Interval between Tests and Thyroxine Estimation
Method Influence Outcome of Monitoring of
Subclinical Hypothyroidism

Jesper Karmisholt, Stig Andersen, and Peter Laurberg
Department of Medical Endocrinology, Aalborg Hospital, Aarhus University Hospital, 9000 Aalborg, Denmark

Context/Objective: Most patients with subclinical hypothyroidism are regularly monitored when treatment is not started. We have studied how interval between follow-up visits and how different T₄ estimates influence diagnostic outcome in a cohort of patients with untreated subclinical hypothyroidism, and studied whether assessment of clinical symptoms and signs aids evaluation of an individual subclinical hypothyroidism patient.

Design/Patients: During 1 yr, monthly measurements of TSH and three different T₄ estimates, and recording of hypothyroid symptoms and signs were performed in 21 patients with subclinical hypothyroidism confirmed on two occasions 3 months apart.

Results: One patient was euthyroid at all visits, and one started treatment for profound overt hypothyroidism. The remaining patients were subclinical hypothyroidism at 74%, overtly hypothyroid at 22%, and had normal thyroid function tests in 4% of the visits. Increasing frequency of visits associated significantly with decreasing number of patients characterized as subclinical hypothyroidism after 1 yr (P = 0.016). Diagnosis of overt hypothyroidism differed between T₄ estimates (P = 0.005) and was highly dependent on T₄ reference limits. The hypothyroid clinical score did not differ between biochemical diagnoses (P = 0.29).

Conclusions: The monitoring procedure itself may influence the outcome of control of subclinical hypothyroidism. Specifically, the interval between visits, type of T₄ estimate used, and lower T₄ reference limit influenced the outcome when untreated subclinical hypothyroidism patients were followed for 1 yr. The hypothyroid clinical score did not aid the evaluation in individual subclinical hypothyroidism patients.

Subclinical hypothyroidism is a common condition characterized by serum-TSH above and serum T₄ within the reference range for the assay. Whether this condition needs to be treated is debated (1–4). Subclinical hypothyroidism patients with large goitre, TSH above 10 mU/liter, and pregnant women are often treated promptly. In many cases repeated testing of thyroid function is performed, and treatment is initiated only if subclinical hypothyroidism progresses to biochemically overt hypothyroidism (OH), or if patients have symptoms or signs compatible with hypothyroidism. Thus, the evaluation of subclinical hypothyroidism includes measurement of TSH and of an estimate of T₄, as well as an evaluation of symptoms and signs related to hypothyroidism.

Two biochemical outcomes of monitoring patients with subclinical hypothyroidism are of interest. One is normalization of thyroid function tests, a state in which further control is often discontinued, and the other is development of OH in which L-T₄ substitution therapy is normally started. Both outcomes rely on the results of TSH and T₄ testing. However, both TSH and T₄ display large variations within the individual (5–8), which may occasionally cause them to cross the outer limits of the reference ranges. In subclinical hypothyroidism patients this is particularly likely because TSH is only marginally high and T₄ is low within the reference range in the subclinical hypothyroidism state (9). Thus, it may be speculated that during a certain period of time,
TSH and T4 may intermittently cross the reference limits, and the number of tests performed over this time period may influence the outcome of monitoring of patients with subclinical hypothyroidism. In addition, different methods may be used to estimate T4, and this may further affect the outcomes of monitoring subclinical hypothyroidism.

We prospectively followed a group of subclinical hypothyroidism patients with monthly blood samplings during a 1-yr period to study the influence of different control intervals and how the use of different T4 estimates would affect the frequency of initiation of therapy or stop of control. Moreover, we investigated whether assessment of symptoms and signs of hypothyroidism aided in the evaluation of the individual patient with subclinical hypothyroidism.

