

The diagnosis of subclinical hypothyroidism is severely limited by a single set of thyroid function tests and the biologic variation in thyroid testing from visit to visit

Karmisholt J, Andersen S, Laurberg P. Interval between tests and thyroxine estimation method influence outcome of monitoring of subclinical hypothyroidism. *J Clin Endocrinol Metab* 2008;93:1634-40.

SUMMARY

BACKGROUND Although subclinical hypothyroidism is a common diagnosis, there is no consensus concerning when treatment should be initiated and how untreated patients should be monitored. This prospective study evaluates the reliability of the information obtained from sequential clinical observations and monthly thyroid-function tests measured over a 13 month period.

METHODS The study subjects were selected from 34 individuals who fulfilled the following criteria: no previous history of thyroid disease, not pregnant within the past 2 months, no change in medicine in the past 3 months, serum thyrotropin (TSH) levels of 5 to 12 mIU/L (detection limit, 0.005; reference range, 0.27 to 4.2 mIU/L), total thyroxine (T₄) within the laboratory reference range (0.4 detection limit; range, 4.7 to 10.8 ng/dl L),* free thyroxine (FT₄) within the laboratory reference range (detection limit, 0.02; reference range, 0.9 to 1.7 ng/dl),* and stable thyroid-function tests on repeated testing after 3 months. At each visit serum was obtained to measure T₄, FT₄, and T₄/T₄ (thyroid-binding globulin). Hypothyroid signs and symptoms were evaluated as described by Zulewski et al(1). The study participants were evaluated monthly for 13 months. Blood samples were obtained at 9 to 10 a.m., and were determined immediately, and again at the end of the study in serum samples separated and frozen at -20°C. Three patients were taking stable doses of oral contraceptives or estrogen.

*Total T₄ ng/dl × 12.9 = nmol/L

*Free T₄ ng/dl × 12.9 = pmol/L

RESULTS The study entrance criteria were met by 21 patients, 19 (90%) of whom were women. The mean (±SD) patient age was 57±12.2 years, and lean mean body mass index was 28.4±4.9 kg/m². Serum antithyroid peroxidase antibodies (TPOAb) were detected in 18 patients (86%). During a period of 13 months, the mean serum TSH was 7.59±2.3 mIU/L (range, 3.3 to 14.7) and the mean FT₄ was 1.03±0.12 ng/dl (range, 0.81 to 1.6). After meeting the entrance criteria, one patient had normal thyroid-function tests throughout 13 months of study, and another had overt hypothyroidism after four visits. During the 13-month study period, the criteria for subclinical hypothyroidism were satisfied in 15% to 100% of the patients at various times, and in 29% of the patients during all the visits; the diagnoses were variable 67% of the

time. Overall, the hypothyroid score did not differ between patients with overt or subclinical hypothyroidism.

The number of patients fulfilling the criteria for subclinical or overt hypothyroidism, or for euthyroidism at each of the 13 visits is shown in Figure 1. Overall, subclinical hypothyroidism would have been diagnosed during 74% of the visits, overt hypothyroidism in 22%, and euthyroidism in 4%. This and subsequent figures are drawn from the data of Karmisholt et al.

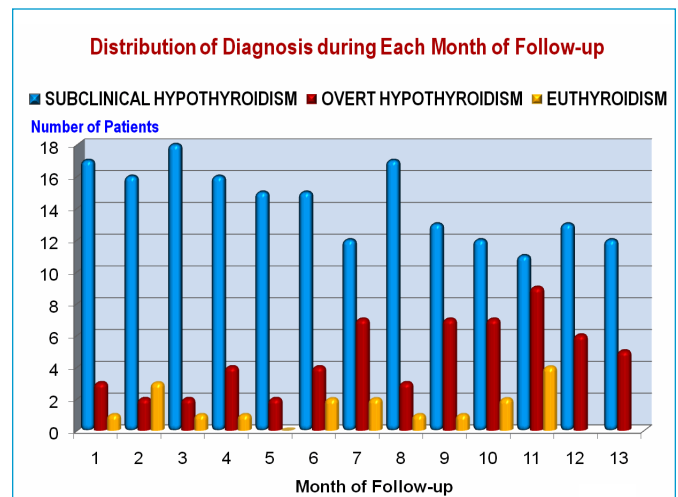


Figure 1. The number of patients fulfilling the criteria for subclinical or overt hypothyroidism, or for euthyroidism at each of the 13 visits is shown. Overall, subclinical hypothyroidism would have been diagnosed during 74% of the visits, overt hypothyroidism in 22%, and euthyroidism in 4%. This and subsequent figures are drawn from the data of Karmisholt et al.

