Guest Editorial

Subclinical Thyroid Disease: To Treat or Not to Treat?

Subclinical thyroid disease is a rather common disorder encompassing the opposite conditions of subclinical hypothyroidism and subclinical hyperthyroidism, which are defined as states with serum thyrotropin levels either below or above the reference range, respectively, and normal serum thyroid hormone concentrations in the absence of clinical signs and symptoms. The prevalence of both these conditions varies widely according to age, gender, and the environment. As reported in iodine sufficient areas, subclinical hypothyroidism occurs in 4% to 9.5% of the general population, being more frequent in women and in the elderly (1,2). A prevalence of 0.4% to 3.2% for subclinical hyperthyroidism has been reported in iodine sufficient areas (1–3). This condition is much more frequently observed in iodine deficient areas, in which up to 10% or more of the elderly population may be affected (4–7). The need for providing the clinicians with guidelines for the day-to-day approach of this frequent disorder is widely recognized, but the appropriate management of subclinical thyroid disease is itself a matter of controversy.

The issue has been addressed by a panel of endocrinologists and nonendocrinologists led by Surks (1), which recently published guidelines for diagnosis and management of subclinical thyroid disease based on an extensive and careful review of the available scientific literature. While the scientific value and the importance of this contribution were largely recognized, the leadership of the American Association of Clinical Endocrinologists (AACE), the American Thyroid Association (ATA), and The Endocrine Society (TES) felt that in several areas alternative interpretations and recommendations were warranted. An ad hoc task force was appointed to reconsider the entire question, the conclusions of which are published in the present issue by Gharib et al. as a joint statement of the three associations (8). To better understand this debated issue, it is worth considering the uncertainties underlying the controversy, which involve the definition of subclinical thyroid disease as well as the terminology. The stringency of the evidence-based strategy to be applied to subclinical hypothyroidy and hyperthyroid disorders is an additional matter of discussion, since it is required that these conditions themselves be better defined.

Subclinical thyroid disease is defined on the basis of laboratory data (high serum TSH levels with “normal” serum thyroid hormone levels) in the absence of clinical signs or symptoms. Strictly speaking, such a definition is more pertinent to the term “subclinical thyroid dysfunction,” which is commonly used as a synonym of subclinical thyroid disease. As a matter of fact, any subtle thyroid abnormality, such as micronodules incidentally discovered in the gland, could be labeled as “subclinical thyroid disease.” Regardless of this point, the definition is widely recognized as somewhat arbitrary. It is pertinent to quote in this respect the evidence recently provided by Andersen et al. (9) that individual variations in serum T4 and T3 in normal subjects are rather narrow, as opposed to the wide range of population-based reference values. In their view, what we call “serum thyroid hormone concentrations” within the “normal” range may well not be normal for the individual subject. Consequently, the distinction between subclinical and overt thyroid disease based on the presence of “normal” or “abnormal” serum T4 and T3 concentrations respectively, when compared to population-based reference values, would be undermined because of the changed concept of individual normality.

It is a common saying that nomina sunt consequentia rerum. In the case of subclinical hypothyroidism, the problem is that the facts (rerum) themselves are not clearly defined. Over the years, different terms have been used for this condition: compensated hypothyroidism, preclinical hypothyroidism, subclinical hypothyroidism, mild thyroid failure, mild hypothyroidism. Each of these terms implies to some extent a different diagnostic, prognostic, and therapeutic attitude. “Compensated hypothyroidism” in essence indicates the absence of a “real” thyroid hormone deficiency, suggesting that the treatment, if any, should not be addressed to the hypothyroidism per se, but rather to the correction of the cause leading to this condition (i.e., factors impairing thyroid function). “Preclinical hypothyroidism” stresses the point that clinical signs and symptoms, albeit not present at the time of observation, will develop sometime in the future (which frequently but not always occurs). “Subclinical hypothyroidism” expresses the concept that hypothyroidism, although not perceived, is present to a very mild degree. It is worth noting that by and large the clinical recognition of signs and symptoms is very much dependent on the alertness of both the physician and the patient. This is in keeping with the frequently reported retrospective recognition of hypothyroid symptoms after adequate treatment. With regard to its therapeutic implications, this term is somewhat ambiguous because it may also indicate that in this case hypothyroidism does not reach clinical relevance deserving a therapeutic intervention. “Mild thyroid failure” more directly points to the fact that there is indeed a thyroid hormone deficiency. Finally, “mild hypothyroidism” in our view is probably the least ambiguous term, since it defines the degree of severity of this condition, while at the same time it indicates that we are dealing with a reduced thyroid hormone action. Most recently, the term “isolated hyperthyrotropinemia” has been introduced to indicate an elevated serum TSH level associated with normal thyroid hormones in the absence of any recognized thyroid alteration (10). This term takes into account the etiological factors leading to an elevated serum TSH concentration. There are several conditions that may be associated with an elevated serum TSH level and normal serum thyroid hormone concentrations. They may be transient or permanent. The former condition is typical of the recovery phase from postpartum thyroiditis and subacute thyroiditis, of nontropical thyroiditis, and of some drug (amiodarone, lithium) treatments. Conversely, a permanently elevated TSH may be due to chronic autoimmune thyroiditis or may be caused by a previous treatment of hyperthyroidism, by congenital hypothyroidism (including inactivating mutations of the TSH receptor), or by external radiotherapy. Circulating bioinac-
tive TSH and heterophilic antibodies against mouse protein can induce falsely elevated levels of TSH. It is commonly acknowledged that the diverse etiology of these conditions should be taken into account in their management. In our view, this implies that once an elevated serum TSH level is recognized, appropriate diagnostic procedures should be performed to identify the etiology involved. In this regard, as recommended by Gharib et al. (8), due to the high frequency of autoimmunity as the cause of subclinical hypothyroidism, measurements of thyroid autoantibodies is mandatory in this situation.