**Patients and Methods**

The inclusion of the patients has been described previously (10). In brief, we informed the general practitioners in our area about the study. They referred 34 patients who were eligible and willing to participate. These were aged 18–80 yr, had no previous thyroid disease or diseases influence on thyroid function, none was pregnant within the last 12 months, and none had changes in medication during the last 3 months. All patients had a TSH in the interval 5–12 mU/liter with estimated total T4 within the reference range. We repeated measurements of TSH and total T4 after 3 months, and in 21 patients, TSH was still in the 5–12 mU/liter interval with normal total T4. These patients were included. Participants were investigated monthly on a total of 13 occasions. The patients’ mean age was 57 yr (SD 12.2), mean body mass index was 28.4 kg/m² (SD 4.9), 19 were women (men: patient nos. 7 and 18), and 18 had measurable thyroid peroxidase antibodies (negative: patient nos. 4, 7, and 18). The mean TSH and mean free T4 (fT4) of the individual patients during the 13 investigations are shown in Table 1. At the first visit, thyroid gland volume was measured by ultrasound (Siemens Sonoline Versa Pro; Siemens, Munich, Germany) using a 70-ml 7.5-MHz linear transducer, as previously described (11). One patient (no. 9) had a thyroid volume of 40.3 ml; the remainder had a thyroid size ranging from 5.5–14.6 ml. Three patients had a family history of thyroid disease (nos. 1, 5, and 9). Three patients (nos. 5, 19, and 21) received oral contraceptives or estrogen supplementation with unchanged doses during the study.

Hypothyroid symptoms and signs were evaluated at each visit as described by Zulewski et al. (12). The evaluation was performed without knowledge of the results of the thyroid function tests. The clinical evaluation included seven thyroid-related symptoms and five signs that were summarized in a total score. A higher score indicates more hypothyroidism-related symptoms and signs. In general, euthyroid individuals score below two and hypothyroid patients above five (12).

Blood samples were drawn between 0900 and 1200 h using short venous occlusion, and after the patients had been in supine position for 30 min. Serum was separated, and samples were frozen at −20°C shortly after the investigational session. In addition, thyroid function tests were performed at each visit according to protocol to detect any severe deterioration in thyroid function. All investigational sessions except one were performed by the same person (J.K.). All participants signed an informed consent before entering the study, and the study was approved by the Regional Ethics Committee in North-Jutland and Viborg County, Denmark.

**Assays**

Measurements of TSH, total T4, and fT4 were performed with an Electro-Chemi Luminescence ImmunoAssay method on Modular Ana-

| TABLE 1. Diagnoses of thyroid function in the individual patients at the 13 monthly investigational sessions |

