

REVIEW

Variation in thyroid function in subclinical hypothyroidism: importance of clinical follow-up and therapy

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Abstract

Subclinical hypothyroidism (SCH) is a common condition that is often observed without therapy. However, no evidence-based recommendation exists with regards to how patients with untreated SCH should be monitored.

Monitoring involves regular assessment of symptoms and signs of hypothyroidism (HYPO) and biochemical tests of thyroid function. An important question when repeated tests of thyroid function are performed is how large a difference in test results is needed to be confident that the change is real and not just due to chance variation.

Recent data show that the least significant difference between two tests in SCH is 40% for TSH and 15% for free thyroxine and free triiodothyronine, with 90% confidence. Furthermore, monitoring has to be based on biochemical function testing because serial evaluation of symptoms and signs related to HYPO is rather insensitive in detecting worsening of thyroid insufficiency.

When the presence of thyroid peroxidase auto-antibodies (TPO-Ab) in serum has been demonstrated, repeated measurements do not add much useful information in the monitoring of individual subclinical hypothyroid patients, as levels of TPO-Ab vary in parallel with TSH in these patients.

Lastly, we discuss how differences in the monitoring procedure influence the diagnostic outcome, and we suggest a follow-up approach for untreated subclinical hypothyroid patients.

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Introduction

Subclinical hypothyroidism (SCH) is a state where serum TSH is above the upper reference limit for the assay while an estimate of free thyroxine (fT₄) is within the reference interval of the assay. SCH is a frequently observed biochemical abnormality (1–3), and the prevalence is especially high in populations with high iodine intake (2, 4, 5), in older age groups and women (6, 7) and in Caucasians (8). Currently, the most widely accepted interpretation of the biochemical findings in SCH is that the increased TSH is an indication of mild hypothyroidism (HYPO) with a slightly reduced peripheral thyroid hormone effect. The causes of SCH resemble the causes of HYPO, where autoimmune thyroiditis is the most frequent cause (9). Table 1 lists studies of the natural history of SCH (10–18). Progression of SCH to HYPO is in the order of 5–8%/year. Normalisation of thyroid function is another possible outcome, and many patients have stable SCH and do not experience systematic deterioration in thyroid function for years (10–18).

It has been, and still is, much debated whether the abnormality should be treated with levothyroxine (L-T₄) or not (19–24). Biondi & Cooper (25) have authored an

exhaustive review on the aetiology, epidemiology and consequences of SCH and on treatment effects on SCH. A recently published large meta-analysis of 11 prospective cohort studies showed increased risk of cardiovascular morbidity and mortality in patients with TSH above, but not below, 10 mU/l and no increase in total mortality (26). A Cochrane review regarding the effect of L-T₄ replacement therapy in SCH based on randomised clinical studies could not demonstrate consistent evidence of reduced cardiovascular morbidity, improved quality of life or amelioration of symptoms in the treated groups (27), and mortality has not been studied in randomised controlled trials. Overall, data from state-of-the-art randomised clinical trials with recording of adverse events and with sufficient power to be conclusive with regard to beneficial effect of L-T₄ treatment in SCH are lacking. However, consensus has emerged to recommend treatment in women who are pregnant or who plan pregnancy and in patients with serum TSH persistently above 10 mU/l. In addition, many will recommend treatment in patients with goitre or in patients with symptoms and signs suggesting HYPO (23, 24).

A large proportion of patients with SCH do not conform to the categories where therapy is recommended.

Table 1 Follow-up studies with more than two serum samples from each patient with SCH. In the studies, SCH was typically defined as serum TSH above upper reference limit and with a normal serum level of an estimate of thyroxine.

