The relationship between TSH and free T4 is not log-linear and differs between genders and age groups

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ABSTRACT

Background

A central tenet of thyroid physiology is the inverse, log-linear relationship between TSH and free T4. This study evaluated the TSH-fT4 relationship by cross-sectional analysis of a large population.

Methods

We extracted records with concurrent TSH and fT4 over 12 years by a single, predominantly community-based, pathology provider. After applying exclusions, 445,918 records from 152,261 patients were available for analysis and TSH-fT4 relationship was examined in cross-sectional analysis.

Results

In cross-sectional analysis, the relationship between TSH and fT4 was not log-linear but a combination of sigmoidal curves. The rate of change of TSH with fT4 below the reference range was steep, less within the reference range and almost flat for elevated fT4 levels. Within the fT4 reference range, the curves for those on therapy or not did not significantly differ. Over the whole fT4 range the median TSH in thyroid treated individuals was 0.3 mU/L lower than untreated individuals however, for an elevated fT4, thyroid treated patients had a higher median TSH. In subjects with high-normal fT4, the relationship differed between genders with women having lower TSH than men at any given high-normal fT4. In older people, TSH was less elevated in response to low fT4 than in younger people. Within the reference range however, median TSH was higher for older individuals compared with younger individuals.

Conclusion

The relationship between TSH and fT4 is not log-linear but a complex combination of curves which differs between genders and changes with aging. This suggests that there are gender-specific and age-related differences in hypothalamic-pituitary-thyroid function.

METHODS

We extracted thyroid function tests with concurrent TSH and fT4 result performed over a twelve year period (1st January 2000 – 31st December 2011), by Western Diagnostic Pathology. WDP is a private pathology provider which provides pathology services for the entire state with ~85% of pathology provided by general practitioners and ~15% from specialist medical practitioners or hospital referrals. Western Australia is an iodine-sufficient region with a predominantly Caucasian population. The Australian Medicare schedule reimburses fT4 or fT3 measurements only in patients with a TSH outside reference limits, those with known thyroid disease, or those in whom specific history meeting Medicare guidelines for provision of fT4 or T3 is provided by the referring clinician. All results were de-identified prior to further analysis and as this study followed the criteria of an audit, (NHMRC) institutional ethics approval and informed consent were not required. The laboratory reference range for TSH was 0.4 – 4.0 mU/L. The medians were derived previously from data extraction and consensus between local chemical pathologists and endocrinologists.

Exclusions

There were 525,713 records available for analysis and exclusions were then applied. Exclusions (15.2%) included those on medications (except thyroxine) affecting the HPT axis (radio-iodine, anti-thyroid therapy, lithium, anti-epileptics, amiodarone, tetraxon) those with known disorders of the HPT axis (Graves/thyrotoxicosis, goitre/multinodular goitre, thyroid cancer, partial or total thyroidectomy, hypopituitarism) pregnant women, age < 1 year, specialist endocrine, surgical or medical care or any data with unknown time of collection or unknown age of patient. The remaining records (445,984) were from 152,261 subjects. The first record of each individual was retained for further analysis and repeat records excluded.

Single records from the 152,261 individuals were partitioned into 31,858 (21%) on thyroxine therapy and 120,403 (79%) not on thyroxine. Within the reference range however, median TSH was found which was not inverse log linear but better described by 3 lines of different slope. The response decreased with age. When fT4 was elevated young females suppressed TSH most whilst young males suppressed TSH least.

RESULTS

Thyroid function in the cohort (Table 2)

The distribution of TSH results in both treated and non-treated individuals was non-Gaussian. Median TSH in all females was 2.8 mU/L (1.9 in those on thyroxine, 3.3 in those not on therapy). In comparison, median TSH in all males was 3.7 mU/L overall (2.9 in those on thyroxine and 3.8 in those not on therapy). Median free T4 was 14 pmol/L in both men and women. Most free T4 levels were within the reference range (99%) with 4% above and 4% below the reference limits.

RESULTS

Treatment

Untreated

Female

Male

TSH Median (IQR)

5.2 (16.9) 3.5 (1.2, 4.9) 0.06

13.8 (3.9) 13 (12, 15) 9, 20

3.6 (9.9) 1.9 (0.6, 3.9) 0.02

15.8 (3.9) 15 (13, 18) 10, 24

FEMALE Untreated

MALE Treated

5.0 (11.4) 2.5 (0.9, 4.9) 0.03

15.9 (3.9) 15 (13, 18) 10, 25

3.6 (9.9) 1.9 (0.6, 3.9) 0.02

15.8 (3.9) 15 (13, 18) 10, 24

Age Groups

21-40

5.2 (20.7) 2.1 (0.8, 4.4) 0.04

14.1 (4.6) 14 (12, 15) 9, 21

41-60

5.0 (13.7) 3.2 (1.1, 4.9) 0.04

14.1 (4.0) 14 (12, 16) 9, 22

>60

4.9 (15.7) 3.0 (1.0, 4.8) 0.04

20.2 14.2 (4.0) 14 (12, 16) 9, 22

The relationship between TSH and fT4 is not log-linear but a complex combination of curves which differs between genders and changes with aging. This suggests that there are gender-specific and age-related differences in hypothalamic-pituitary-thyroid function.

Low and high fT4 levels

When all free T4 levels below the reference range (<10 pmol/L) were grouped for comparison, there was no significant difference between median TSH with age, nor any difference in the younger and older women, nor in younger and older men. However, with extremely low fT4 results (< 5 pmol/L) (Table 3) a different pattern was observed. The youngest subjects mounted the highest response to severe hypothyroidism (median TSH 190 mU/L) with a significant trend of progressively reducing TSH response with increasing age (p<0.001) to the oldest cohort. For free T4 above the reference range, young males (>21 years) had the highest median TSH of any gender or age band (p<0.001). In contrast, young women (1-20 and 21-40 years) suppressed TSH the most compared with any other gender or age cohort (p=0.001). (Table 3)

CONCLUSION

In this large study, a complex relationship between free T4 and median TSH was found which was not inverse log linear but better described by 3 lines of different slope. The relationship between TSH and median TSH was altered by thyroxine therapy, gender and age. Men, (both untreated and on thyroxine) had a higher overall median TSH for fT4 compared to women. The effects of age and gender were different depending on fT4 level. When fT4 was normal, median TSH for a given fT4 was always higher in males, (up to 1.13 mU/L higher), and median TSH increased in both genders with age. In severe hypothyroidism, the youngest (of either gender) mounted the highest TSH response and this response decreased with age. When fT4 was elevated young females suppressed TSH most whilst young males suppressed TSH least.