A raised thyroid stimulating hormone result—a 12-month follow-up study in general practice

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ABSTRACT

INTRODUCTION: Subclinical hypothyroidism (SCH) is common in older patients.

AIM: To review the management of patients identified with a raised thyroid stimulating hormone (TSH) result in a 12-month period and compare this to current guidelines from the New Zealand Best Practice Advocacy Centre (BPAC).

METHODS: We collected laboratory data on thyroid function tests (TFTs) that were reported between December 2005 and November 2006 from two general practices with an adult population of approximately 21 000. Data were collected on symptoms, investigations, thyroid medication, family history and comorbidities. We used chi-squared tests to compare findings by age, gender and ethnicity.

RESULTS: Older women of European descent were more likely to be to have initial results suggesting SCH. The number of follow-up tests ranged from 0 to 5 tests in a 12-month period. Forty-eight percent of individuals did not have any follow-up investigations. Seventy-three percent of FT4 tests taken are requested concurrently with TSH. Of those who had a repeat TSH test, just over 40% had a result within the reference interval. Twenty-eight percent had two TSH results consistent with SCH. Thirty-five percent of patients with antibody results were positive. The most commonly-recorded symptoms were tiredness and weight gain.

DISCUSSION: We found inconsistencies in the management of SCH which were not related to patient characteristics such as age, gender or ethnicity. Further research is needed to determine if SCH is associated with increased morbidity and to provide a clear rationale for management of patients with SCH.

KEYWORDS: Hypothyroidism; family practice; quantitative research; general practice

Introduction

Subclinical hypothyroidism (SCH) is common in middle-aged and elderly individuals.[1] SCH is diagnosed by demonstrating elevated levels of serum thyroid stimulating hormone (TSH) with levels of free thyroxine (FT_4) within the normal reference range.[2] International literature estimates the prevalence of SCH at 6.4–10%.[1,3–5] There is a lack of consensus amongst 'expert groups' on the management of SCH.[6–13]

TSH is a frequently requested test with over 850 000 samples assayed in New Zealand each year.[14] Current TSH assays have high sensitivity and are recommended as a first-line strategy for identifying changes in thyroid function.[13, 15-18] Whilst widespread testing will identify patients with overt hypothyroidism, where treatment options are well recognised, a larger number of patients will be identified with SCH.

BPAC guidelines recommend that initial testing for thyroid dysfunction be based on clinical suspicion and that TSH be used as the sole test in most situations.[13] Rationale for this is the log-

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linear relationship between TSH and FT_4, which shows that a twofold change in FT_4 represents a 100-fold change in TSH. Therefore TSH has greater sensitivity in detecting changes in thyroid hormone levels, well before these changes will show on testing.[19]

We reviewed the medical notes of a cohort of adults identified by thyroid function tests (TFTs) suggestive of SCH to ascertain their management in the subsequent 12 months and compared their management to current guidelines from the New Zealand Best Practice Advocacy Centre (BPAC) on investigating thyroid function.[13]

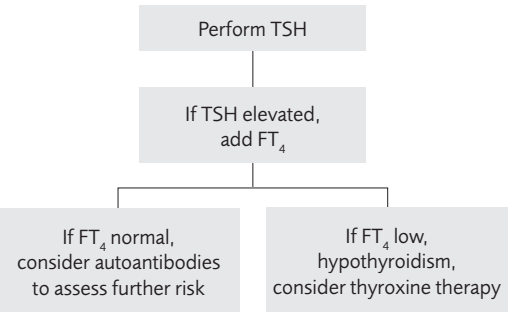
Methods

The study population was derived from two general practices in Hamilton, New Zealand with approximately 21 000 patients who were 18 years of age and over, representing 25% of the Hamilton City population (NZ Census 2001; www.stats.govt.nz/census). As part of a larger study to identify the epidemiology of thyroid dysfunction, data were collected to identify patients with diagnosed thyroid dysfunction from three sources; disease codes, laboratory data ordered for thyroid function, and prescriptions for drugs to treat thyroid dysfunction including thyroxine, carbimazole and propylthiouracil (PTU). Patients with known thyroid disease, on prescriptions for drugs commonly used to treat thyroid dysfunction including thyroxine, carbimazole and PTU were excluded, leaving 20 628 for analysis.[20]

We collected laboratory data on TFTs that were reported between December 2005 and November 2006. These tests were from the two community laboratories in our area. We sought to identify new cases of SCH and retrospectively identify how these patients were managed in the subsequent 12 months in general practice.

