

## Hypothyroidism—Talking Points 2006

a report by

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In 1603 Paracelsus described endemic cretinism. Over 150 years later, in 1878, Ord proposed the term myxedema to describe the clinical features of the “cretinoid” affection occasionally observed in middle-aged women”. In 1883, Emil Theodor Kocher reported myxedema after thyroidectomy. This led to a 1909 Nobel Prize in Medicine “for his work on the physiology, pathology and surgery of the thyroid gland.” Modern endocrinology’s birth followed in 1891 when Murray injected sheep thyroid extract into a patient with myxedema. Just one year later injection was replaced by “eating ground or fried sheep thyroid or tablets of dried thyroid tissue.”

Much has happened since then. Kendall discovered thyroxine in 1914. Dietary iodine supplementation followed Marine and Kimball’s work on the role of iodine in the treatment of goiter in 1920. Harrington worked out the structure of thyroxine (T4) and synthesized it in 1926. A second and more potent thyroid hormone, triiodothyronine (T3), was discovered and synthesized by Gross and Pitt-Rivers in 1952. Utiger and Odell developed the first thyroid stimulating hormone (TSH) assays in the 1960s. In 1970, Braverman, Ingbar, and Sterling demonstrated that most T3 was produced by the extrathyroidal conversion of T3 from T4. By the mid-1970s, congenital hypothyroidism screening programs were implemented, virtually eliminating congenital hypothyroidism in developed parts of the world.

Since then, more sophisticated serum assays have enabled us to diagnosis mild or early hypothyroidism, termed ‘subclinical hypothyroidism’. Reliable thyroid hormone preparations have enabled clinicians to precisely and safely treat hypothyroidism, whatever its degree. Thus, after about a century of clinical milestones and triumphs in thyroidology, clinical practice has shifted considerably. Most patients now have subclinical or mild hypothyroidism rather than disease that is quite evident clinically.

The recent shift in clinical focus has led to a number of newer questions and issues which I will touch briefly on, and, perhaps to the chagrin of the reader, as well as the author, not offer many definitive answers. My comments will generally pertain to ambulatory patients without

acute or major chronic illness, who are not being treated with medications known to alter thyroid hormone economy, and whose clinical circumstances allows them to have confirmatory laboratory determinations at least three or so weeks apart.

### How Diagnosis of Hypothyroidism is Made

Secondary or central hypothyroidism is far less common than primary hypothyroidism. Estimates range from 1 in 20 (5%) to less than 1 in 200 (0.5%). The former statistic is much higher than that seen in primary care physicians’ offices but may reflect endocrinologists’ practices, particularly those with patients with pituitary and hypothalamic disorders. Since primary hypothyroidism, in most ambulatory settings, is heralded by a rise in serum TSH well before measures of free thyroxine (T4) and triiodothyronine (T3) fall, TSH serves as the mainstay in the laboratory diagnosis of hypothyroidism. Moreover, since measures of T3 generally do not fall until measures of T4 fall, T3 assays have virtually no role in the diagnosis of hypothyroidism. Anti-thyroid antibodies are markers of primary autoimmune thyroid disease. Although they do not establish or rule out a diagnosis of hypothyroidism, high titers, particularly in combination with substantially elevated TSH values, are a predictor for the progression of hypothyroidism.

Symptoms of hypothyroidism are non-specific and serve as an unreliable approach to diagnosing hypothyroidism, while treatment of mild hypothyroidism frequently does not lead to their resolution.

