Thyroxine, thyrotropin, and age in a euthyroid hospital patient population

Richard Davey

The diagnosis of thyroid disease now often can be achieved reliably by measuring thyrotropin (TSH) alone. Thyroxine (T₄), triiodothyronine, and other analytes are only needed if TSH and the accompanying clinical condition are discordant. We describe here work that confirms the age independence of TSH in both inpatient and outpatient euthyroid hospital populations between ages 20 and at least 80 years, and demonstrates that although free T₄ does vary with age, the range of variation remains within the T₄ reference interval. On this basis, TSH-based thyroid diagnostic algorithms can be used reliably in adults without reference to age-related reference intervals.

The rapid evolution in thyroid function testing (TFT) in the past decade [1] has left some clinicians and laboratory workers still skeptical [2] of the value of the contemporary assays’ results and of their value in the diagnostic process. As a preliminary phase to a definitive study to validate a thyrotropin (TSH)-based TFT algorithm [3], we also investigated the influence of age and other factors on TSH and free thyroxine (FT₄) with the Ciba Corning ACS:180 assay (Ciba Corning Diagnostics) in a suburban hospital population.

This study was undertaken at Western Hospital, Melbourne, Australia. The hospital services >600,000 people in Melbourne’s industrial west. It provides complete pediatric, adult medicine and surgery, obstetrics and gynecology, psychiatric, and geriatric services to both inpatients and ambulatory outpatients. It draws patients from the surrounding general practitioner-treated pool. There are no large private hospitals in the area and no areas of large personal wealth. As a result the hospital patients uniformly represent the regional population. The ethnic composition of the population is ~70% Caucasian and 30% Asian. There is a negligible negroid component and there are a few aboriginal Australians.

Materials and Methods

One thousand consecutive requests for TFT where both TSH and FT₄ results were examined in early 1995 to see whether the patients in question were known to be in any of the following categories for which Australian Medicare rebate payments are made for the initial assay of both TSH and FT₄:

- patients with thyroid diseases (including those patients being treated for thyroid disease, as for instance with l-T₄)
- patients suspected of having thyroid or pituitary disease
- patients with psychoses or dementia
- patients being investigated for infertility
- patients taking drugs known to interfere with thyroid gland function

For every patient tested, the clinician’s request form was scrutinized and, where necessary to find further information, the patient medical record was consulted.

Patient age and ambulatory/inpatient status were noted, and, for women, whether or not they were pregnant. Full blood examination (FBE) and renal function test (RFT) data were accessed and categorized into within or outside reference intervals, or alternatively were unknown. Hence, for this latter study, all results except those from patients with thyroid disease were included. After the patients with thyroid disease
were excluded, 754 sets of measurable TSH and FT4 results in patients between ages 1 and 101 years remained for analysis. None of the patients was excluded from this study on the basis of any other medications being taken, even though several commonly used medications have been reported to alter TFT.

Patients were sorted into five-year age groups: ages 1–4, 5–9, 10–14, and so on until the final group, age 94 and older. Patients <1 year of age were excluded because they have different, and constantly differing, reference ranges compared with older individuals [5]. The one patient found in the group >100 years of age, a woman age 101 years, was included in the >94 years of age group.

Statistical calculations were performed with the Stata package (Release 3: Computing Resource Centre, 1992). Arithmetic means for FT4 and geometric means for TSH, with 95% confidence intervals (CI), were calculated for each age group, first for males and females, second for inpatients and ambulatory patients, and finally in total, for each of TSH and FT4. To provide a perspective of the result spread, the 5th and 95th percentile values for the total result in each age group were also calculated.

Two-way ANOVA among the FT4 and TSH results was undertaken for age (as a continuous variable), gender, and patient location, and analysis of covariance (ANOCOVA) for age with gender and for age with patient location. The Stata program accommodates designs such as found in this study on the basis of any other medications being taken, the data here, with imbalance, even to the extent of missing cells. CI overlaps were noted and Student’s t-tests were performed post hoc where indicated among the results found in the age group data, with age as an arbitrarily categorical variable. Linear regression analysis was performed where needed.