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Investigation</th>
<th>TSHa</th>
<th>fT4b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SH SH OH OH SH SH OH OH OH OH OH OH</td>
<td>12.3 (4.4)</td>
<td>11.7 (1.2)</td>
</tr>
<tr>
<td>2</td>
<td>OH OH SH SH SH OH OH OH OH OH OH OH</td>
<td>6.9 (1.2)</td>
<td>11.7 (0.8)</td>
</tr>
<tr>
<td>3</td>
<td>SH SH SH SH SH SH SH SH SH SH SH</td>
<td>6.4 (1.1)</td>
<td>12.7 (0.6)</td>
</tr>
<tr>
<td>4</td>
<td>SH SH SH SH SH SH SH SH SH SH SH</td>
<td>5.3 (0.3)</td>
<td>13.3 (0.4)</td>
</tr>
<tr>
<td>5</td>
<td>SH SH SH SH SH SH SH SH SH SH SH</td>
<td>6.6 (1.7)</td>
<td>13.3 (1.0)</td>
</tr>
<tr>
<td>6</td>
<td>SH SH SH SH SH SH SH SH SH SH SH</td>
<td>9.5 (2.4)</td>
<td>14.3 (1.1)</td>
</tr>
<tr>
<td>7</td>
<td>SH SH SH SH SH OH OH OH OH OH OH</td>
<td>6.4 (0.7)</td>
<td>12.3 (1.1)</td>
</tr>
<tr>
<td>8</td>
<td>SH EU SH EU EU EU SH SH SH SH SH</td>
<td>4.4 (0.7)</td>
<td>17.1 (1.0)</td>
</tr>
<tr>
<td>9</td>
<td>EU EU EU EU EU EU EU EU EU EU</td>
<td>3.3 (0.5)</td>
<td>13.4 (0.8)</td>
</tr>
<tr>
<td>10</td>
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<td>14.7 (16.9)</td>
<td>13.4 (4.3)</td>
</tr>
<tr>
<td>11</td>
<td>SH SH SH SH SH SH SH SH SH SH SH</td>
<td>6.4 (0.7)</td>
<td>14.6 (0.4)</td>
</tr>
<tr>
<td>12</td>
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<td>8.1 (1.7)</td>
<td>17.0 (1.0)</td>
</tr>
<tr>
<td>13</td>
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<td>11.3 (2.2)</td>
<td>10.5 (1.2)</td>
</tr>
<tr>
<td>14</td>
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<td>5.3 (1.0)</td>
<td>13.6 (1.0)</td>
</tr>
<tr>
<td>15</td>
<td>SH SH SH SH SH SH SH SH SH SH</td>
<td>7.9 (2.1)</td>
<td>13.8 (0.8)</td>
</tr>
<tr>
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<td>SH SH SH SH SH SH SH SH SH SH</td>
<td>4.4 (0.6)</td>
<td>14.7 (0.9)</td>
</tr>
<tr>
<td>17</td>
<td>SH SH SH SH SH SH SH SH SH SH</td>
<td>4.9 (0.5)</td>
<td>12.3 (1.1)</td>
</tr>
<tr>
<td>18</td>
<td>SH SH SH SH SH SH OH OH OH OH SH SH</td>
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<td>12.7 (0.8)</td>
</tr>
<tr>
<td>19</td>
<td>SH SH SH SH SH SH SH SH SH SH</td>
<td>5.6 (1.2)</td>
<td>12.5 (0.7)</td>
</tr>
<tr>
<td>20</td>
<td>SH SH SH SH SH SH OH OH OH OH OH</td>
<td>11.4 (4.7)</td>
<td>12.5 (1.2)</td>
</tr>
<tr>
<td>21</td>
<td>SH SH SH SH SH SH OH OH OH OH OH</td>
<td>11.6 (1.6)</td>
<td>11.9 (0.6)</td>
</tr>
</tbody>
</table>

Diagnoses were based on the TSH and fT4 assays. EU test, TSH 0.3–4.2 mU/liter and fT4 12–22 pmol/liter; OH, TSH more than 4.2 mU/liter and fT4 less than 12 pmol/liter; and SH, TSH more than 4.2 mU/liter and fT4 12–22 pmol/liter. SH, Subclinical hypothyroidism.

a Mean (SD) of TSH (mU/liter) during the 13 investigations.

b Mean (SD) of fT4 (pmol/liter) during the 13 investigations.

c TSH within the reference range, and fT4 below the reference range at this particular visit.

d i-T4 treatment initiated and continued for the rest of the study period.
lytics E170 (Roche, Mannheim, Germany). Assay characteristics given by the manufacturer with detection limit and reference ranges were as follows: TSH, 0.005 and 0.27–4.2 mU/liter; total T₄, 5.4 and 60–40 nmol/liter (laboratory reference range); and fT₄, 0.3 and 12–22 pmol/liter. Intraserial coefficients of variation for the TSH, total T₄, and fT₄ assays were 2.4, 1.6, and 1.8%, respectively. T₄ binding globulin (TBG) was measured with RIA (TBG RIA; B-RAH-M-S Aktiengesellschaft, Hennigsdorf, Germany), with a detection limit of 5 mg/liter, and intra- and interserial coefficients of variation of 3.2 and 3.0%, respectively. A total T₄ to TBG ratio (13, 14) was calculated (T₄/TBG), and the serial and interserial coefficients of variation of 3.2 and 3.0%, respectively.

