

Consensus Statement #1

Subclinical Thyroid Dysfunction: A Joint Statement on Management from the American Association of Clinical Endocrinologists, the American Thyroid Association, and The Endocrine Society

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SUBCLINICAL THYROID DYSFUNCTION is a common clinical problem for which there are many controversial issues regarding screening, evaluation, and management. Subclinical hypothyroidism is defined as an elevated serum thyroid-stimulating hormone (TSH) level associated with normal total or free thyroxine (FT₄) and free triiodothyronine (FT₃) levels. The overall prevalence is 4% to 10% in the general population, and up to 20% in women older than 50 years (1–3). Several alternative names have been proposed to describe this condition and include “compensated hypothyroidism,” “preclinical hypothyroidism,” “mild thyroid failure,” and “mild hypothyroidism.” While each term has subtle implications that may be more or less appropriate in various circumstances, we will use the term “subclinical hypothyroidism” in the interest of consistency with a recent publication that is the topic of this discussion. Subclinical hyperthyroidism is defined as low serum TSH levels associated with normal FT₄ and FT₃ levels. The prevalence is approximately 2%, being more common in women, in blacks, and in the elderly (4,5).

In order to develop an evidence-based approach to the various unresolved clinical issues regarding subclinical thyroid disease, the American Association of Clinical Endocrinologists (AACE), the American Thyroid Association (ATA), and The Endocrine Society (TES) jointly sponsored a Consensus Development Conference, which was held in September 2002. A number of questions were presented to a panel of 13 experts, including 8 experts in thyroid disease; the remaining 5 had expertise in cardiology, epidemiology, biostatistics, evidence-based medicine, health-services research, general internal medicine, and clinical nutrition. The consensus panel report is the result of an extensive review of the published literature on these topics available at the time. The conference participants meticulously followed the principles of evidence-based medicine (EBM) to summarize

all existing pertinent data (a summary of the data reviewed is available at www.endo-society.org/education/evidence-report.cfm) and to make EBM recommendations on the controversial issues of screening, evaluation, and management of patients with subclinical thyroid disease. The recently published consensus panel’s conclusions and recommendations (6) were developed independently and therefore did not require official review or approval by the three sponsoring societies. Recognizing the EBM methodology cannot adequately address gray areas where existing evidence is inadequate and that EBM-based guidelines cannot specifically address the multitude of variations encountered by clinicians in their management of individual patients, the consensus authors also published an accompanying case-based discussion illustrating how the guidelines could be applied in several patient scenarios (7). The authors of these two outstanding articles are to be congratulated for these excellent publications and thanked for their service to the community of providers who care for patients with thyroid disorders.

Subsequently, having carefully studied the consensus conference data, summaries, and recommendations, the leadership of AACE, ATA, and TES determined that it would not be appropriate for practicing clinicians and the regulatory elements of the health care industry to be left with the impression that the membership of these three organizations unanimously agreed with all of the consensus conference recommendations, despite their sponsorship of the conference itself. They felt that the data in several areas were inconclusive and that further alternative interpretations and recommendations was not only reasonable but also warranted in the interest of academic fairness. Two members from each of these respective organizations were therefore invited to form a panel to review the consensus conference recommendations to determine if there were areas of legitimate and significant disagreement. All members of this panel

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This report was prepared by a Task Force created by the American Association of Clinical Endocrinologists (AACE), the American Thyroid Association (ATA), and The Endocrine Society (TES).

(the authors of the present discussion) are regularly involved in the clinical care of patients with thyroid disease and all have previously published literature in the thyroid field although not necessarily on the topic of subclinical thyroid disease. The participants were not chosen specifically for their views on subclinical thyroid disease but rather to represent the membership of the three organizations.

Panel members were or became thoroughly familiar with the body of literature that provided the data on which the consensus conference recommendations were based. They did not conduct an independent data analysis. Instead, they relied on the existing data presentation from consensus conference and offered their own alternative interpretations, conclusions, and recommendations that they believed were warranted based on the strength of the evidence presented by the consensus conference and based on their own extensive clinical experience. The present opinion paper was then submitted to the leadership of each of the three organizations, which presented it to each of their governing bodies, who made further recommendations and then endorsed it in its current form as a reasonable alternative and an appropriate response, not to refute, but to present a reasonable counterbalance to the recommendations made by the consensus conference.

