Thyroid Hormones: Positive Relationships With Cognition in Healthy, Euthyroid Older Men

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Background. Although the association of clinical hypothyroidism with cognitive deficits is well known, the cognitive effects of thyroid hormones in euthyroid subjects are less studied and understood. The purpose of this study was to examine thyroid-cognition relationships in healthy, euthyroid older men.

Methods. We examined healthy men (N = 44, mean age = 72), excluding clinically hypothyroid/hyperthyroid or diabetic/hyperglycemic subjects and those with dementia, depression, CNS medications, or recent illness. Plasma samples obtained across a 24-hour period were pooled, then assayed for total thyroxine (T4), total triiodothyronine (T3), and T3 resin uptake. Free thyroxine index (FT4I) was calculated. A broad cognitive battery (including the Wechsler Adult Intelligence Scale-Revised [WAIS-R], the Dementia Rating Scale [DRS], and the Rivermead Behavioral Profile [PROFILE]) was administered to all subjects.

Results. Regression analyses controlling age and education showed T4 and FT4I to have significant positive relationships with measures of overall cognition; T4 accounted for 8% to 12% of the variance in omnibus cognitive measures such as WAIS Performance, WAIS Verbal score, and GLOBAL cognitive scores.

Conclusions. Our findings suggest that within "normal" range of variation in plasma thyroid hormones, T4 but not T3 positively associates with general cognition in healthy elderly men.

The association between thyroid hormones and cognition has been recognized since the realization that cretinism stems from iodine and thyroid deficiencies (1,2). Clinical hypothyroidism in elderly people is well known to be associated with cognitive disturbances (3,4). Thyroxine treatment in these cases has often remedied both hypothyroidism and cognitive problems simultaneously (3,4). Both aging and a number of health conditions affect thyroid hormones (5). For serum thyroid stimulating hormone (TSH), age brings a decline in both the circadian patterns and maximal nocturnal levels (6). In older subjects, T3 and free T3 (FT3) have been negatively associated with age (7–9) although T4 may not be (5). Very low levels of T4 have been associated with increased mortality during critical illness (10,11), and decreased TT3 and FT3 have been observed in many cases of non-thyroidal illnesses (5). Altered T4 and TT3 may also be related to physical fitness (12). Inadequate caloric intake will decrease serum TT3 and T4 levels but increase less active reverse triiodothyronine [rT3; (13,14)]. Clinical hypothyroidism has been associated with clinical depression (15), which may respond favorably to thyroxine treatment.

The cognitive associations of clinical hypothyroidism are well known, but much less research has been done with the thyroid-cognition relationships when thyroid hormones are within normal ranges. Primary clinical hypothyroidism is usually defined when FT4 and T4 fall below certain fixed values, but these predetermined values may not be optimal for older adults. This study, designed to address the issue of functionally optimal thyroid levels in older adults, examined the relationship between cognition and thyroid hormone levels in healthy, older men who were euthyroid by current clinical diagnostic criteria.

METHODS

Subjects

Fifty-six male volunteers (mean age = 72) were screened extensively for physical and psychological health by physical examination, clinical interview, and laboratory tests. Forty-four men met all criteria.

Recruitment and screening.—Subjects were recruited from western Washington State to participate in a larger study on hormones, sleep, and cognition in normal aging. Public service announcements in local newsletters as well as letters to senior
centers, retirement communities, and groups of retired professionals were used to elicit interest in the study. Respondents were screened via a 3-step protocol. The first step consisted of a 30-minute telephone interview focusing on age, tobacco use, medical history, sleep patterns, and the use of medications. Individuals who passed the telephone screening came to the University of Washington Medical Center (UWMC) for a physical exam by a research nurse and an interview with the study coordinator. The physical exam focused on neurological, endocrine, cardiovascular, and respiratory signs and symptoms. A complete medical history, description of alcohol use, and a list of medications used by the subject were obtained during the examination. During the interview, the coordinator assessed depression [using the Center for Epidemiological Studies Depression Scale (16)]; acute and chronic stress [Reeder Daily Stress (17)]; the SCL-90 Anxiety Scale (18); a modified Life Events Survey (19); Life Satisfaction Index Z (20)]; and mental status ([Mini-Mental State Examination) (21)]. The study protocol was approved by the University of Washington Human Subjects Committee. Informed consent was obtained from all subjects.

Exclusionary and inclusionary criteria.—All participating subjects met the inclusion/exclusion criteria listed in Table 1. Hypothyroid subjects (FT4 ≤ 4.6 μg/dL; TSH ≤ 5.0 μU/ml) were excluded from the study; hyperthyroidism did not occur in this population.