Hennigsdorf, Germany), with a detection limit of 5 mg/liter, and intra-

The significance of the difference between paired data was calculated with the Wilcoxon signed rank test, and differences between multiple groups were tested with the Kruskal-Wallis test. Differences in categorical data were calculated with the Cochran Q test. P values less than 0.05 were considered statistically significant. SPSS 11.0 (SPSS, Inc., Chicago, IL) and Excel 2003 (Microsoft Corp., Redmond, WA) were used for calculations.

Results

Thyroid diagnosis at visits

The diagnoses in individual patients determined from thyroid function tests at each of the 13 monthly visits are listed in Table 1. Patient no. 9 normalized TSH after the inclusion visits, and thyroid function tests remained within reference ranges at all subsequent visits. Patient no. 10 developed OH and started l-T₄ replacement after visit 4, according to protocol, because TSH was 54 mU/liter and fT₄ 4.6 pmol/liter. The diagnoses varied in the remaining patients, with thyroid function tests indicating subclinical hypothyroidism at 15–100% of the visits in the individual patients. Subclinical hypothyroidism was diagnosed at all visits in 29% of the patients, variable diagnosis was seen in 67%, and one patient was diagnosed with both normal thyroid function (EU), subclinical hypothyroidism, and OH. Overall, subclinical hypothyroidism would have been diagnosed at 74% of the visits, whereas thyroid function tests corresponded to OH at 22% of the visits, and test results were within reference ranges at 4% of the visits.

Frequency of visits and diagnostic outcome

We estimated the diagnostic outcome of monitoring subclinical hypothyroidism for 1 yr in a theoretical setup with biochemical testing of thyroid function performed every month, every 2nd, 3rd, 4th, 6th, or every 12th month. The occurrence of EU or OH was considered definite because EU at a particular visit would be considered “cure” and cause termination of further testing, whereas test results corresponding to OH would cause start of l-T₄ replacement therapy and a permanent diagnosis of (treated) OH. If thyroid function tests indicated subclinical hypothyroidism, a new visit would take place after the designated time interval. The overall diagnostic outcome was registered after 1 yr.

As shown in Table 2, 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 OH was 58% higher with monthly testing compared with testing every 12th month (Cochran Q test, P = 0.016).

T₄ estimate and diagnostic outcome after 1 yr with regular follow-up

Three different estimates of T₄ were obtained at each visit. To evaluate the influence of using different T₄ estimates on the diagnostic outcome, we assumed that thyroid function had been obtained every third month for 1 yr, five visits in all. Again, once a diagnosis of EU or OH was recorded, this was the final outcome. Thus, the patients who finally were recorded as having subclinical hypothyroidism had thyroid function tests corresponding to subclinical hypothyroidism at all visits. The three patients who received estrogen were excluded from this analysis. Figure 1 shows the diagnoses after 12 months for the three different T₄ estimates. The percentage of patients that would be diagnosed with OH at some point in time depended highly on the type of T₄ estimate used, ranging from 22–67% (Cochran Q test, P = 0.005). In addition, we calculated the outcome of using different lower reference limits of fT₄. Figure 2 shows a Kaplan-Meyer plot of the probability of being diagnosed with OH during 1 yr with monthly tests.

Correlation between biochemical and clinical assessment

A clinical hypothyroid score according to Zulewski et al. (12) was obtained at each visit to study the association with the biochemical diagnosis. Figure 3 shows mean (±2 SEM) hypothyroid score during the 13 visits in the individual patients. The hypothyroid score differed markedly between patients (Kruskal-Wallis, P < 0.001). There were 12 patients classified as both subclinical hypothyroidism and OH during the 13 investigations. Seven of these patients had on average higher scores when they were OH than when they were subclinical hypothyroidism, whereas five patients scored higher when they were subclinical hypothyroidism. Overall, the clinical hypothyroid score did not differ between the OH and subclinical hypothyroidism states (Wilcoxon signed rank test, P = 0.29). Six patients had EU tests.

