Author's response to reviews

Title: Is annual surveillance of all treated hypothyroid patients necessary?

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Editors
BMC Endocrine disorders

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Dear Editors,

We would like to thank the reviewers for their comments and suggestions which have been helpful. We have addressed the issues point by point as noted below. The manuscript has been altered accordingly.

We accept that this is a retrospective study and has its limitations. However we hope the editors acknowledge the views stated by reviewer 1 that it is "an article of importance in its field" and the paper deals with a common and important issue of the long term follow-up of treated hypothyroid patients.

Response to reviewers report:

Reviewer 1: John Henry H Lazarus

No major compulsory revisions recommended.

1. This paper analyses a large number of patients with a 10 or more year follow-up on thyroxine therapy for hypothyroidism and concludes 18 monthly surveillance is adequate for those patients less than 60 years of age on a stable thyroxine dose of between 100 and 150 mcgs per day. The authors found more abnormal thyroid testing in the 12 monthly group compared to the 18 month. Have the authors any explanation for this finding?

We acknowledge that this is a retrospective study, without randomization to frequency of follow-up, which has its limitations. There aren't any published prospective long-term follow-up studies of treated hypothyroid patients. The Grampian thyroid register provided us with an opportunity to evaluate the appropriate frequency of testing in the long term follow-up of treated hypothyroid patients.

The majority of treated hypothyroid patients in the thyroid register are on 18 monthly follow-up. One might expect 18 monthly follow-up patients who are seen less frequently to have more abnormal tests. We undertook a retrospective study to see if this was true and to gather further evidence to support more
frequent testing. However our study found that 18 monthly follow-up was not associated with an increase in adverse outcomes compared to annual surveillance.

On the other hand we were surprised to note that patients on 12 monthly follow-up had more abnormal tests. Both the groups were well matched at baseline (table 1) in relation to age & sex distribution, thyroxine dose and duration of follow-up, and we cannot readily account for the difference in outcome. The other possible explanations are:

Compliance & physician bias: At the time of registration, physicians allocated individuals to either 12 monthly or 18 monthly follow-up. There were no set guidelines or criteria on which this was based. It is of course possible that there may have been a physician bias while allocating individuals to annual surveillance taking into account factors such as compliance. This might explain why the 12 monthly group had more abnormal results.

Increased frequency of testing: The 12 monthly group had more frequent testing which may explain why they had more abnormal tests that prompted further dose adjustments. We didn't find that more frequent testing or dose changes had any impact on the final dose or maintenance of the euthyroid state. This further supports our view that patients who are on a stable thyroxine dose of 100-150mcg and are less than 60 years of age can have less frequent testing as long as there are robust recall systems in place.

2. When an abnormal result was detected, did this mean that all patients were required for follow-up or were some of the abnormal results of such a minor nature that an out-patient visit was not required?

This has been discussed in the methodology section. All abnormal results were flagged up by the register and reviewed by a thyroid specialist. If the abnormal tests were of a minor nature then a dose change and/or an early review with repeat TFTs would be recommended. This information was conveyed to the patient and his/her GP thereby reducing the number of abnormal tests requiring a review at the hospital thyroid clinic.

3. Do the authors have any data on the death rates in the two groups?

There was no statistically significant difference in the mortality between the groups. Total number of documented deaths were 206. 10% (122/1060) in the 18 monthly group and 9% (84/1060) in the 12 monthly group.

4. Perhaps the authors could identify the total cost of the Grampian Follow-up Register and express the potential savings as a percentage.

The total cost of running the hospital thyroid register has not been formally evaluated. We agree that a detailed health economic evaluation would be helpful and this is currently being considered.

Reviewer 2: John Walsh

Annual surveillance (12 monthly follow-up) was associated with more abnormal test compared to 18 monthly follow-up. How do the authors explain this?

Already answered

1. What was the method used for TFTs and what were the laboratory reference ranges? Was it the same method throughout the study period? What was the lower limit of the TSH reference range and was it the same as the cut-off which prompted dosage adjustment?
The method used for thyroid function test varied during the study period and the details have been included in the methods section.

Up to 1995: RIA (radio-immuno assay)
Reference range: Total T4 70-150 nmol/L, TSH 0.35-3.3 mU/L

1995-2000: Immuno-1 automated immunoassay analyzer (Bayer diagnostics)
Reference range: FT4 10-25 pmol/L, TSH 0.35-3.3 mU/L

2000 to present: Advia Centaur automated immunoassay analyzer (Bayer diagnostics)
Reference range: FT4 10-25 pmol/L, TSH 0.35-3.3 mU/L

As outlined in the methodology section every abnormal result was reviewed by the thyroid specialist, who, depending on the trend, recommended a dose change and/or an early review.

2. On page 5, "suppressed" TSH should be defined (i.e. below the level of assay detection, below 0.1 mU/L, or below the lower limit of the reference range).

Suppressed TSH was defined as <0.01 mU/L and this has been added in the text

3. If cost containment is the issue, why do the authors measure fT4 rather than TSH alone?

The Grampian automated thyroid register was set up in the late 1960s and traditionally TSH and FT4 estimations were undertaken. We agree that TSH estimation alone is adequate in the long-term follow-up of treated hypothyroid patients and this is supported by the recently published UK guidelines for the use of thyroid function tests (British Thyroid Association). We plan to implement these changes to the thyroid register to achieve additional cost savings.

4. Page 6, para 2 and Table 2: since the groups are of unequal size, the mean number of tests per person would be a helpful addition.

As per the suggestion we have replaced the total number of tests by mean number of test per person over the duration of follow-up. The table has been modified.

5. Page 7, para 1. The proportion of abnormal tests which prompted dosage adjustment should be given for both groups.

66.9% of patients on annual surveillance required a dose change as opposed to 62.7% on 18 monthly follow-up (p<0.05). This has been included in the results section.

6. Do the authors know if their patients had TFTs checked apart from the occasions on which the registry dictated it (i.e did patients' GPs check TFTs independent of the register system)? They might find that the 18 month group had more "off-protocol" testing which negate the cost savings with this strategy.

GP's enroll their patients on the thyroid register for regular surveillance. At a pre-set follow-up interval patients are informed to visit their GP for a review and thyroid test. In other words the thyroid register organized follow-up and blood tests through primary care and if the GP had already carried out TFT (independent of the register recall), this information was passed on to the thyroid register. In addition the thyroid register administrative staff regularly accessed the lab data of defaulters to find out if they had any recent thyroid test before sending a reminder to avoid duplication.

It is possible that patients had additional thyroid tests during emergency hospital admissions which aren't accounted in this study. This is likely to be a small number and would affect both groups equally.
7. There are numerous typos, eg page 9 "thyroid; the first authors' names in refs 4 and 9; "thyrotropin" in ref.6; "consensus" in ref. 9

Page 9, para2 'thyroid': corrected
Ref 4 & 9 first authors: corrected
Ref 6 & 9 typos: corrected

We hope the above comments and revisions to the manuscript have addressed all the highlighted issues. If you require any further clarification please feel free to contact us. We look forward to hearing from you.

Yours sincerely

A K Viswanath