements [8, 15] differ in their conclusions and recommendations, often a consequence of difficulties in interpreting inadequate and conflicting data. In the midst of this uncertainty, clinicians still desire expert guidance for the diagnosis and management of subclinical thyroid disease. So in the present study we tried our best to summarize all the concepts and controversies about the subclinical hypothyroidism.

Methods

In the present study relevant articles were identified by searching Google Scholar, PUB Med Central, MEDLINE search, the Cochrane library, several National Health Services (UK) databases, including the Database of Abstracts of Reviews of Effectiveness, other articles that are freely available for reading full text, and a local database of thyroid related articles. Key search terms were subclinical hypothyroidism or thyroid deficiency; the following areas were evaluated - epidemiology, screening (*screening of thyroid function tests*), treatment (*therapy or treatment or radiotherapy or surgery or complication*), and consequences of no treatment (*complications or mortality*). Articles reviewed for the present study includes all English-language research articles published on the topic from 1990 to December 2010 were reviewed. Excluded were editorials, individual case studies, studies enrolling fewer than 10 patients, and many nonsystematic reviews.

What is Subclinical Hypothyroidism?

Patients with subclinical thyroid disease have few or no symptoms or signs of thyroid dysfunction and thus by its very nature subclinical thyroid disease is a laboratory diagnosis. Subclinical hypothyroidism is defined as a serum thyroid stimulating hormone (TSH) above the defined upper limit of the reference range, with a serum free thyroxine (T4) within the reference range. Other causes of a raised TSH, a past history of thyroid disease and patients on T4 hormone treatment need to be excluded. It is therefore critically important that the reference limits for TSH be standardized. The TSH method used should have a high functional

sensitivity (at least 0.02 mU/L), although this is of most importance for the diagnosis of subclinical hyperthyroidism.

The reference range for TSH should be based on the third National Health and Nutrition Examination Survey (NHANES-III)[24]. According to NHANES-III the range was 0.45–4.12 mU/L and varied with age, sex, and ethnic background, although these differences were small. The mean concentration was 1.4 mU/L consistent with a skewed distribution and a tail toward higher TSH concentrations. The panel concluded the upper limit of the range should not be reduced as suggested by some associations [25] and a range of 0.45–4.5 mU/L should ultimately be adopted. Whilst the normal reference interval was felt to be adequately defined, the TSH range defining subclinical hypothyroidism remained elusive. An upper limit of 10 mU/L has been quoted in the literature. [17, 19, 20, 26] Perhaps this is because of patients found to have an elevated TSH level, the majority (approximately 75%) have values lower than 10 mU/L [1]. However, the highest TSH quoted in the cross-sectional prevalence studies examined by the panel was 7.0 mU/L [18, 38].

Epidemiology

This is clearly likely to be affected by the TSH range used to define the problem. Certainly different studies reviewed by us utilized different ranges. The prevalence of subclinical hypothyroidism in the United States adult population is 4–8.5%, [1, 24] although this figure increases with age, may differ among ethnic groups and less consistent data is available among men [24]. The progression to overt hypothyroidism is approximately 2–5% per year. The rate of progression is proportional to baseline TSH concentration and is higher in individuals with antithyroid antibodies. [27]

Evaluation of Subclinical Hypothyroidism

If the serum TSH concentration is high and serum FT4 concentration has not been measured, the TSH measurement should be repeated along with an FT4 measurement at a minimum of 2 weeks, but no longer than 3 months, after the initial assessment. We recommend thyroid hormone therapy in individuals with elevated serum TSH concentrations whose FT4 concentration is below the reference range (0.8–2.0 ng/dL [10.3–25.7 pmol/L]). If a high serum TSH concentration is confirmed on repeat testing and serum FT4 is within the reference range, the patient should be evaluated for signs and symptoms of hypothyroidism, previous treatment for hyperthyroidism (radioiodine, partial thyroidectomy), thyroid gland enlargement, or family history of thyroid disease. Lipid profiles should

be reviewed. Women who are pregnant or hope to become pregnant in the near future deserve special consideration. The evidence was insufficient to recommend either for or against routine measurement of anti-TPO antibodies in patients with subclinical hypothyroidism. The presence of anti-TPO antibodies identifies an autoimmune etiology for thyroid dysfunction and predicts a higher risk of developing overt hypothyroidism (4.3% per year vs 2.6% per year in antibody-negative individuals) [27]. Still, antibody presence or absence does not change the diagnosis of subclinical hypothyroidism (which is based on serum TSH measurements) or the expected efficacy of treatment. [14]