<table>
<thead>
<tr>
<th>No. of visits per yr</th>
<th>% Patients diagnosed with OH after 1 yr</th>
<th>Distribution of diagnoses after 1 yr (OH/SD/EU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>52</td>
<td>11/4/6</td>
</tr>
<tr>
<td>7</td>
<td>52</td>
<td>11/5/5</td>
</tr>
<tr>
<td>5</td>
<td>48</td>
<td>10/7/4</td>
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<td>48</td>
<td>10/6/5</td>
</tr>
<tr>
<td>3</td>
<td>38</td>
<td>9/8/4</td>
</tr>
<tr>
<td>2</td>
<td>33</td>
<td>7/9/5</td>
</tr>
</tbody>
</table>

For the evaluation it was assumed that the patients were observed for 1 yr, or until the development of OH or EU.

* There were 13 visits that corresponded to 1 month between control visits, and two visits corresponded to 12 months between control visits, etc.

* Biochemical tests included measurement of TSH and fT₄. Definition of diagnoses corresponds to Table 1.
on at least one occasion during the study period. Of these, one patient had EU tests at all time points, one became biochemical euthyroid after L-T4 replacements, and two had EU tests at only one investigation (patients 15 and 19). In the remaining two patients with either EU tests or subclinical hypothyroidism on several occasions, one had a lower score with EU tests and the other the reverse.

**Discussion**

An important task in monitoring patients with subclinical hypothyroidism is to decide whether to treat, test again, or terminate monitoring (3, 15–17). Yet, few systematic approaches have been made to this everyday clinical consideration. We investigated the effect of different programs of monitoring in patients with untreated subclinical hypothyroidism and found that rather small differences in the monitoring procedure may have a considerable impact on the outcome of subclinical hypothyroidism. Furthermore, our results indicate that repeated evaluation of hypothyroid symptoms and signs is of limited value when assessing individual subclinical hypothyroidism patients.

Reference ranges in clinical biochemical laboratories are set as the central 95% interval of the test in a reference population. With repeated testing the group falling outside the reference range will most likely not include the same individuals at each occasion. SH, Subclinical hypothyroidism.
Because of the intraindividual biological variation. Studies of the intraindividual variation of thyroid function tests in people with EU have revealed both circadian rhythms, and seasonal variation in T₄ and TSH concentration in serum (6–8, 18–21). Furthermore, it has been found that repeated tests in an individual vary within a range that is only around half of the group based reference range.

The individual variation in thyroid function tests has previously been analyzed in the present cohort of subclinical hypothyroidism patients and found to be quite similar to healthy controls (22). However, in subclinical hypothyroidism patients the range of TSH values in an individual is not within the reference range, but above this range, although with some overlap with normality depending on the mean level of TSH. In the present cohort, the subclinical hypothyroidism patients with an average TSH over the year less than 6.0 mU/liter had 13% of their TSH values within the reference range. In the patients with average TSH above 6.0 mU/liter, this was 0.6% only.

T₄ is by definition normal in subclinical hypothyroidism, but all the patients in the present cohort had mean fT₄ levels in the lower part of the fT₄ reference range, and occasionally values were below the reference range. In the group of patients with average TSH above 6.0 mU/liter, 28% of the measured fT₄ were below the lower limit of the reference range compared with 10% in the group with TSH less than 6.0 mU/liter. The span in test results across the limits of the reference range explains a main finding of the present study: a high number of tests within a certain period of time will increase the likelihood of diagnosing OH on at least one occasion. It also follows that even minor differences in the T₄ estimation method or minor changes in reference ranges of the T₄ assays will considerably influence the results of monitoring subclinical hypothyroidism. We confirmed this in the present study by using different T₄ estimation methods and finding a 75% difference in diagnostic outcome after 1 yr when using the total T₄ assay compared with the fT₄ assay. Notably, the present study gave no information on which T₄ estimation method gave the optimal results for deciding whether to treat or not.

Several investigations have studied the natural course of untreated subclinical hypothyroidism (23–28). Different assays were used, and the interval between follow-ups varied markedly, i.e., from 3 months to 2 yr. As might be expected, the probability of diagnosing OH in these investigations varied noticeably with an estimated yearly probability ranging from 3–18%. In the present cohort of patients with subclinical hypothyroidism confirmed using two TSH and total T₄ measurements 3 months apart, OH would have been diagnosed at 22% of the visits, when thyroid function was tested with a fT₄ assay every month during 1 yr.