Authors (references)	Publication year	Patient types	Number of patients	Follow-up time (years)	Follow-up intervals (months)	Risk of developing HYPO ^a /year (%)
Nystrom <i>et al.</i> (10)	1981	TSH < 14 mU/l	16	4	12	18
Tunbridge <i>et al.</i> (11)	1981	TSH > 6.0 mU/l or +TPO-Ab	163	4	24	1.2
Gray <i>et al.</i> (12)	1983	TSH 5.6–46.3 mU/l, diabetes pt.	59	4.2	12–36	3.6
Rosenthal <i>et al.</i> (13)	1987	TSH > 4 mU/l, elderly pt.	23	4	12	7.5
Parlè <i>et al.</i> (14)	1991	TSH > 5 mU/l, age > 60 years	73	1	3	18
Kabadi (15)	1993	TSH > 5.0 mU/l	30	8.2	3–6	6.5
Huber <i>et al.</i> (16)	2002	TSH > 4 mU/l	82	0.5–26.3	12	3.0
Diez <i>et al.</i> (17)	2004	TSH > 5.0 mU/l, age > 55 years	107	0.5–6	6	9.8
Rosario <i>et al.</i> (18)	2009	TSH < 10 mU/l, women	117	3	6	9.1

^aHYPO – hypothyroidism, typically defined as serum TSH above upper reference limit and with a low serum level of an estimate of thyroxine. The calculated risk of developing HYPO per year was calculated as the total number of participants who developed HYPO divided by the follow-up time. In a few studies, the participants had different follow-up times, and calculation on raw data may give a slightly different estimate.

After an initial diagnostic work-up, regular biochemical control of thyroid function without therapy is recommended in these SCH patients (23). The diagnostic work-up includes a history, physical examination, biochemical measurements of TSH, an estimate of fT₄ and thyroid peroxidase auto-antibodies (TPO-Ab) in serum and possibly an ultrasound examination of the thyroid gland. Serum TSH above the upper reference limit may be a transient finding, and confirmatory tests of TSH and T₄ obtained 2 weeks to 3 months after measuring a single increased TSH are recommended (23). Once the diagnosis of SCH has been confirmed, a programme of regular monitoring has to be established.

The rationale for regular monitoring of patients with SCH is the possibility of early detection of development of HYPO as SCH patients have increased risk of developing HYPO. Another argument for regular monitoring is to recognise symptoms and signs that may be attributable to HYPO and thus potentially may be ameliorated with L-T₄ replacement therapy.

We discuss the data available to clinicians to judge if a certain change in symptoms and signs or change in results of thyroid functions tests indicates progression in the thyroid failure or if the results are part of random variation.

Intra-individual variation in thyroid function tests

The intra-individual variation of thyroid function tests has been studied in individuals with normal thyroid function (28–37). This has revealed both a considerable circadian rhythm and a small seasonal variation in TSH secretion, but over time TSH in an individual varies within a range of only half of a population-based reference range. The narrow intra-individual variation compared with the inter-individual variation makes population-based reference intervals less suitable for use in serial measurements (38), because a TSH change

that is significant for the individual may still occur within the TSH reference interval. In patients with stable SCH, i.e. no systematic deterioration or improvement of thyroid function over 1 year, the intra-individual variation in serum TSH of 16% resembles that of euthyroid individuals. On the other hand, the variation in fT₄ is 4.1% and 4.0% for free triiodothyronine (fT₃) in SCH patients compared with 9.5% for fT₄ and 7.9% for fT₃ in euthyroid individuals (35, 39).

The interpretation of the test results of repeated measurements of a variable that may already be outside the reference range is different compared to a case finding or a diagnostic situation. In the serial measurement situation, knowledge of the intra-individual variation is important for correct interpretation of improvement or worsening of disease (40, 41). Is the difference between the previous and the current test result caused by random variation or is it a sign of change in disease activity? Figure 1 illustrates the principle in the calculation of a repeated test result based on the knowledge of the intra-individual variation. It is a plot of the probability of a true change versus the relative difference between two tests. A significance level of 90% is often considered clinically relevant. From this, the least significant difference between two tests, called the reference change value, for TSH and fT₄ or fT₃ has been estimated to be 40 and 15% respectively (42). In other words, if the result of a repeated TSH test is within the ±40% range of the previous TSH test, then the result may well be due to random variation, whereas if the result is outside the ±40% range, the difference represents a true change in thyroid function with 90% confidence.