General Procedures

Subjects stayed in the UWMC Clinical Research Center (CRC) from early Tuesday evening through Friday morning. They were encouraged to adhere to customary bed and rise times, and discouraged from napping. The CRC Nutrition Research Kitchen provided all meals, with a total daily composition of 52% carbohydrate, 18% protein, and 30% fat. Total daily calories provided were based on gender, age, height, and weight.

Night 1 (Tuesday) was an adaptation night; the only procedure was finger clip oximetry during the night to confirm the absence of sleep apnea. During the following day (Wednesday), subjects were cognitively tested. An indwelling catheter was placed in a forearm vein at 8 AM Thursday. Beginning at 9 AM, a 3 ml blood sample was remotely drawn through the catheter every 20 minutes for 24 hours. Although subjects could not leave the CRC during the blood sampling period, they were encouraged to remain as active as possible during daytime hours (e.g., walking around the unit). A slow heparinized saline infusion (2000 units/liter saline) kept the catheter patent during the 24-hour sampling period, with a maximal infusion of 6000 units of heparin over 24 hours. To ensure successful sampling in this older population, a small electric heating pad set at the lowest setting was typically secured to the forearm. Nighttime samples were drawn remotely from the room next door through a long extension of the catheter. The study was completed at the end of the blood sampling period (9 AM Friday).

Cognitive Measures

A series of cognitive tests were given to evaluate memory, performance intelligence, verbal abilities, reaction time speed, and other factors. These tests were given in two blocks of approximately 1.5 hours in the morning and 1.5 hours in the afternoon. The cognitive instruments are described in the following comments.

Category Fluency (CATMEAN).—A neuropsychological test frequently used to assess verbal fluency and categorization abilities that has been used with normal, demented, and elderly subjects (22).

FAS Verbal Fluency (FASMEAN).—A neuropsychological test of verbal fluency that has been used on normal demented and elderly subjects. It has also been referred to as the Controlled Word Association Test (23, 24).

Figure Rotation (FRRAWP).—This test measures spatial orientation and is derived from the Schaie-Thurstone Adult Mental Abilities Test. The form OA for older adults (25) was used.

Finding As (FINDMEAN).—A test of perceptual processing speed from the Kit of Factor Referenced Cognitive Tests (26) that is similar to Schaie-Thurstone’s “letter A” test.

Folstein Mini-Mental State (MMSE).—This is a short cognitive mental status examination used with subjects of varying ages and conditions (21).

Median Reaction Time (RTMED).—A test of reaction time and perceptual speed administered by computer.

Rivermead Behavioral Profile (PROF = Raw Score, STD PROF = Standardized Score).—A test of everyday memory administered to a wide age range of normal and brain-damaged individuals (27).

Dementia Rating Scale (DRS = DRS Mean scale, DRSSUM = total of all DRS scales).—The Dementia Rating Scale (DRS) provides a brief and objective measure of
general cognitive abilities for individuals with brain dysfunctions. Norms are based on adults 65–81 years of age. The DRS measures a large range of higher cortical functions and is more sensitive to differences at the lower end of functioning (28).

Wechsler Adult Intelligence Scale–Revised (WAIS-R).—The WAIS-R is a widely used age-normed, general intelligence test. The complete WAIS-R has 11 subtests, 6 of which test verbal abilities, 5 of which test Performance. Because verbal tests in elderly subjects measure crystallized intelligence or lifetime learning rather than current functioning, a subset rather than the full verbal battery was used. The Vocabulary scale was chosen because it has high reliability and stability over time; additionally, Vocabulary is the subscale most highly correlated with total WAIS-R Verbal scores in subjects 65–74 years old (r ≥ .90). Digit Span was also included because of its high reliability and stability, and its assessment of memory. All WAIS-R Performance subtests were included (Picture Completion, Picture Arrangement, Block Design, Object Assembly, and Digit Symbol (29)).

Blood Processing Procedures

Every 20 minutes blood samples were drawn into tubes containing the anticoagulant EDTA and then processed for plasma. The plasma was stored at -80°C until assay. Prior to thyroid assay, a 24-hour pooled sample was created for each subject by combining equal aliquots from the sequential 20-minute samples. The 24-hour pooled sample was used for several reasons. Studies have indicated that there are circadian cycles in T4, T4, and T3, and that advanced age may disturb such cycles. Pooled, averaged 24-hour samples provide an estimate of mean 24-hour level that is unconfounded by circadian factors.