### The Upper Normal of Serum TSH

A consensus development conference report published in the *Journal of the American Medical Association* in 2004 used a value of 4.5mU/ml as an upper normal value. This was largely based on the National Health and Nutrition Examination Survey (NHANES III) which was published in 2002. A number of authors have analyzed NHANES III total population and disease-free population subsets. As a result some have proposed that the upper normal value should be significantly lower,



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ranging for example from 2.5 to 3.0. This argument has several key components:

- The distribution of TSH values used to establish the normal range is not a 'normal' or Gaussian, but significantly skewed by a right-sided 'shelf' or 'pathologic hump' of values of 3.1 to 5.0, reflecting early disease.
- In keeping with (a) the mean and median normal value of approximately 1.5 is much closer to the lower end of the reported normal range than the upper end of the purported range.
- When risk factors for thyroid disease are excluded the upper limit of normal is somewhat lower.
- Early disease may have adverse cardiovascular and psychiatric adverse consequences that can be prevented with treatment.
- Establishing that early disease is present, and following patients with early disease, is the best way to prevent the development of severe hypothyroidism, whether or not treatment is initiated.

On first pass, the implications for recognizing an upper normal cut-off as low as 2.5 or 3.0 appear to be enormous. The number of Americans, across all major ethnic subgroups, believed to have hypothyroidism, would more than double or increase by over 10 million. However, the same consensus group argues that available evidence does not support treating most patients with TSH values between 4.5 and 10. Since clinical manifestations generally correspond with the degree of TSH elevation there is virtually no evidence to treat the vast majority of those with even earlier or milder hypothyroidism. Not only would it not confer any short-term benefit, but it would be costly, increase the chances for adverse effects related to thyroid hormone therapy, and in many cases would lead to treatment for an asymptomatic condition which will never progress to overt or clinically important disease.

#### **When, if Ever, Mild Disease Should be Treated**

Several situations dictate treating mild disease. This applies to settings in which mild disease has a greater likelihood of having a negative impact and particularly when progression is likely. Several important examples follow:

- Pregnancy typically increases thyroid hormone requirements. Hypothyroid patients who are clinically and biochemically euthyroid on stable doses of thyroid hormone generally need significantly more thyroid hormone during pregnancy than they did prior to

pregnancy. Untreated hypothyroidism during pregnancy, and as a corollary, suboptimally treated hypothyroidism during pregnancy, increases maternal and fetal risk. Therefore, in order to prevent mild hypothyroidism from becoming overt, evaluating the thyroid status of those with hypothyroidism as early as possible in pregnancy is strongly recommended.

- Infertility—thyroid hormone treatment may improve the chances for conception and eliminate the possibility that it is contributing to infertility. Most important, once pregnant, the argument laid out for treating mild hypothyroidism during pregnancy applies.
- Mental Illness—marked hypothyroidism can cause depression while lesser degrees may contribute to it. Psycho-pharmacologists often maintain that antidepressants are less effective in patients with even mild hypothyroidism. Bipolar patients cycle more rapidly when they are hypothyroid. A number of psychotropic drugs such as lithium, carbamazepine, and sertraline may increase thyroid hormone dose requirements. Thyroid status should be monitored closely when these drugs are about to be introduced and titrated.

#### **When the Risk of Therapy Outweighs its Benefit and Groups that Should be Treated Most Conservatively**

The principal adverse effects from long-term therapy with excessive amounts of thyroid hormone, or clinically evident or subclinical hyperthyroidism, are cardiovascular and skeletal. Studies have shown that up to 20% of patients treated with thyroid hormone are found to have subclinical hyperthyroidism making the risk substantial.

Atrial fibrillation is more common in elderly patients with thyroid hormone excess. It is unknown if the risk is equal in those with mild thyroid hormone excess regardless of whether it is endogenously produced or from overtreatment with thyroid hormone. Different T3 to T4 ratios could account for a difference. Analyses of previously published studies may provide some insight into whether it is more likely in the former situation, which is generally characterized by higher T3 to T4 ratios. In any event, it may be best to follow rather than treat patients with mild and certainly marginal asymptomatic, hypothyroidism with a history of atrial fibrillation or ischemic heart disease, particularly if they are unstable.

Overtreatment with thyroid hormone leads to bone loss, particularly in postmenopausal women. This group constitutes a substantial percentage of those with subclinical hypothyroidism. Care should be taken to avoid overtreatment.