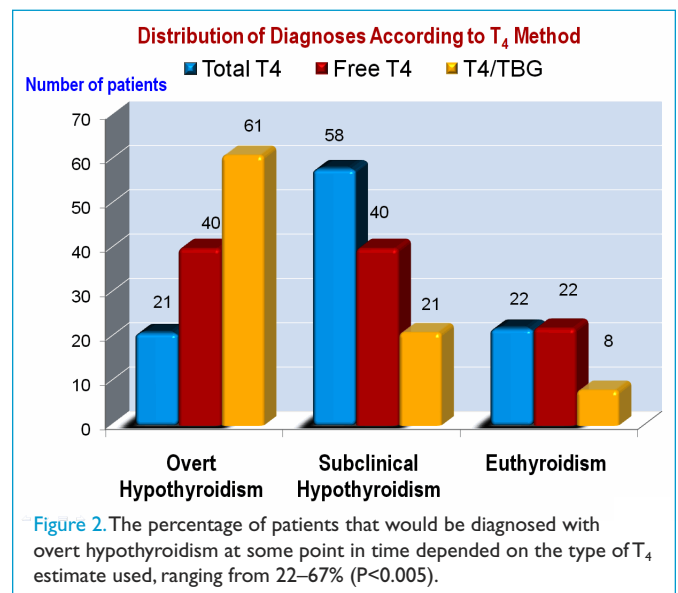


Figure 2. The percentage of patients that would be diagnosed with overt hypothyroidism at some point in time depended on the type of T₄ estimate used, ranging from 22–67% (P<0.005).

Distribution of Diagnoses at 1 Year According to the Length of Follow-up

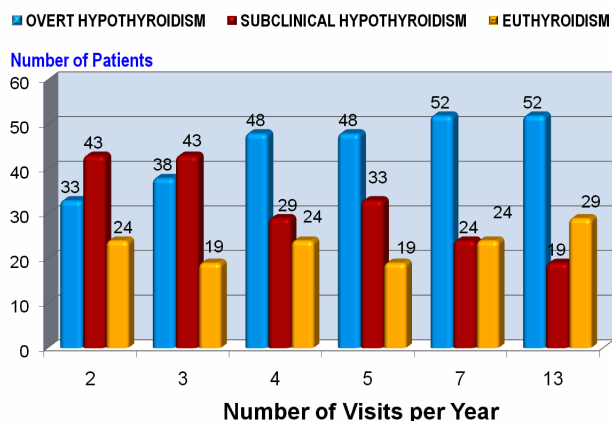


Figure 3. Using thyroid-function tests performed every 2nd, 3rd, 4th, 6th or 12th month, resulted in a steady fall in the diagnosis of overt hypothyroidism and a rise in the diagnosis of subclinical hypothyroidism, which varied from 19% with monthly testing to 43% after testing every 6th or 12th month.

overt hypothyroidism in 22%, and euthyroidism in 4%. The diagnoses varied according to the three different estimates of T_4 (Figure 2). It also varied according to the extent of follow-up (Figure 3). In a theoretical scenario, patients who fulfilled

the criteria for overt hypothyroidism were permanently treated with levothyroxine and those meeting the laboratory criteria for euthyroidism no longer underwent follow-up, while the patients with subclinical hypothyroidism continued to undergo follow-up. Using thyroid-function tests performed every 2nd, 3rd, 4th, 6th or 12th month, resulted in a steady fall in the diagnosis of overt hypothyroidism and a rise in the diagnosis of subclinical hypothyroidism, which varied from 19% with monthly testing to 43% after testing every 6th or 12th month. The number of patients still classified as subclinical hypothyroidism after 1 yr was highly dependent on the number of testings. It varied from 19% with monthly testing to 43% after testing every 6th or 12th month. The percentage of patients diagnosed with overt hypothyroidism was 58% higher with monthly testing compared with testing every 12th month ($P < 0.016$) (Figure 3). The rate of euthyroidism remained relatively steady during the 13 months of follow-up.

CONCLUSION The diagnosis of subclinical hypothyroidism is severely limited by a single set of thyroid-function tests and their variation from visit to visit. As a result, a relatively large number of euthyroid patients might be assigned to permanent levothyroxine therapy.

COMMENTARY

This study shows that relatively small differences in the monitoring paradigms for patients with subclinical hypothyroidism have considerable influence on the stability of the diagnosis and that systematic assessment of symptoms and signs of hypothyroidism do not differ between patients with overt hypothyroidism and those with subclinical hypothyroidism. The authors of this study recently reported (2) that serum TSH concentrations varied more in normal controls than it did in the same set of patients with subclinical hypothyroidism in the present study; however, the percent variation in TSH was lower in patients with subclinical hypothyroidism than in euthyroid controls, but increased with higher mean serum TSH levels. In that study they found that the number of tests required for a diagnosis of subclinical hypothyroidism was high, and that two tests in the same patient must vary by 40% for TSH and by 15% for FT_4 and

FT_3 to be truly different. In a previous 12-month longitudinal study of 16 healthy men, the same group of investigators (3) found that each individual had unique thyroid function, with individual and reference ranges for TSH and T_4 within a narrow range as compared with group reference ranges used to develop laboratory reference ranges. In yet another study, Andersen et al. (4) found that even TSH within the reference range may be associated with slightly abnormal thyroid function. As shown in Figure 3, the number of patients classified as having subclinical hypothyroidism after 1 year is highly dependent on the number of tests performed. The main message of these studies is that a long period of follow-up without therapy is necessary to establish the correct diagnosis of subclinical hypothyroidism.

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References

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