Thyroid Assay Procedures

Total T4 was assayed using the Diagnostic Products Corporation (Los Angeles, CA) Coat-A-Count Total T4121 radioimmunoassay. Within- and between-assay coefficients of variation (CVs) were 5 and 6.2%, respectively. Total T3 was assayed through the Ciba Corning (Norwood, MA) Magic Lite TT3 procedure, a competitive binding assay having within- and between-assay CVs of 7 and 9.2%, respectively. T3 resin uptake was assessed through the Tri-Tab T3 Uptake Diagnostic Kit (Nuclear-Medical Laboratories, Irving, TX). Within- and between-assay CVs ranged from 1.5 to 2.5%. Normalized free T4 index (FT4I) was calculated from TT4 and T3 uptake (FT4I = T4 × T3 uptake)/39 and is reported without units. All thyroid assays were performed in duplicate.

Data Analyses

Multiple regressions tested the relationships between thyroid hormones (our predictor variables) and cognitive measures (our dependent measures), while controlling covariates such as age and education. In these regression equations, age was always entered first in the equation, followed by education, followed by forced entry of a single thyroid hormone (either TT4, FT4I, or TT3). To avoid potential collinearity problems between the thyroid hormones, each was examined separately; they were not entered simultaneously in any equation. Regressions were examined for outliers and adjusted accordingly. In general, the plan was to start by examining thyroid-cognition relationships with omnibus regressions that used larger, more inclusive indices of cognitive function, and then proceed with finer examination of subscales included in these measures. Accordingly, for the omnibus tests, we examined WAIS Performance, WAIS Verbal, and a general cognition factor consisting of the average z score of FASMEAN, MMSE, DRS Sum, CAT Mean, FINDMEAN, Figure Rotation, Standardized Profile, and median Reaction Time (this latter z score was subtracted rather than added to the other seven variables, because shorter reaction times are associated with higher cognition). In the Results section we refer to this composite average as GLOBAL. WAIS Verbal and WAIS Performance scales were created by averaging appropriate WAIS subscales (WAIS Digit Span and Vocabulary for WAIS Verbal; Picture Completion, Picture Arrangement, Block Design, Object Assembly, and Digit Symbol for WAIS Performance).

RESULTS

Descriptive statistics and correlations.—Table 2 shows the means and standard deviations for the demographic variables, the thyroid hormone measures, and the cognitive outcome. Simple correlations showed age to have significant negative relationships with 14 of most cognitive measures; education had significant positive relationships with many cognitive scales (see Table 3).

Multiple regressions.—Multiple regression analyses controlling age and education revealed a number of significant positive
and no negative relationships between thyroid and cognitive measures. Omnibus multiple regressions found TT4 levels to be significantly associated with WAIS Performance \(F(2,42) = 4.34, p < .05\), TT4 accounting for 8% of total variance, WAIS Verbal \(F(2,42) = 6.39, p < .05\), TT4 accounting for 12% of total variance, and GLOBAL \(F(2,42) = 8.17, p < .01\), TT4 accounting for 12% of total variance after accounting for the effects of age and education. In contrast, when free T4 index (FT4I) was used in similar regression analyses, it significantly predicted only one omnibus measure, GLOBAL \(F(2,42) = 4.91, p < .05\), FT4I accounting for 7% of total variance. When TT3 was tested in regression analyses, none of the omnibus measures were significant. Where an omnibus result was significant, we conducted post hoc examination of its subscales. Because TT4 was significant on all three omnibus measures, we have presented results for all relevant subtests in Table 4. The results with FT4I are weaker; we have presented them for comparative purposes in Table 4. Because our omnibus tests did not find any significant results with TT3 or with TSH, we did not pursue additional analyses with subscales.

**Discussion**

Results indicated, after covarying the effects of age and education, that a number of positive relationships remained between plasma thyroxine and cognitive measures. In regression analyses TT4 showed the greatest number of significant relationships with cognitive measures, followed by FT4I. TT3 and TSH were unrelated to cognition. We found some of our strongest thyroid-cognition relationships with the WAIS scales, results similar to what Monzani and colleagues (30) had observed in their population. Our hypotheses are also supported by the finding that our GLOBAL measures of non-WAIS tests showed significant positive relationships with TT4 and FT4I as well, suggesting that this is a robust general relationship, and not simply an epiphenomenon of any particular aspect of cognition, such as spatial or verbal performance.

Our findings suggest that although TT4 and FT4I show are intercorrelated \((r = .73)\), and similar patterns are evident with both hormones, a somewhat stronger pattern of hormone-cognition relationships was apparent for TT4 than FT4I. It must be noted that we did not measure free T4 directly by radioimmunoassay or dialysis, which are more accurate procedures than free T4 index. Thus, we cannot conclude definitely that TT4 is more important than FT4 in affecting cognition. Our results could suggest an important influence of the total TT4 pool, which is mediated principally by thyroid binding globulin, albumin, and transthyretin, which in turn are regulated by androgens, estrogens, and nutrition.