In my opinion, those with marginal hypothyroidism and anxiety disorders, particularly ones characterized by somatic preoccupation and heightened concerns about any medical intervention require special consideration. Those with mild disease should discontinue therapy if the benefits of treatment are not evident within several months of achieving a euthyroid state.

A four-year prospective study from The Netherlands reported in 2004 of 85-year-olds demonstrated that mild hypothyroidism was associated with a longer lifespan without an increase in disability, depression, or deterioration of cognitive function. This suggests, but does not prove, that treating mild hypothyroidism in the ‘oldest old’ may not be necessary and may even be ill advised. Randomized control trials will be required to confirm this.

### Patients Who Should be Screened and Who Should be Tested

The US Preventive Services Task Force (USPSTF) recommends doing a screening test when detecting asymptomatic disease leads to better outcomes than diagnosing clinically evident disease. USPSTF believes that there is insufficient evidence for or against routinely screening adults for hypothyroidism.

The consensus group guideline referred to above, went a step further, perhaps, by making a recommendation “against population-based screening for thyroid disease” including women who are pregnant or planning to become pregnant (consonant with the position of the American College of Obstetrics and Gynecology). “Aggressive case finding”, however, was recommended in the absence of signs or symptoms of thyroid disease for patients with the following features:

- female over 60
- type 1 diabetes mellitus;
- atrial fibrillation;
- family history of thyroid disease;
- history of radioiodine therapy for hyperthyroidism; and
- history of external beam radiotherapy overlapping the thyroid region

Other professional societies recommendations, however, differ with the USPSTF and the consensus group:

- The American Association of Clinical Endocrinologists (AACE) recommends screening pregnant patients (1999) and older women (2002).
- The American Thyroid Association recommends screening those who are age 35 and every five years thereafter (2000).

- The American College of Physicians recommends case finding in women older than 50 with one or more symptoms possibly caused by thyroid disease.
- The American Academy of Family Physicians recommends screening those older than 60.

These conflicting recommendations may place policy makers and third-party insurers in a quandary about whether to promote thyroid screening for large populations of patients. However the consensus group recommendation “to make individual patient assessments when determining the need for testing and treatment” and to test those with “signs or symptoms suggestive of thyroid dysfunction” enables clinicians to easily justify ordering a TSH measurement for most patients in these subgroups. This is because symptoms of hypothyroidism are common in euthyroid patients—being present in approximately 60% of those surveyed in the Colorado Thyroid Disease Prevalence Study published in 2000.

### Therapeutic Endpoints

TSH normalization is generally aimed for. Some confusion surrounds the distinction between an upper normal TSH value and the TSH level to use as a therapeutic endpoint, once therapy has begun. A goal TSH value in the lower half of the normal range, for patients who continue to have symptoms consistent with hypothyroidism, is not tantamount to saying that values in the upper half of the normal range reflect hypothyroidism. Rather it gives the patient the “benefit of the doubt” that optimal thyroid hormone replacement for them is in the upper 50% of the population as opposed to the lower 50%. When patients remain as symptomatic as they were prior to initiating thyroid hormone therapy, despite reaching a value in the lower half of the normal range, further adjustments not indicated. Moreover, in this situation discontinuing thyroid hormone should be considered. Similarly, patients who no longer have symptoms of hypothyroidism with TSH values in the upper half of the normal range or mildly elevated values do not require more thyroid hormone.