We employed two practice nurses to review their general practice computerised records to identify aspects of the management of SCH up to 12 months from the patient's initial SCH result. Data were collected on symptoms noted leading to first test; use of thyroid antibodies; further relevant investigations since first test, symptoms noted since first test; use of thyroid medication; use of Read codes for thyroid disease; family history of thyroid disease, and history of diabetes, heart failure or depression. Data was analysed using Stata 8 (Stata Corporation, 2003) and Microsoft Excel (Microsoft Corporation, 2003).

Figure 1. BPAC recommendations for order of tests with symptomatic patients



Symptoms sought from notes relating to hypothyroidism included: tiredness/lethargy, weight gain, cold intolerance, constipation, dry skin, hair loss, sluggish thinking, general slowing, deepening voice, shortness of breath on exertion, menorrhagia, and ataxia.

Laboratory tests were from two laboratories in Waikato with different analysers and reference intervals. Pathlab Medical Laboratory used an Abbott Architect i-2000 analyser with a TSH reference interval of 0.3–3.1 mU/L and FT_4 reference interval of 9–19 pmol/L. Medlab Hamilton used a Roche e170 analyser with a TSH reference interval of 0.3–5 mU/L and FT_4 reference interval of 10–25 pmol/L. Subclinical hypothyroidism was defined as being above the laboratory reference interval for TSH and below 10 IU/mL and, where available, a FT_4 within the reference interval. We sought to confirm a diagnosis of SCH by two TFTs being taken at least three months apart.

It is recommend that asymptomatic patients not be screened for thyroid dysfunction. BPAC recommends the order of tests as shown in Figure 1.

Descriptive statistics used Chi-squared tests to calculate statistical significance between age groups (test for trend), gender (2x2 contingency)

and ethnicity groups (2x2 contingency). We examined whether there was an association between having a 2nd TSH test and age, gender or ethnicity.

This study was approved by the Northern Y ethics committee.

Results

Thyroid function testing was performed on 3459 patients during the study period. Of these, 270 individuals fitted the inclusion criteria with laboratory results suggestive of SCH. Five patients were excluded following note review—one recently diagnosed with hypothyroidism, one with an alternative NHI number which revealed a previous history of hypothyroidism, and three patients with histories of thyroid operations which were not noted on GP computerised records until 2007 (after our larger study). This left 265 individuals in the study—a total of 6.4% of tested individuals.

The patients were aged between 19 and 93 years (median age 61yrs, SD 17.4yrs). Eighty-two males (31.0%) and 183 females (69.0%) were identified. From initial TFTs, women had nearly twice the rate of SCH as men (16.6 vs 8.5 per 1000 population) but this was not statistically significant when compared with the number of TFTs performed by gender (2830 vs 1308, p=0.81). Two hundred and twenty-five (84.9%) patients with SCH were of European descent, 10 (3.8%) Maori, 15 (5.6%) Asian, six (2.3%) Pacific and nine (3.4%) were of other ethnicities. The number of follow-up tests in individuals ranged from 0 to 5 tests in the 12-month period.

Forty-eight percent (128/265) of patients had no follow-up TSH testing, including seven who had transferred out of the practice and four patients who had died. Two patients were prescribed thyroxine replacement medication; one of them coded for hypothyroidism. No further investigations of any kind had been recorded in this group of patients. Another three patients had thyroid hormone testing only (FT_4 and/or FT_3) and four patients had thyroid antibody testing only (anti-TPO and anti Tg); one patient had a positive anti-TPO result. No further investigations were recorded in this group during the 12-month follow-up. Of the three patients with negative thyroid antibodies, one had been placed on thyroxine replacement therapy.

Overall, a second TSH test was performed on 49% (130/265) of patients. There was no difference in 2nd testing by age group (p=0.9357), gender (p=0.0631) or ethnicity (p=0.9869) compared with no follow-up TSH testing. The time difference between first and second TSH tests ranged between 5 and 362 days (mean 149 days, median 109 days).