In addition to biochemical evaluation, assessment of hypothyroid symptoms and signs is often performed when monitoring patients with subclinical hypothyroidism. We found that hypothyroid symptoms and signs corresponded poorly to the biochemical diagnoses attained. Zulewski et al. (12) validated the hypothyroid score in 93 patients with subclinical hypothyroidism. They found that 29% of the patients scored less than 2, 47% scored between three and five, and 24% scored above five. In the present study, the overall mean score was 1.8 (SEM 0.3). We found a high individuality in perception of symptoms because hypo-

**FIG. 3.** The mean of hypothyroid scores (12) in individual patients obtained at the 13 investigations are marked with a horizontal line, and error bars are ±2 SEM. The patients were sorted by increasing mean serum-TSH. OH (triangles) was the mean hypothyroid score from investigations when the patients were biochemically overt hypothyroid, whereas SH (X) was mean hypothyroid score when SH. Six patients (patient nos. 8–10, 15, 16, and 19) were biochemically euthyroid (EU) at one or more time points during the study; the mean hypothyroid scores at these investigations are illustrated with EU (circles). Patient identification (id) and definition of hormonal states correspond to Table 1. Patient 9 was EU at all investigations, and patient 10 was treated with L-T₄ after the fourth investigation. According to Zulewski et al. (12), euthyroid individuals in general score less than 2, whereas patients with OH in general score above 5.
thyroid score differed much more between individuals than between diagnoses in an individual. For instance, patient 10 who was treated with l-T4 showed only minor changes in hypothyroid score after l-T4 treatment. As seen in Fig. 3, this patient in general scored much lower than patient 9 who had thyroid function tests within the reference limits at all visits. This is in keeping with the large overlap in the perception of symptoms in patients with hypothyroid disease and the frequent finding of similar symptoms in euthyroid individuals (29, 30).

We investigated in a theoretical setup how the monitoring procedure itself would influence the outcome of monitoring subclinical hypothyroidism patients. We did not aim to identify the optimal interval between control visits or the most appropriate T4 estimate. We chose to study the effect of using an automated fT4 assay, a total T4 assay, and a T4 to TBG ratio because these are three essentially different principles used for T4 estimation.

We used a total T4 assay for the inclusion of patients into the study. If a different T4 estimate had been used for inclusion, another subset of subclinical hypothyroidism patients might have been included. However, the overall findings of the study would probably have been unaltered. The patients were included after subclinical hypothyroidism had been confirmed on two occasions 3 months apart. If these two sets of test results had been part of the study period, and patients included on the basis of the primary test results from their general practitioner, 34 and not 21 patients would have been included. Of these 34 patients, 13 would already have had EU tests at the subsequent visit.

The hypothyroid score published by Zulewski et al. (12) was developed in a German speaking area and published in English. We have used the score in a Danish-speaking cohort, and no further systematic validation has been performed.

Conclusions

Subclinical hypothyroidism is frequent, and there is no consensus with regards to when treatment should be initiated and how untreated patients should be monitored. A clear and early progression of thyroid dysfunction is seen in a few patients only. In the majority of subclinical hypothyroidism patients, TSH and T4 vary around the outer limits of the reference ranges for the tests. The present study highlights the limited information obtained from a single set of thyroid function tests and how biological variation may change the diagnosis from visit to visit. The knowledge that the monitoring process itself is of considerable importance for the outcome of monitoring subclinical hypothyroidism may be of value when discussing future control or therapy of the informed patient with subclinical hypothyroidism.

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Address all correspondence and requests for reprints to: Jesper Karmisholt, M.D., Department of Medical Endocrinology, Aalborg Hospital, Aarhus University Hospital, 9000 Aalborg, Denmark. E-mail: jsk@rn.dk.

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