Areas of Contention

Our panel agreed substantially with many of the recommendations made by our colleagues who participated in the consensus conference (6). There are three areas, however, with which we have some significant disagreement. Specifically these are the consensus conference recommendations against the following: (1) routine screening for subclinical thyroid disease in the general population; (2) routine screening for subclinical thyroid disease in women who are pregnant or planning pregnancy; (3) routine treatment of patients with subclinical hypothyroidism with serum thyrotropin (TSH) levels of 4.5–10 mU/L.

Our reasons for disagreement on these issues are centered on the consensus conference participants' heavy, if not exclusive, reliance on EBM methodology to substantiate these negative recommendations. Their negative recommendations are inappropriate, in our opinion, because they are based primarily on a lack of evidence for benefit rather than evidence for a lack of benefit. The consensus authors felt that there was insufficient "good strength" evidence to support testing or treating in these circumstances, meaning there were no large randomized controlled trials to document unequivocal benefit; however, there is clearly also no "good strength" evidence that they are not beneficial or that they may somehow be harmful. Accordingly, rather than the evidence being deemed "insufficient to recommend for," such inconclusive evidence should at the very least be termed "insufficient to recommend for or against" the testing or treatment in question. There are subtle but quite important distinctions between these statements that have clear, practical implications for physicians actively involved in the care of patients. Whereas the former statement could be viewed as being restrictive, the latter term more clearly allows for the flexibility that is critical to the physician's role of melding the existing scientific data, the patient's input, and his or her

own clinical judgment to make the best possible decision for each individual patient.

Ellrodt et al. (8), reviewing evidence-based disease management, state that "if inadequate research evidence is available, the disease management team may decide to make no specific recommendations, thus avoiding inappropriate micromanagement and allowing clinical flexibility." We strongly support this position, maintaining that if adequate trials are not available to assess outcomes for treatment of a condition, it is not appropriate to offer guidelines stating that treatment is not indicated. The precepts of EBM indicate that recommendations are based first on "good evidence," then on "fair evidence," and finally on expert opinion. In the area of subclinical thyroid dysfunction, while "good" evidence is unavailable, there is a sizable amount of "fair" evidence and an abundance of opinions by experts in the field. In the opinion of our panel members, the consensus conference recommendations in the areas delineated above are contrary to the practice of many, although not all, experts in the field of thyroid disorders.

EBM is usually rated against a standard of "significant health outcomes of morbidity and mortality (8)." When considering any subclinical condition, such as subclinical hypothyroidism, this issue becomes a problem. We believe that the clinical entity of hypothyroidism is a continuum from subclinical, to overt, to life threatening myxedema coma. By separating out the mildest disease for analysis (TSH levels of 5–10 mU/L), one raises the bar so high that an intervention becomes difficult to justify because the events of morbidity and mortality are many years away.

Screening for Thyroid Disease in the General Population

The consensus conference found "insufficient evidence to support population based screening," using U.S. Preventive Services Task Force (USPSTF) criteria (9,10), and therefore recommended "against population-based screening for thyroid disease." A review of the same published data in a subsequent publication from the USPSTF concluded instead that the available data are "insufficient to recommend for or against routine screening for thyroid disease in adults (10)." As discussed above, these statements may seem similar, but they have very different clinical implications. Because the available published data are admittedly insufficient to allow for a rigorous EBM recommendation with regard to screening, it is appropriate to also consider previously published guidelines that were based predominantly on expert opinion. While population screening has not been supported unanimously, expert panels of most professional societies have endorsed routine TSH screening. For example, the ATA recommends screening both men and women, beginning at age 35 years and every 5 years thereafter (11); AACE recommends screening older patients, especially women (12); the American Academy of Family Physicians recommends routine screening for patients older than age 60 (13); and the American College of Physicians recommends case-finding in women older than age 50 years with one or more symptoms possibly caused by thyroid disease (14).

The views of the consensus conference participants and our panel may not be as far apart on this matter as it appears. The primary issue at variance concerns the advisabil-

ity of population screening for subclinical thyroid disease, which on a practical basis means making TSH measurement a part of the routine periodic health examination in asymptomatic people. While our panel supports routine screening, the consensus panel did not; until additional information is available we will just have to agree to disagree on this matter. However, both the consensus conference participants and our panel agree on the need for "aggressive case-finding." This may be an even more pertinent issue for practicing clinicians than is "routine screening," because case-finding is the situation that exists whenever a provider believes there is a reason to measure a serum TSH level based on a patient's symptoms, signs, personal history, or family history. In such a situation guidelines for routine screening should never be used to discourage or preclude the exercise of clinical judgment on the provider's part.