This work was performed in accordance with the appropriate standards of the Western Hospital Research and Ethics Committee.

Results

The results of the analyses with calculated means and 95% CIs are shown in Tables 1 and 2 where the data for each gender, for each location status, and the pooled data are all given. Only pooled data are shown on the graphs where observed medians, interquartile ranges, and the adjacent values are shown and outside values individually plotted (Fig. 1). Adjacent values are formally defined as three-halves of the interquartile range rolled back to where data persist; they run the length of the whisker. Outside values are more extreme than the adjacent values.

Discussion

The pituitary gland is an exquisitely sensitive monitor of circulating FT4 because there is an inverse log/linear relation between TSH and FT4 [6]. TSH has been shown to be an adequate initial, sole screening test for thyroid disease [7].

Age-dependent reference intervals have previously been used for TSH [8], but more recent work has shown that although there are minor variations in both TSH and FT4 values as between younger and older adults, the limits of the variation lie within the accepted reference intervals (TSH 0.5–5.0 mU/L and FT4 9–24 pmol/L) (Ciba Corning Diagnostics, assay kit insert data) and should not

Table 1. TSH values by age, gender, and ambulatory status in patients without thyroid disease (mU/L).

<table>
<thead>
<tr>
<th>Age group</th>
<th>Years</th>
<th>Male</th>
<th>Female</th>
<th>Inpatient</th>
<th>Outpatient</th>
<th>Total</th>
</tr>
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<tbody>
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<tr>
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<tr>
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<td>0.8–10.8</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>20–24</td>
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<td>1.4–4.2</td>
<td>1.3</td>
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<td>8</td>
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<td>1.0–2.9</td>
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<td>17</td>
</tr>
<tr>
<td>7</td>
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<td>8</td>
<td>2.29</td>
<td>1.3–4.0</td>
<td>1.3–1.8</td>
<td>18</td>
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<tr>
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<td>1.61</td>
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<td>22</td>
</tr>
<tr>
<td>9</td>
<td>40–44</td>
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<td>0.99</td>
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<td>1.8–3.0</td>
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<td>2.33</td>
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<td>1.3–2.1</td>
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<td>1.0–1.6</td>
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<td>0.2–2.9</td>
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<td>19</td>
<td>90–94</td>
<td>3</td>
<td>1.51</td>
<td>0.4–6.0</td>
<td>0.9–2.5</td>
<td>8</td>
</tr>
<tr>
<td>20</td>
<td>&gt;94</td>
<td>1</td>
<td>2.96</td>
<td>1.07</td>
<td>0.4–3.3</td>
<td>2</td>
</tr>
</tbody>
</table>

The results of the analyses with calculated means and 95% CIs are shown in Tables 1 and 2 where the data for each gender, for each location status, and the pooled data are all given. Only pooled data are shown on the graphs where observed medians, interquartile ranges, and the adjacent values are shown and outside values individually plotted (Fig. 1). Adjacent values are formally defined as three-halves of the interquartile range rolled back to where data persist; they run the length of the whisker. Outside values are more extreme than the adjacent values.
Table 2. T₄ values by age, gender, and ambulatory status in patients without thyroid disease (pmol/L).

<table>
<thead>
<tr>
<th>Age group</th>
<th>Years</th>
<th>Male</th>
<th>Female</th>
<th>Inpatient</th>
<th>Outpatient</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n</td>
<td>Mean</td>
<td>95% CI</td>
<td>n</td>
<td>Mean</td>
</tr>
<tr>
<td>1</td>
<td>1-4</td>
<td>2</td>
<td>13.35</td>
<td>0-29.2</td>
<td>0</td>
<td>14.30</td>
</tr>
</tbody>
</table>

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result in diagnostic algorithms needing modification on an age-dependent basis [9]. This cross-sectional study confirms and redefines these findings.

TSH

In the population studied here TSH does not vary with age (ANOCOVA, $F > 0.885$). Nelson et al. [10] studied the complex $FT_4$-TSH interplay in infants, children, and younger adults to age 45 years. They found that an adult plateau in TSH concentrations is reached at age 31 years. Our numbers in the age groups <20 years are too few to compare with Nelson's work but thereafter would suggest that the adult plateau has been reached by as early as 20 years of age.