A strict evidence-based medicine approach has been used in the guidelines of Surks et al. (1), which, except for undertreated hypothyroid patients, advise treatment for subjects with serum TSH >10 mIU/L and not for those with a serum TSH above normal but <10 mIU/L. As stated above, in our opinion it is difficult to adopt a stringent evidence-based strategy in clinical conditions lacking clear-cut definition, and we share the opinion of Gharib et al. (8) that a more flexible approach should be used. This would allow the clinician to make the best possible decision for each individual patient. An additional point to be considered is the concept that the degree of hypothyroidism encompasses a wide spectrum from very mild to overt clinical manifestations. In this setting the subdivision of subclinical hypothyroidism into two subgroups according to TSH level (<10 mIU/L or >10 mIU/L, respectively) does not appear justified.

The opportunity of screening for thyroid disease and particularly for subclinical hypothyroidism is another matter of debate. Its benefits have not been considered sufficient by Surks et al., who rather advocated aggressive case-finding in subjects at risk. In our view, the relatively high frequency of subclinical thyroid disease in the adult, particularly in the elderly, and the impact of maternal hypothyroidism on fetal brain development are strong arguments in favor of screening for thyroid disease in these groups. This is in keeping with the recommendations of the ATA and the AACE, as reported by Gharib et al. (8).

The management of subclinical hyperthyroidism is, to some extent, less controversial, but uncertainties in the definition and the terminology should also be considered for this condition. Subclinical hyperthyroidism is defined on the basis of laboratory data: low serum TSH level with respect to the reference value (0.4–4 mIU/L) and normal thyroid hormone levels in the absence of clinical symptoms and signs. The evidence that partial TSH suppression (i.e., serum TSH levels of 0.1–0.4 mIU/L) is per se indicative of any degree of hyperthyroidism is scanty or even completely lacking, while there is clear evidence that the degree of thyrototoxicosis in patients with profound TSH suppression (<0.01 mIU/L) differs from those with a lesser degree of suppression (0.01–0.1 mIU/L). This distinction is particularly relevant in iodine deficient areas, in which longstanding goiters with partial TSH suppression are very common. In Europe, the term “partial thyroid autonomy” rather than “subclinical hyperthyroidism” is frequently used for goitrous subjects with partial TSH suppression. Several conditions may be associated with a decreased serum TSH. A transient decrease may occur in silent and subacute thyroiditis during the first trimester of pregnancy, in nonthyroidal illness, with levothyroxine therapy or treatment with several drugs including dopamine, glucocorticoids, amiodarone, and interferon. The most common causes inducing a permanent decrease of TSH levels, indicative of hyperthyroidism whether clinical or subclinical, are Graves’ disease, functioning thyroid adenoma, and nodular goiter. Different types of subclinical hyperthyroidism require different approaches. Thus, as in the case of subclinical hypothyroidism, appropriate diagnostic procedures should be undertaken in order to define the appropriate therapeutic measures. In this context, thyroid antibody determination and thyroid ultrasound examination are useful tools to distinguish between Graves’ disease and nodular goiter and should be considered.

In conclusion, it is important to stress that the entire question of subclinical thyroid disease remains, to some extent, unsettled and requires further investigation.

REFERENCES

1. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin 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.


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