Forty-one percent (53/130) of patients had a 2nd TSH result that fell within the reference intervals. Of these, 22/53 (41.5%) had their 2nd TSH test within three months of the first. From this subset, 10 had no further TSH tests during the 12 months; one with positive anti-TPO, one with both positive anti-TPO and anti-Tg, and one with negative anti-TPO and anti-Tg. A further three patients were prescribed thyroxine replacement therapy; one who was also coded for hypothyroidism. Ten patients had subsequent tests outside of the three-month window which were within the reference interval, including one with negative thyroid antibodies. Along with the remaining 30 patients that were within TSH reference intervals this indicated that the first raised TSH result may have been transient. Overall, 75% (40/53) had a TSH within the reference interval and 25% (13/53) could not be confirmed.

Fifty-nine percent (77/130) had a 2nd TSH result that remained above the reference interval. Of these, 29% (22/77) had their 2nd TSH test within

WHAT GAP THIS FILLS

What we already know: Where outcomes of treatment are uncertain, the actions of the GP may be influenced by factors such as tradition, routine and convenience. Best Practice Guidelines to investigate and manage thyroid dysfunction are available in New Zealand.

What this study adds: There is a high degree of variability in the way GPs manage a raised thyroid stimulating hormone result. This repeated departure from guidelines is not influenced by patient characteristics such as age, gender or ethnicity.

three months of the first, of these four patients had no further TSH tests after this (one who had been placed on thyroxine) and 18 patients had subsequent tests outside of the three-month window (one with positive anti-TPO and anti-Tg and was referred to an endocrine specialist). The remaining 55 patients had raised TSH results, including two patients with positive anti-TPO and anti-Tg results and five patients with negative anti-TPO and anti-Tg results. Overall, 95% (73/77) of patients, who had a 2nd TSH outside of the three-month window and had remained above the reference interval, were likely to have a diagnosis of SCH. Five percent (4/77) could not be confirmed.

In total, 55% (146/265) of patients had at least one FT_4 test during the 12-month follow-up period. 41/146 (28.1%) patients had one or more repeat FT_4 tests. There was no difference in FT_4 testing by age group (p=0.2512), gender (p=0.1420) or ethnicity (p=0.5197). The time difference between TSH and 1st FT_4 test ranged between 0 and 304 days (mean 26 days, median 0 days).

Of the patients who had a FT_4 test, as previously mentioned, 74% (108/146) had a request concurrently with their first TSH test. A further 5% (8/146) were tested within two weeks, 8% (11/146) by three months, another 10% (14/146) at six months and additionally 3% (5/146) between six and 12 months. All FT_4 results were within the reference interval except two individual results who had slightly low results (FT_4=8 p/mol/L). Neither of these individuals were prescribed medication, coded for hypothyroidism, had a family history or had antibody testing.

Eight percent (20/265) of patients had thyroid antibody testing results; four patients had no further TSH tests (one with positive anti-TPO), seven patients had 2nd TSH results within the reference intervals (two with positive antibody/ies), and nine patients had raised 2nd TSH results (four with positive antibody/ies). Overall, 35% (7/20) of patients having thyroid antibody testing had positive results—three patients with anti-TPO and four patients with both anti-TPO and anti-Tg.

Of the 5% (13/265) of patients placed on thyroxine replacement medication, no patient had a TSH result greater than 10 mIU/mL. Two patients had no follow-up investigations (one was coded for hypothyroidism) and one had no TSH follow-up and negative autoantibodies. Four patients had one or more follow-up TSH results all within the reference interval; possibly the result of thyroxine replacement. Six patients on medication had results indicating SCH, two were coded for hypothyroidism and one had their second test within the three-month window and therefore could not be confirmed. No other blood tests or investigations were carried out in this group.

Symptoms leading to first TFTs were reported in 29% (77/265) of patients with the GP recording from one to three symptoms. The most common symptoms reported was tiredness/lethargy in 33% (25/77) of patients, weight gain (14.3%) and sluggish thinking (14.3%). Cold intolerance, constipation, dry skin, hair loss, general slowing, heart failure, deepening voice, shortness of breath on exertion, menorrhagia and ataxia were also recorded.

In the 12-months following first test, 26% (68/265) of patients had symptoms recorded. Tiredness/lethargy remained the most commonly reported symptom in 47% (32/68) of patients, followed by weight gain (20.1%). Of the 88 patients with both height and weight measures, BMI ranged from 19 to 44 (average and median=29).

Recorded co-morbidities included depression in 16% (42/265) of patients, followed by diabetes in nearly 10% (26/265) and heart failure in 5% (14/265) of patients. Of other possible investigations, one patient had a thyroid ultrasound (NAD) and one patient had an inpatient Technitium scan performed. One patient had been referred to Endocrinology (SCH with positive antibodies).