Correlations of serum TSH to other biochemical parameters

In individual patients with SCH, variations in serum TSH correlate significantly with variations in fT₄,

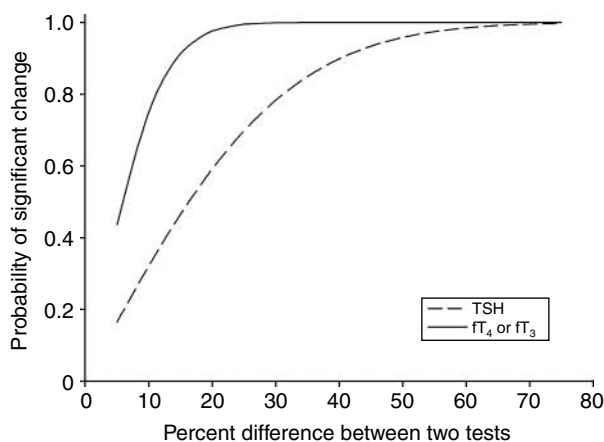


Figure 1 Relative differences between two serum TSH measurements (dashed line) and of fT_4 or fT_3 (solid line) and the corresponding probability this represents of significant change shown on the y-axis. The variations of fT_4 and fT_3 are almost identical, and a single line represents both parameters. The probability of a significant change between two test results was calculated from: relative difference between two tests = $Z \times CV_{total} \times 2^{1/2}$, where Z denotes the confidence interval, i.e. $Z = 1.65$ for 90% CI (40). See Ref. (42) for details.

TPO-Ab in serum and with urinary iodine excretion as evaluated from within-person correlations (43).

We studied whether the fluctuations in TSH and TPO-Ab in serum and urinary iodine excretion were in phase or not by calculating Pearson coefficients of correlations for the individual patients with time shifts between the variables. There was a positive correlation between TPO-Ab and TSH over a broad time interval from TPO-Ab measured 2 months before, to 1 month after TSH. The only substantial correlation between urinary iodine excretion and TSH was obtained using the urinary iodine excretion value taken 1 month before the TSH value. It was also evident that the urinary iodine excretion obtained 1 month before the TPO-Ab value gave the highest and positive mean correlation value. This may indicate an additive effect of an increase in iodine intake and a surge in thyroid autoimmunity on thyroid failure in patients with SCH. Supplementary iodine given to individuals with euthyroid Hashimoto's thyroiditis has previously been associated with increased risk of a decline in thyroid function without change in thyroid autoimmunity (44), whereas serum TSH and TPO-Ab increased in some patients with euthyroid endemic goitre treated with potassium iodide (45).

Should other parameters than serum TSH and serum T_4 be measured?

Both TSH and T_4 are used for the definition of SCH, and measurement of both hormones is paramount. The presence of TPO-Ab in serum is an independent risk factor for the development of HYPO in patients with

SCH (16, 17, 46). Serum values of TPO-Ab and TSH have a parallel course in patients with SCH (43). In other words, regular measurement of TPO-Ab in addition to TSH confirms the significance of a change in TSH. It plays no particular role as an independent indicator of disease activity or severity.

In clinical practice, HYPO-related symptoms and signs are often the argument for institution of $L-T_4$ treatment. Randomised clinical trials on HYPO-related symptoms and signs in patients with SCH have shown contradictory effects of $L-T_4$ replacement therapy (27, 47–53). As a consequence of the variation in results of thyroid function test in patients with SCH, diagnoses may shift between euthyroidism, SCH and HYPO. In a 1-year study of patients with SCH, symptoms and signs related to HYPO varied considerably between patients. However, there was no correlation between symptoms and signs on the one hand and TSH abnormality on the other hand when different patients were compared. Moreover, in the individual patient, there was no correlation between the diagnosis based on a given test result and the symptoms of HYPO at the same point in time (42).

Diez *et al.* (17) found that patients who developed HYPO had higher probability of experiencing symptoms related to HYPO, whereas Huber *et al.* (16) found that the hypothyroid symptom score they used gave results well within the normal range throughout the 9-year follow-up period.