Treatment of subclinical hypothyroidism

The prevalence of sub-clinical hypothyroidism varies from 5 to 13.2% depending upon the population studied. Women are affected twice more than men [28]. The increasing prevalence of hypothyroidism has brought into light the various problems encountered in the epidemiological studies of thyroid disorders namely the of definition e.g. overt hypothyroidism and subclinical hypothyroidism, selection criteria of population studied, the influence of age, sex environmental factors, and the different techniques used in the estimation of thyroid hormones [29] A big argument in favor of screening is that recognition and treatment of subclinical hypothyroidism is beneficial[30].

At first sight this seems paradoxical because free thyroxine concentrations are normal and some regard the exclusion of symptoms as a criterion for diagnosis [19, 26] However, many patients do have non-specific symptoms, such as tiredness and weight gain, which could be due to hypothyroidism. After all, the thyroid function tests needed to establish the biochemical diagnosis have usually been performed because of this suspicion. Also, after treatment with thyroxine the patient may notice an improvement in symptoms previously unrecognized because of the slow progression of thyroid failure and its variable manifestations. As thyroid stimulating hormone concentrations >2 mU/l reflect a disturbance of the thyroid-pituitary axis, values above the upper level of the typical reference range (4.5 mU/l) are highly significant departures from normal rather than one tail of the normal distribution. Although T4 therapy was considered to be the hallmark of thyroid replacement in hypothyroidism till very recently, but Robertas Burnevicius Group from North Carolina published their data showing that most patients feel better with addition

of TI where the dramatic improvement was observed in mental functioning [31].

Disadvantages of treatment

Are there risks from taking thyroxine which argue against treating subclinical hypothyroidism? Providing thyroid stimulating hormone concentrations are restored to the reference range, the answer is no, and even if too much is given, the risks of osteoporosis are more theoretical than real. A meta-analysis of studies of excessive thyroxine treatment found no reduction in bone mass in premenopausal women, although postmenopausal women had a significant excess annual bone loss of 0.9%/year after 10 years [32]. However, no increased rate of fractures occurs, despite this loss, and it is also important to distinguish those who are taking thyroxine for iatrogenic hypothyroidism from those with spontaneous hypothyroidism: in the first group there has usually been a period of hyperthyroidism which contributes to the bone loss [33].

The other main concern is the action of excessive thyroxine on the heart. Subclinical hyperthyroidism in people aged 60 or older is associated with a trebling of the risk of atrial fibrillation over 10 years [34]. It is not clear whether the risk applies equally to patients taking thyroxine for iatrogenic hypothyroidism and those with spontaneous hypothyroidism [35]. This study is the most persuasive reason to maintain normal thyroid stimulating hormone concentrations in all patients receiving thyroxine, whether for subclinical or overt hypothyroidism. On balance, the risks of properly monitored thyroxine treatment are almost non-existent.

Conclusion

Of particular interest to laboratories, is that having defined subclinical hypothyroidism as a laboratory rather than a clinical diagnosis, the panel made little reference to the role of the laboratory and its interaction with the physician. A recent research article publication from a British group sheds some light on this [36]. The hospitals serviced by the laboratories had adopted the RCP guidelines which advise routine testing of TPO antibodies. We found in order to better advise clinicians and to achieve compliance with accepted protocols, automatic cascade testing for TPO antibodies as well as appropriate interpretive reports should be an integral part of the investigation of subclinical hypothyroidism. Thus, although guidelines may be generally accepted, they may not necessarily be put into clinical practice.

The recommendations of the consensus panel have been previously criticized [37] and it has been suggested that they may be no more valid than those previously published by other professional groups. However, based on a thorough examination of available evidence, and although unfortunately there is a paucity of evidence addressing the important clinical questions posed. Until there is widespread consensus, and appropriate large, well executed trials upon which to base recommendations, we suggest clinicians to continue to make individual patient assessments when determining the need for testing and treatment of thyroid dysfunction.

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