### Preferred Methods of Treatment and the Alternatives

The standard replacement regimen consists of levothyroxine. Enthusiasm for T4 and T3 combinations followed a 1999 *New England Journal of Medicine* report that substituting 50mcg of a hypothyroid patient’s T4 dose with 12.5mcg of T3 was followed by improvement in several quality of life indices, mood, and psychometric parameters. Later analyses indicated that athyreotic patients benefited while those with chronic thyroiditis, presumably with some residual thyroid

function, by and large did not. Euthyroid controls were not studied. Subsequent reports, employing a range of T4 to T3 ratios have failed to replicate these findings. Nonetheless, four studies out of five that studied patient preferences concluded that patients preferred combination therapy to T4 only therapy. In some instances this was associated with weight loss. Some authorities believe that T3 administration to patients who are subclinically or clinically hyperthyroid poses a greater risk of inducing atrial fibrillation than thyroxine does. This may be a result of the surge in T3 levels following T3 ingestion.

Desiccated thyroid, which in the US is principally porcine in origin, has not been studied the way synthetic T4 and T3 combinations have been. However, studies from the late 1970s strongly suggest that this form of thyroid replacement is comparable to T4 and T3 combination therapy. There is insufficient published peer reviewed data to conclude whether the absorption characteristics are still comparable to currently available synthetic T4 and T3 preparations. Manufacturer-provided data cite different amounts of T4 and T3 per grain of compound than an earlier study disclosed, while weight ratios are reported to be approximately 4:1.

One commercially available, fixed dose T4 and T3 combination remains on the US market, with a weight ratio of T4 to T3 of 4:1.

The ratio of T4 to T3 by weight of 4:1 does not reflect normal T4 to T3 secretory rate ratios, which are at least twice as high.

A sustained rise in thyroxine levels and a drop in TSH levels characterize the early stage of normal pregnancy. Early fetal central nervous system (CNS) development requires adequate transplacental thyroxine transport. Preliminary data from Europe that suggest that babies born to mothers with relatively low normal range thyroxine levels have subnormal intellectual development is in keeping with data derived largely from animal models.

Based on the above, it appears reasonable to conclude the following:

- Thyroxine is the preferred form of replacement therapy for patients with hypothyroidism.
- T4 and T3 combinations should continue to have limited roles and not be used for those:
  - with or at high risk for atrial fibrillation or
  - planning pregnancy or who are pregnant.

- Desiccated thyroid is a form of combination fixed dose T4 and T3 combination that has not been subjected to sufficient study to warrant recommending its use.

### Does Thyroxine Formulation Matter?

Thyroxine has a narrow “toxic to therapeutic ratio”, making it a “narrow therapeutic index” drug. As little as a 12.5% difference in dosage may have a major influence on TSH levels and a substantial clinical impact as well. Many patients on thyroxine formulations have thyroid hormone levels outside of the normal range. Compliance, infrequent monitoring, and drug interactions may contribute to this, as might a difference in formulation potency. For example, one relatively recent US Food and Drug Administration (FDA) approved generic formulation proved to have 12.5% greater bioavailability than the proprietary preparation it was deemed to be bioequivalent to. If these formulations were interchanged after a conservative dose change of 12mcg or 13mcg was introduced, a net change of approximately 25mcg more or 25mcg less would follow—a dose difference that is often large enough to result in subclinical hyperthyroidism or hypothyroidism. Consistently prescribing the same levothyroxine preparation is one way of reducing the chances for fluctuations in thyroid hormone levels.

### What the Immediate Future Holds

AACE is currently updating its guideline on the treatment of hypothyroidism. A substantial portion of the guideline will be devoted to reviewing evidence related to the diagnosis and treatment of hypothyroidism, as touched upon by this piece.

An unsettled issue is the role of T3 in the treatment of patients with hypothyroidism. This may be further clarified by the introduction of presumably more physiologic sustained release formulations of T3.

### Conclusion

Thyroid dysfunction, particularly hypothyroidism, is common. Some controversy surrounds whether screening for hypothyroidism is appropriate, who to treat, and how best to treat them. There is considerable agreement, based on well-established information, about treating those who stand to benefit the most from therapy; namely, those with moderate and severe disease. However, there is currently much less consensus and much more discussion about the optimal approach for the majority of patients with hypothyroidism, those with mild disease, whose benefit from early diagnosis and treatment is much less certain. ■