From age 20 to 80 years our findings probably concur with those of Hershman et al. [11]. They compared geometric mean TSH (and 95% CI) in 216 persons >70 years of age with 211 of their offspring, ages 40–60 years. They do not give any more detail as to the age composition. Their results and ours for the older group are 1.24 (0.29–5.40) and 1.32 (1.15–1.52), and for the younger 1.45 (0.54–3.90) and 1.41 (1.17–1.68) mU/L, respectively. The results are statistically indistinguishable, although it should be noted that our greater subject numbers produce much narrower CIs. When age is treated as a continuous variable, we find no difference between the results of men and women (ANOCOVA, $F > 0.883$), nor is there any interaction between age and gender ($F > 0.846$). In the 40–44 years age group there is a statistically significant difference (mean ± SD 0.99 ± 2.11 vs 2.31 ± 2.67, $P < 0.039$), but this is considered to be a sampling phenomenon only. No difference is seen in any of the other categorical age groupings.

Visual inspection of the graphed TSH data suggests that from age 80 years and up, TSH concentrations decline, and although the TSH mean (±SD) from age 80 years (0.88 ± 3.32 mU/L) does not differ from the mean found through the 20–79 years of age adult plateau (1.61 ± 2.23 mU/L), the difference approaches significance ($P < 0.079$). This is partly in agreement with Hersh-
man et al. [11], whose older women had slightly lower TSH values than their younger offspring (1.21 vs 1.52 mU/L, P < 0.05). Beyond age 90 years, the subject numbers in our age groups are smaller than in the groups up to age 90 years, and are thus less reliable.

Klee and Hay [8] mention “studies of 448 euthyroid subjects [who] did not show significant age differences in [TSH in] adults between 20 and 80 years . . . ” in their review of TSH in the diagnosis of thyroid disease. Our data agree and extend the age limit to 90 years. Although our octogenarians’ TSH values trend downwards, they are still unequivocally within the reference interval and do not give cause for concern when using a TSH-based diagnostic algorithm.

No difference was seen between the TSH results of inpatients and those of the ambulatory outpatients (ANCOVA, F > 0.294), nor was there any interaction between age and patient location (F > 0.298). Although not absolutely contiguous, the boundaries of the in/outpatient groups are probably very close to those of the acute vs chronic illness groups. Because all these results are from hospital patients, a minimum background of chronic disease could be expected, or at least perceived illness by the referring community practitioner, in the outpatient group. Acute disease, or an acute exacerbation of chronic disease, will be found in the inpatients. No differences between the two groups’ TSH results is in accord with the primary study [3], in which the finding that a patient had an abnormal FBE or RFT, indicating disturbance in those basic body systems, did not distinguish among TSH results.

\[ T_4 \]

At the two extremes of the adult range of our study population, ages 20–24 years vs 85–89 years, the mean FT4 ± SD differs (12.96 ± 2.36 vs 15.84 ± 3.48 pmol/L, respectively, P < 0.0003), but both means are unequivocally within the reference interval, 9–24 pmol/L.

Szabolcs et al. [12] found that FT4 ranges in their euthyroid geriatric (>60 years of age) and healthy young (ages 20–40 years) groups were indistinguishable. They noted that although FT4 did apparently independently decrease with increasing age and increase with severity of illness, the mean values were still clearly within the reference interval. Higher FT4 values with paradoxically nonsuppressed TSH occurred more frequently with increasing severity in the clinical disease status. They caution that their conclusions should be restricted to “hospitalized chronic geriatric patients.” By contrast, our results relate to a free-range human population, albeit half with acute illness justifying hospital admission.