A related issue was the consensus conference conclusion that, "The evidence was insufficient to recommend either for or against routine measurement of anti-TPO antibodies in patients with subclinical hypothyroidism (6)." In contrast, we believe that the measurement of anti-thyroid peroxidase (TPO) antibodies is a valuable adjunct in the evaluation of patients with subclinical hypothyroidism because, as the consensus conference states, it "predicts a higher risk of developing overt hypothyroidism (4.3% per year versus 2.1% per year in antibody-negative individuals) (6)." Furthermore, it raises the concern that such patients may be at increased risk of developing other autoimmune diseases, such as adrenal insufficiency and type 1 diabetes mellitus. Even though the consensus participants found insufficient evidence to address this issue, many societies, including AACE (12), the Royal College of Physicians (15), and the ATA (16), endorse the use of anti-TPO antibody determinations in the management of patients with thyroid dysfunction. In fact, many clinical endocrinologists use the TPO antibody test as a diagnostic tool in deciding whether to treat a patient with subclinical hypothyroidism (17), and we endorse this practice.

Screening During Pregnancy

The consensus panel also recommended against routine screening for thyroid dysfunction in pregnancy. However, because the association between subclinical hypothyroidism and adverse outcomes of pregnancy for either the fetus or mother was rated as "fair," they felt that "a TSH level might be obtained in pregnant women and women who wish to become pregnant" if they are at risk for thyroid disease based on personal or family history, physical examination findings, symptoms or other autoimmune disorders (6). While we agree with aggressive case finding in all women of childbearing age, we disagree strongly that thyroid function testing should be limited to women thought to be at increased risk for the development of thyroid disease based on clinical factors. Because the prevalence of subclinical hypothyroidism in women in the childbearing age range may be as high as 5% (2,3) and because elevated serum TSH levels in pregnant women represent sufficient thyroid hormone deficiency to endanger both the optimal brain development (18) and survival (19) of the fetus, we believe that TSH testing (followed by free T₄ measurement when the TSH is abnormal) should be performed routinely during the prepreg-

nancy evaluation or as soon as pregnancy is diagnosed. Although additional studies may be required to mandate universal population screening in pregnancy, our position is in complete agreement with a previous position paper from AACE supporting thyroid testing in pregnancy, leaving the specifics of management "to the judgment of the physician in consultation with the patient (20)." The American College of Obstetrics and Gynecology (ACOG), however, has stated that "there are insufficient data to warrant routine screening of asymptomatic pregnant women for hypothyroidism (21)."

Treatment of Subclinical Hypothyroidism

The consensus panel recommended against routine treatment of patients with subclinical hypothyroidism with serum TSH levels of 4.5–10 mU/L, but indicated that treatment was "reasonable" for patients with TSH levels greater than 10 mU/L. Again, these recommendations were based on the existing evidence being insufficient to recommend for treatment in patients in the 4.5–10 mU/L range, while the evidence, though still considered inconclusive, was more compelling for patients whose TSH value is greater than 10 mU/L. The evidence reviewed consisted of published data regarding the projected rate of progression from subclinical to overt hypothyroidism and the effects of levothyroxine treatment on symptoms, depression, lipid profiles, and cardiac function. Although our panel agrees that the data for treating patients with TSH levels greater than 10 mU/L is more compelling, we also believe that, in our opinion based on the available data and our collective clinical experience, most patients with serum TSH levels of 4.5–10 mU/L should be considered for treatment, with the key determinant being the clinical judgment of the provider. This belief is in agreement with a published opinion survey of thyroid specialists (17) and a previously published recommendation by one of the present authors (22). We consider thyroid failure to be a continuum with patients having TSH levels of 4.5–10 mU/L (or possibly lower) on one end and patients with myxedema coma are on the other end. Milder disease would, of course, be expected to have milder adverse effects and the demonstration of beneficial treatment effects would accordingly require larger numbers of subjects and longer treatment periods to be conclusive. We agree that adequate data is not yet available in this category. However, again the lack of definitive evidence for a benefit does not equate to evidence for lack of benefit.

Interventions must also be evaluated for evidence of potential harm. A published report indicates that up to 20% of patients on levothyroxine therapy are overtreated (2). However, as educators and providers, we should not view this as an immutable statistic that justifies an argument against a potentially beneficial intervention, but rather as an issue that can be addressed and substantially improved through physician education programs.