These results also suggest that TT4 is more highly correlated with cognition than TT3. Consistent with this, a recent study of nondemented hypothyroid patients (aged 33–99, mean age 69) showed that TT4 was more strongly correlated to memory tests than TT3 (31). These results are also consistent with a number of in vivo studies. Studies using radioactively labeled peripheral T4 and T3 indicate that active T3 in the cerebral cortex is predominately derived (approximately 80%) from peripheral T4 rather than peripheral T3 (32). Peripheral T3 seems to be degraded by tyrosyl ring dioxidase (5D) before it reaches neuronal space (33). Consistent with this, rat studies indicate that

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**Table 3. Simple Correlations of Age, Education, With Cognitive Measures \((N = 45)\)**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Age</th>
<th>Education</th>
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<tbody>
<tr>
<td>CATMEAN</td>
<td>.39**</td>
<td>.23</td>
</tr>
<tr>
<td>DRSSM</td>
<td>.20</td>
<td>.45**</td>
</tr>
<tr>
<td>DRSSUM</td>
<td>.41**</td>
<td>.52**</td>
</tr>
<tr>
<td>FASMEAN</td>
<td>.35*</td>
<td>.27</td>
</tr>
<tr>
<td>FINDMEAN</td>
<td>.41**</td>
<td>.38**</td>
</tr>
<tr>
<td>FFRAWP</td>
<td>.28</td>
<td>.10</td>
</tr>
<tr>
<td>MMSE</td>
<td>.31*</td>
<td>.17</td>
</tr>
<tr>
<td>PROFILE</td>
<td>.13</td>
<td>.39**</td>
</tr>
<tr>
<td>RTMED</td>
<td>.37*</td>
<td>-.19</td>
</tr>
<tr>
<td>STDPROF</td>
<td>-.34*</td>
<td>.33*</td>
</tr>
<tr>
<td>WAIS Digit Span</td>
<td>-.26</td>
<td>.34*</td>
</tr>
<tr>
<td>WAIS Vocabulary</td>
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<td>.31*</td>
</tr>
<tr>
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</tr>
<tr>
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<td>.00</td>
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<tr>
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<td>.24</td>
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<tr>
<td>WAIS Verbal</td>
<td>-.33*</td>
<td>.40**</td>
</tr>
<tr>
<td>WAIS Performance</td>
<td>-.33*</td>
<td>.13</td>
</tr>
</tbody>
</table>

**Notes:** CATMEAN = category fluency mean score; DRSSM = memory substest of Dementia Rating Scale; DRSSUM = Total score of Dementia Rating Scale; FASMEAN = Verbal Fluency, Mean score; FINDMEAN = Finding As, mean score; FFRAWP = figure rotation; MMSE = Mini Mental State Exam, total score; PROFILE = Total Profile Score of the Rivermead Behavioral Memory Test (RBMT); RTMED = median simple reaction time; STDPROF = Standardized Profile Score of the RBMT; WAIS = Wechsler Adult Intelligence Scale.

\*p < .05; **p < .01.

**Table 4. Summary of \(R^2\) (variance explained) in Regression Analyses Using Age, Education, and Plasma Thyrozine Hormones to Predict Cognitive Outcomes**

<table>
<thead>
<tr>
<th>Cognitive Measure</th>
<th>TT4</th>
<th>FT4I</th>
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<tbody>
<tr>
<td>Picture Completion</td>
<td>6</td>
<td>NS</td>
</tr>
<tr>
<td>Picture Arrangement</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Block Design</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Object Assembly</td>
<td>4</td>
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</tr>
<tr>
<td>Digit Symbol</td>
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<td></td>
</tr>
<tr>
<td>WAIS Verbal</td>
<td>11*</td>
<td>NS</td>
</tr>
<tr>
<td>Digit Span</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Vocabulary</td>
<td>16**</td>
<td></td>
</tr>
<tr>
<td>GLOBAL</td>
<td>12**</td>
<td>7*</td>
</tr>
</tbody>
</table>

**Notes:** CATMEAN = category fluency mean score; DRSSM = memory substest of Dementia Rating Scale; DRSSUM = Total score of Dementia Rating Scale; FASMEAN = Verbal Fluency, Mean score; FINDMEAN = Finding As, mean score; FFRAWP = figure rotation; MMSE = Mini Mental State Exam, total score; PROFILE = Total Profile Score of the Rivermead Behavioral Memory Test (RBMT); RTMED = median simple reaction time; STDPROF = Standardized Profile Score of the RBMT; WAIS = Wechsler Adult Intelligence Scale.