By contrast with Szabolcs et al., we see the TSH in the same age groups trending, appropriately, downwards, while remaining within the reference interval, as noted above. This relation reflects the expected response in the healthy pituitary/thyroid axis and suggests that the trend seen in the data we present is a real phenomenon in the aging human. It is not affected by hospital admission for acute illness or the acute exacerbation of chronic illness, or by the possibility of concurrent dementia (data available on request.) It partly confirms the findings of van Coevorden et al. [13] who compared only eight “healthy . . . men” 67–84 years of age with eight “normal . . . men” 20–27 years of age, but did assay TSH at 15-min intervals over 24 h. They found that the 24-h mean TSH concentration in the older men was ~50% lower than that in the younger (0.78 ± 0.37 vs 1.43 ± 0.41 mU/L, P < 0.01). In their eight elderly men, “basal T4 levels were normal.”

Covariance analysis suggests that there may be gender-related variation in FT4 (F < 0.041), and interaction is demonstrated between age and gender (F < 0.016). An explanation is found in gender-isolated linear regression studies of FT4 with age. Among males there is no statistically significant trend, but among females FT4 is age related (FT4 = 0.035age + 12.087, P < 0.0001, adjusted R^2 = 0.056). The difference in FT4 seen between the two ends of the age spectrum thus appears limited to women, although, as noted above, the variation identified remains definitely within the reference interval. The spread of results among men is also unequivocally within that interval but is wider and thereby eliminates any gender differences when FT4 results are compared by categorical age groups.

There was no difference seen between the inpatients’ results and those of ambulatory patients for FT4, except in the 25–29 years of age group (15.31 ± 3.41 vs 12.26 ± 1.90 pmol/L, P < 0.003). One such event, again, can be attributed to the effect of a sampling phenomenon. The ANOCOVA result reflects the effect of the difference in the 25–29 years of age group (F < 0.022) when patient location alone is examined, but there is no interaction between age and patient location overall (F > 0.216).

SYNTHESIS

The primary study from which these data were drawn a posteriori found that a TSH-based thyroid disease screen is broadly efficacious in ruling out thyroid disease [3]. It also touched on the question of ruling in thyroid disease. This current study into the effect of age on TSH and T4 concentrations did not examine the question of the relation between age and the ability of TSH to rule in thyroid disease; i.e., we did not determine how many false-negative results might occur in a population of patients who truly have thyroid disease when TSH alone is used to screen them and age-related reference intervals are not used. In the primary study, 2.7% of abnormal FT4 results (from 6.4 to 29.5 pmol/L) were missed because the patient had a TSH within reference intervals, but those abnormal FT4 results were only marginally outside their reference interval and no age-related trend was found among them on subsequent analysis.

The answer to the diagnostic conundrum of the false negative may never be known. An accepted method for finding patients with preclinical thyroid disease involves
testing for thyroid antibodies, but this is not generally accepted as a part of an initial thyroid screen, except in an algorithm-triggered mode, and with the fiscal climate in a permanently contractionary mood, it is highly unlikely that having ousted FT₄, we can replace it with even more expensive immunologic tests looking for subclinical disease.

The symptoms of thyroid disease are, however, admit-tedly vague and protean, and the disease process may be well advanced before it is brought to clinical notice. Clinicians’ abilities to discern the presence of the disease have been poor [3, 14], but they do need to maintain a high suspicion for the diagnosis and accept that there is now a reliable, inexpensive, and highly robust screening method to exclude thyroid disease when it does not exist. In selected cases where there is discord between initial testing results and clinical suspicion it may become appropriate to add the antibody tests.

This study confirms earlier findings that the pituitary gland is not only an exquisitely sensitive monitor of thyroid status but that it is also an extremely stable monitor into late adult life. It shows that the effect of intercurrent illness, which becomes more likely as we age, does not appear to interfere with TSH values so sufficiently as to render them diagnostically useless. In particular, the occasional case of the sick euthyroid syndrome with depressed TSH values must be considered, but those cases do not negate the usefulness of TSH as the primary screen for disease; they merely necessitate the further assay of FT₄. And, having been tested in the challenging arena of an acute general hospital’s patient population and found to be robust, TSH-based algorithms can be used safely across the range of primary healthcare.

Diagnostic algorithms for the exclusion of thyroid gland disease, based on TSH, can confidently be used over the full range of adult life. Age-dependent TSH reference intervals should be abandoned.

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References