The consensus conference recommendation that levothyroxine doses should be increased in patients already receiving treatment for hypothyroidism if their serum TSH values even minimally exceed the normal range is a tacit acknowledgment that having TSH values within the normal range is preferable to having TSH levels that are mildly elevated. Our panel agrees completely. In contrast, the conference participants did not recommend starting levothyroxine in patients

whose untreated serum TSH levels are 4.5–10 mU/L, whereas our panel does recommend this early intervention. We believe that the risk–benefit ratio is the same in both instances. The benefits of normalizing the serum TSH level must certainly be the same and the risks of overtreatment should also be similar regardless of whether the TSH is lowered by adjusting the preexisting dose or by initiating new therapy. While it has been reported that up to 20% of levothyroxine-treated patients may be receiving excessive thyroid hormone doses (2), no distinctions were made between patients who had recently started thyroid hormone therapy and those who had been on long-term stable therapy.

We again believe that in this overall area, however, the views of our panel and those of the consensus panel are not far apart in principal. Here again, the concept of “routine treatment” is the central issue. While reflex treatment of any TSH elevation without proper consideration of the context of the patient’s clinical features would be unwise, any time the serum TSH level is measured for a reason, the situation becomes case-finding rather than screening. The reason for measuring the TSH level, in most cases, makes it no longer “routine” but rather a reasonable intervention based on the clinical circumstances. The critical issue, therefore, is that data-based treatment guidelines in areas where that data are insufficient should not be stated in a way that might be considered restrictive, but should instead allow providers the flexibility to use the sound clinical judgment that they, having knowledge of each patient’s individual circumstances, are the most qualified to render. Based on our clinical experience, our panel believes that many patients with persistent serum TSH elevations of any degree will benefit from therapy and that the physician’s judgment, in conjunction with patient input, should be paramount in this decision making process.

Subclinical Hyperthyroidism

Subclinical hyperthyroidism is much less common than subclinical hypothyroidism (10,23,24). We found the consensus panel’s recommendations to observe and monitor patient’s with partial TSH suppression (0.1–0.4 mU/L) but to treat patients with complete TSH suppression (< 0.1 mU/L) acceptable and consistent with previous published guidelines (12,16). While we agree with the consensus panel’s recommendations in regard to subclinical hyperthyroidism, it is important to point out that the strength of evidence is, in our opinion, as insufficient for making definitive recommendations for this condition as it is for subclinical hypothyroidism.

Conclusions

In our view as both practicing and academic endocrinologists, the potential benefits of early detection and treatment of subclinical thyroid dysfunction significantly outweigh the potential side effects that could result from early diagnosis and therapy. Because the potential harm of early detection and treatment appear to be so minor and preventable, it seems prudent to err on the side of early detection and treatment until there is sufficient data to address these issues definitively. Therefore, we favor routine screening for subclinical thyroid dysfunction in adults, including pregnant women and those contemplating pregnancy. We also

strongly agree with an aggressive approach to case-finding in patients presenting with symptoms and/or signs that suggest the possibility of thyroid dysfunction. Until adequate data are accumulated, we believe that it will be necessary for clinicians and patients to consider each individual’s unique situation in determining the need for testing and treatment.

The correct approach to subclinical thyroid dysfunction remains unsettled. However, a strict evidence-based strategy, in the absence of “good evidence,” does not help clinicians dealing with this problem on a day-to-day basis. It is clear that large, randomized, prospective, adequately powered trials are needed to provide answers for proper evaluation and treatment of subclinical thyroid disorders. In 2004, we believe that expert opinion based on evidence from observational studies and small randomized trials, as well as informed decision, remain essential to proper decision making in the management of subclinical thyroid dysfunction. Thus, we advise that routine screening for thyroid disease is warranted in the general population, especially pregnant women, and that most patients with subclinical hypothyroidism and some with subclinical hyperthyroidism should be treated. It is also important to allow flexibility and decision-making to the physician taking care of these patients. It is equally important to recognize that many primary-care physicians, physician assistants, and nurse-practitioners may use guidelines as a care tool, under the assumption that they are the best distillation of advice from research and experts in the field. Furthermore, individual agencies, health maintenance organizations, and the Center for Medicare and Medicaid Services often use published guidelines to limit reimbursement for both testing and therapy. It is the position of both the consensus panel and this task force, that until adequate data are available, best clinical practice continues to combine “clinical judgment and patients’ preferences (6).”