\*p < .05; **p < .01.

†Total triiodothyronine and serum thyroid stimulating hormone (not shown) were unrelated with omnibus cognitive measures. Definitions of cognitive tests are given in Table 3 and in the Methods section.
normal peripheral levels of T3 do not ensure normal brain levels of T3 if circulating T4 is low (34). Human studies also indicate that free T4/T3 levels in brain are two to five times higher than in peripheral plasma, consistent with specific thyroid transport mechanisms into the brain (35). One major mechanism is transthyretin in choroid plexus. Here T4 binds 10 times more strongly than T3; bolus venous injections of T4 enter and remain in CSF to a greater extent than similar injections of T3. Finally, studies in which euthyroid, healthy adult humans were given thyroxine supplementation resulted in improved performance in a signal detection paradigm (36), whereas supplemental T3 in a similar paradigm did not improve performance (37). In short, this suggests that levels of CNS thyroid hormones are dependent on peripheral T4, rather than T3.

Our data suggest that older subjects may require circulating thyroid hormones in middle to high levels in order to maintain optimal brain functioning. The aging brain may require more T4 than needed for peripheral metabolism. Our observations suggest that variations in these levels can have significant cognitive consequences, even in apparently euthyroid subjects. The basis for this enhanced need could derive from age changes in thyroid transport into CNS target tissues, altered brain conversion of T4 to T3, or decreased brain thyroid receptor number or affinity (5). Additionally, a number of subclinical abnormalities that could influence the thyroid-cognition relationships observed here might be evident in the thyroid system of older adults.

Although the criteria for clinical primary hypothyroidism is relatively simple and well defined, subclinical hypothyroidism may have subtle but significant effects in elderly people. The two main criteria for subclinical hypothyroidism are elevated basal TSH and normal TT4/FT4; or, normal baseline TSH, but exaggerated TSH response to TRH (38). Close examination of elderly populations invariably reveals more subclinical than clinical hypothyroidism; estimates of hypothyroidism frequency vary regionally from 0.5% to 5% for clinical, and 5% to 15% for subclinical hypothyroidism (5). Therefore, it is quite possible that there is a substantial population of undetected, subclinically hypothyroid individuals in the general population who may suffer subtle cognitive deficits, long before hypothyroidism becomes manifest by obvious metabolic symptoms. Although thyroid supplementation of subclinical patients has been relatively uncommon, it is gaining support. A recent study showed that when patients with subclinical hypothyroidism were treated with thyroxine, performance on Wechsler Memory scales improved (30).

**Limitations and advantages.**—The present study has a number of advantages over many of the previous investigations of thyroid hormones and cognition. We controlled for age and education. We excluded subjects with health problems such as diabetes, hypertension, clinical depression, dementia, psychiatric illness, sleep disorders, recent history of myocardial infarction or cancer, current illness, use of CNS medication, and severe obesity. We controlled diet during the 60 hours preceding and during blood sampling. This study's hormonal measures represent pooled averages across 24 hours and are free of individual differences in the timing of circadian rhythms. Similarly, we employed multiple cognitive measures, not depending on a single instrument or a small sample of subscales. In short, a number of potential confounds and sources of measurement error were either excluded or controlled in our study, making it unlikely that our results were contaminated by some of the problems potentially compromising previous studies of clinical or hospitalized elders.

Because we did not measure TSH response to TRH challenge or direct binding proteins for thyroid hormones, we cannot rule out the possibility that subclinical hypothyroidism or binding protein abnormalities might have influenced our findings. Our findings might also be explained through other thyroid changes associated with aging: in older subjects thyroid receptors could be less responsive; thyroid antibodies could disrupt normal thyroid function; and/or T4 could be increasingly converted into dysfunctional T3. Finally, although we have explained our findings in terms of thyroid deficits, it could also be that low normal T4 and FT4 might be associated with other endocrine perturbations, such as low sex steroids and/or high stress hormones, which could lead either directly or indirectly to cognitive dysfunctions. Our findings suggest a number of possible explanations, but further research is necessary to determine the precise mechanisms responsible for the observed relationships.

In conclusion, pooled 24-hour samples of thyroid hormones (particularly TT4) have significant positive associations with measures of overall cognition, even when hormones are within normal ranges, and in the absence of overt physical or mental illness. These results suggest that older men with low normal TT4 or FT4 might benefit cognitively from modest thyroxine treatments that bring their TT4 and FT4 to midrange or upper normal levels.

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