Less than 2% (5/265) of patients with raised TSH had a subsequent (not concurrent) FT_4 and, where this was normal, had antibody testing. However, three out of five patients had FT_4 and antibodies taken concurrently. Therefore, less than 1% of patients in this follow-up study appeared to be managed according to BPAC guidelines.

Discussion

This study followed a cohort of patients with no prior thyroid dysfunction who had been tested for thyroid dysfunction and found to have laboratory results suggesting SCH. An examination of test requests, results and follow-up investigations were undertaken. These were compared to current guidelines from the New Zealand Best Practice Advocacy Centre (BPAC) on investigating thyroid function.[13] We also examined recorded symptoms relating to before and subsequent to the first TSH test.

What we found was a lack of consistency with the guidelines following from a raised TSH result. Of the 265 individuals with results indicating SCH, over 48% had no follow-up investigations. Of those with further tests, nearly 45% of patients had no FT_4 test. Forty percent of FT_4 tests were taken concurrently with TSH and a further 3% were tested within two weeks of the initial TSH test. BPAC suggest 'reflex testing', which relates to further testing from retained blood samples at the laboratory and indicated by the TSH result.[13] This gives the opportunity for GPs to directly request an FT_4 test using the original blood sample without the need to recall the patient.

Ninety-three percent of patients had no thyroid antibody tests despite the BPAC recommendation to do so when FT_4 remains within the reference interval. Hashimoto's thyroiditis is the most common cause of primary hypothyroidism in the Western world and has been associated with an increased likelihood of progression from SCH to overt hypothyroidism.[21]

The number of TSH tests returning to within the reference interval (40.8%) was similar to international literature which ranges from 37.5% in the first 12 months to 50% over five years.[22, 23]

The use of symptoms in the clinical picture is less clear in the literature. BPAC advises the decision to initiate treatment based on evidence of symptoms. In our study, the most likely indicated symptoms were tiredness/lethargy and weight gain. Symptoms were recorded in 29% of patients; however, this does not necessarily indicate that those without recorded symptoms had no symptoms. Reviewing symptomatology using clinical notes may be problematic if, for example, basic clinical information such as weight is inconsistently recorded. Of 265 patients in our cohort, 23% (61/265) of patients had no weight recorded.

Data from practice management systems were consistent with findings from recent focus groups.[24] GPs had identified a range of responses to retesting which corresponded with our findings of 0–5 further tests in a 12-month period. Symptoms identified in focus groups such as tiredness/lethargy and weight gain were also the most prominent symptoms, if any, that were recorded.[24]

For the 48% of patients with no further investigations, TFTs examined in isolation may not give a full clinical picture. In the context of co-existing acute illness the test may give results that are potentially misleading as they may echo non-thyroidal illness. BPAC guidelines advise against testing thyroid function at such times as TSH is altered independent of thyroid status.[13]

We found inconsistencies in the management of SCH and these were not related to patient characteristics such as age, gender or ethnicity

For patients with untreated SCH, TSH monitoring is recommended every six to 12 months. Our study may underestimate retesting due to the exact 12-month cut-off that we used. Due to a lack of FT_4 tests, SCH was confirmed by two raised TSH results no less than three months apart, which may not provide a true picture of aetiology of thyroid function or confirmation of SCH.

We found inconsistencies in the management of SCH and these were not related to patient characteristics such as age, gender or ethnicity. No clear pattern emerged in the timing of FT_4 tests, repeat TSH testing, antibody testing, prescribing or recording of symptoms and this

is reflected in the number of patients whose management follows guidelines in the study. A departure from guideline recommendations may be due to the GP's wish to maintain a good relationship with their patient through responding to patient requests.[25] In addition, GPs may lack recognition of their need for further training, specifically in topics such as thyroid disease.[26] Unwittingly, GPs may be less able to make informed decisions about their patient care: for instance, when abnormal TSH results present.[27] Guidelines are not always accepted or acceptable by GPs.[28,29]

The lack of consistency in providing a standardised approach in view of current guidelines needs to be addressed in a way which recognises the experience of the GP and the rights of the patient in following a pathway of care. Current guidelines in the assessment and management of SCH provide a theoretical basis which is controversial.[21, 30] Further research is needed to demonstrate the long-term morbidity associated with SCH. This will provide clear rationale to GPs for clinical decision-making.

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COMPETING INTERESTS
None declared.

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