The considerable overlap in traditional hypothyroid symptoms between hypothyroid patients and euthyroid controls also reported by Canaris *et al.* (54) makes hypothyroid symptom scores quite unreliable as indicator of change in thyroid function in patients with SCH. Monitoring of patients with SCH should primarily be based on thyroid function testing, keeping in mind that TSH is a less sensitive marker of HYPO in elderly compared to younger patients (55–57).

Influence of T_4 estimation method and control interval on diagnostic outcome of SCH

An estimate of T_4 within or below the reference range is the biochemical difference between SCH and HYPO. We studied the effect of using different T_4 estimates on the probability of diagnosing HYPO in SCH patients by using three different estimates of T_4 : fT_4 by automated analogue-based method, total T_4 and the total T_4 /TBG (T_4 binding globulin) ratio (58). In the calculations, the patients were investigated in a theoretical setting with visits every third month, and it was assumed that treatment would commence when thyroid function tests corresponded to HYPO and further control would cease if thyroid function tests were normal. The diagnostic outcome of monitoring SCH for 1 year was significantly different for the three T_4 estimates as shown in Fig. 2.

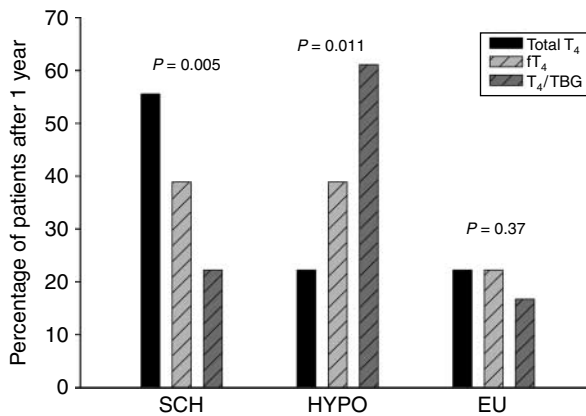


Figure 2 The effect of using different serum T₄ estimation methods on the percentage of patients diagnosed to have either hypothyroidism (HYPO), subclinical hypothyroidism (SCH) or normal thyroid function (EU) after 1 year of observation in patients initially diagnosed with SCH ($n=18$). It was assumed that the patients were tested every third month for a year or until the development of HYPO or EU. HYPO was diagnosed when serum TSH was above 4.2 mU/l and the T₄ estimate below normal, SCH was TSH above 4.2 mU/l and a normal T₄ estimate, and EU was TSH between 0.3 and 4.2 mU/l and a normal T₄ estimate. The T₄ reference ranges were 60–140 nmol/l for total T₄ (black bars), 12–22 pmol/l for free T₄ (light grey bars) and 3.7–7.3 nmol/mg for the T₄/TBG ratio (dark grey bars). The *P* values for the differences were calculated using Cochran's *Q* test. See Ref. (58) for further details.

A 75% higher probability of diagnosing HYPO was found when using the fT₄ assay compared to the total T₄ assay.

Even though T₄ is normal in SCH, it is often low in the reference interval. As discussed above, both TSH and T₄ display considerable biological intra-individual variation also in patients with SCH. Thus, there is a certain probability of both TSH and T₄ being either normal or abnormal during certain time intervals. With repeated testing of biochemical thyroid function, a change in

diagnosis due to variation is likely, and it may be speculated that a higher frequency of testing will increase the likelihood of diagnosing either normalisation of thyroid function or deterioration with development of HYPO.

Indeed, when investigating the effect of using different intervals between control visits, the probability of diagnosing HYPO in SCH patients was found to increase significantly with increasing number of controls per year (58). The risk of diagnosing HYPO increased 45% with quarterly and 58% with monthly controls, compared to yearly controls. Additionally, the precise level of the lower fT₄ reference limit influenced the probability of diagnosing HYPO considerably (58).