References

1. Cooper DS 2001 Clinical practice. Subclinical hypothyroidism. *N Engl J Med* **345**:260–265.
2. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC 2000 The Colorado thyroid disease prevalence study. *Arch Intern Med* **160**:526–534.
3. Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, Braverman LE 2002 Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab* **87**:489–499.
4. Toft AD 2001 Clinical practice. Subclinical hyperthyroidism. *N Engl J Med* **345**:512–516.
5. Parle JV, Maisonneuve P, Sheppard MC, Boyle P, Franklyn JA 2001 Prediction of all-cause and cardiovascular mortality in elderly people from one low serum thyrotropin result: A 10-year cohort study. *Lancet* **358**:861–865.
6. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Colin RH, Franklyn JA, Hershman JM, Burman KD, Denke MA, Gorman C, Cooper RS, Weissman NJ 2004 Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. *JAMA* **291**:228–238.
7. Col NF, Surks MI, Daniels GH 2004 Subclinical thyroid disease: Clinical applications. *JAMA* **291**:239–243.
8. Ellrodt G, Cook DJ, Lee J, Cho M, Hunt D, Weingarten S 1997 Evidence-based disease management. *JAMA* **278**:1687–1692.

9. US Preventive Services Task Force 2002 Guide to Clinical Preventive Services, 3rd ed. Agency for Healthcare Research and Quality, Rockville, MD.
10. US Preventive Services Task Force 2004 Screening for thyroid disease: Recommendation statement. *Ann Intern Med* **140**:125–127.
11. Ladenson PW, Singer PA, Ain KB, Bagchi N, Bigos ST, Levy EG, Smith SA, Daniels GH, Cohen HD 2000 American Thyroid Association guidelines for detection of thyroid dysfunction. *Arch Intern Med* **160**:1573–1575.
12. American Association of Clinical Endocrinologists 2002 Clinical Guidelines for the Evaluation and Treatment of Hyperthyroidism and Hypothyroidism. *Endocr Pract* **8**:457–467.
13. American Academy of Family Physicians 2002 Summary of Policy Recommendations for Periodic Health Examinations Series. Summary of Policy Recommendations for Periodic Health Examinations, Leawood, KS.
14. Anonymous 1998 Clinical guideline, Part 1. Screening for thyroid disease. American College of Physicians. *Ann Intern Med* **129**:141–143.
15. Vanderpump MP, Ahlquist JA, Franklyn JA, Clayton RN 1996 Consensus statement for good practice and audit measures in the management of hypothyroidism and hyperthyroidism. The Research Unit of the Royal College of Physicians of London, the Endocrinology and Diabetes Committee of the Royal College of Physicians of London, and the Society for Endocrinology. *BMJ* **313**:539–544.
16. Singer PA, Cooper DS, Levy EG, Ladenson PW, Braverman LE, Daniels G, Greenspan FS, McDougall IR, Nikolai TF 1995 Treatment guidelines for patients with hyperthyroidism and hypothyroidism. Standards of Care Committee, American Thyroid Association. *JAMA* **273**:808–812.
17. McDermott MT, Haugen BR, Lezotte DC, Seggelke S, Ridgway EC 2001 Management practices among primary care physicians and thyroid specialists in the care of hypothyroid patients. *Thyroid* **11**:757–764.
18. Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, O’Heir CE, Mitchell ML, Hermos RJ, Waisbrun SE, Faix JD, Klein RZ 1999 Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. *N Engl J Med* **341**:549–555.
19. Allan WC, Haddow JE, Palomaki GE, Williams JR, Mitchell ML, Hermos RJ, Faix JD, Klein RZ 2000 Maternal thyroid deficiency and pregnancy complications: Implications for population screening. *J Med Screen* **7**:127–130.
20. Gharib H, Cobin R, Dickey R 1999 Subclinical Hypothyroidism During Pregnancy: Position Statement from the American Association of Clinical Endocrinologists. *Endocr Pract* **5**:367–368.
21. ACOG Practice Bulletin 2002 Clinical management guidelines for obstetrician-gynecologists. Number 37, August 2002. *Obstet Gynecol* **100**:387–396.
22. McDermott MT, Ridgway EC 2001 Subclinical hypothyroidism is mild thyroid failure and should be treated. *J Clin Endocrinol Metab* **86**:4585–4590.
23. Vanderpump MP, Tunbridge WM, French JM, Appleton D, Bates D, Clark F, Grimley Evans J, Hasan DM, Rodgers H, Tunbridge F et al 1995 The incidence of thyroid disorders in the community: A twenty-year follow-up of the Whickham Survey. *Clin Endocrinol (Oxf)* **43**:55–68.
24. Sawin CT, Geller A, Wolf PA, Belanger AJ, Baker E, Bacharach P, Wilson PW, Benjamin EJ, D’Agostino RB 1994 Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older persons. *N Engl J Med* **331**:1249–1252.

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