Some of the differences in the observed probability of developing HYPO or normal thyroid function test between the studies listed in Table 1 are most likely due to differences in subtypes of disease in included patients, different screening procedures prior to inclusion of the patients and differences in age of the included patients. However, differences in interval between the thyroid function tests, T₄ estimation method and T₄ assay lower reference limit also significantly influence the probability of classifying patients as HYPO rather than SCH.

Recommendations for monitoring in untreated SCH

This review presents evidence to guide monitoring of SCH, and some recommendations may be deduced as listed in Box 1. These are, however, the authors' interpretation of the available data, and no randomised studies comparing various monitoring programmes have been performed. As indicated (Box 1), a single

Box 1 Recommendations for monitoring untreated SCH

- Measurement of serum TSH and T₄ is a cornerstone in monitoring SCH, but additional evaluation of symptoms and signs of hypothyroidism should be performed.
- A validated assay with an appropriately established assay-specific reference interval should be used for T₄. Change in T₄ estimation method during the monitoring should be avoided.
- Initial diagnosis of SCH should be confirmed by the measurement of TSH, T₄ and TPO-Ab after 8–12 weeks.
- If normal: no further evaluation is needed.
- If SCH is persistent:
 - i) Thyroid function should be evaluated every 6 months the first 2 years.
 - ii) Thyroid function should be evaluated every year after 2 years.
 - iii) Patients without symptoms, TPO-Ab or goitre can stop control after 3 years.
 - iv) After 3 years thyroid function should be evaluated if the patient gets pregnant, develop hypothyroid symptoms or concomitantly with general health evaluations.
- A decrease in thyroid function is suggested when:
 - TSH rises more than 40%.
 - T₄ decreases by more than 15%.

TSH above the reference range, but below 10 mU/l, should be followed by a confirmatory measurement of serum TSH, an estimate of T_4 and a TPO-Ab measurement after 8–12 weeks. The majority of patients will most likely have a normal TSH on repeated testing, and further testing will be of little value (59). Serial TPO-Ab measurement in antibody-positive individuals is not recommended.

If TSH remains above the upper limit of the reference interval, yearly testing complies with a conversion rate for the development of HYPO in SCH patients in the order of 5% (Table 1). In the individual patient, the rate of progression of thyroid failure is usually slow, and once or twice yearly, biochemical evaluation of thyroid function is sufficient. We suggest evaluation of thyroid function every 6 months the first 2 years and after 2 years, once yearly evaluations. SCH patients without symptoms, goitre or TPO-Ab have particularly low risk of developing HYPO (17), and in such patients, control can be stopped after 3 years.

Whether to commence $L-T_4$ treatment or not is an issue between the patient and the physician. They should keep in mind that the difference between two tests should exceed 40% in serum TSH and 15% in T_4 to suggest a true change in thyroid function.

Conclusion

SCH is a condition that can progress to HYPO or regress to normal thyroid function, but often it remains relatively stable for long periods. In the many patients where $L-T_4$ replacement therapy is not commenced, regular monitoring of the patients is recommended, and criteria for when to start therapy and when to repeat thyroid tests are necessary. No evidence-based recommendations exist on how monitoring should be performed.

When monitoring it should be taken into account that the intra-individual variation in serum TSH resembles that of euthyroid individuals and that the variation in fT_4 and fT_3 is approximately half that of euthyroid individuals. Changes in TPO-Ab parallel changes in TSH, and consequently, serial measurements of TPO-Ab add little valuable information. Serial evaluation of symptoms and signs related to HYPO is customary when controlling the patients, but they are quite unreliable for evaluation of thyroid function as they associate neither to serum TSH nor to biochemical diagnoses.

Differences in the monitoring procedure may have considerable impact on the diagnostic outcome when monitoring patients with SCH. Specifically, the interval between visits, the type of T_4 estimate used and the lower T_4 reference limit influence the outcome when untreated SCH patients are followed.

We suggest that patients with confirmed SCH and who are not treated with $L-T_4$ should have serum TSH

and T_4 measurements and symptoms and signs evaluated every 6 months and after 2 years with stable values, the interval between monitoring can be extended. However, randomised studies on how to monitor untreated SCH patients are needed.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review reported.

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