CLINICAL PARAMETERS CORRELATE BETTER WITH THYROID HORMONE LEVELS THAN WITH TSH LEVELS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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**Abstract**

**Background:** Though the functional states of other endocrine systems are not defined on the basis of levels of controlling hormones, the assessment of thyroid function is based on levels of the controlling hormone Thyroid Stimulating Hormone (TSH). In particular, subclinical thyroid dysfunction is defined as the combination of abnormal levels of TSH with normal levels of thyroid hormones. We therefore addressed the question as to whether thyroid hormones (free thyroxine (FT4), total triiodothyronine/free triiodothyronine (T3/FT3)), or TSH levels, within and beyond the normal ranges, provide the better guide to the range of clinical parameters associated with thyroid status.

**Methods:** A PubMed/Medline search of papers up to October2019, examining correlations of levels of thyroid hormones and TSH, taken simultaneously in the same individuals, with clinical parameters was performed. We analysed atrial fibrillation, other cardiac parameters, osteoporosis and fracture, cancer, dementia, frailty, mortality, features of the metabolic syndrome and pregnancy outcomes. Papers were assessed for quality using a modified Newcastle-Ottawa score. PRISMA guidelines were followed. A meta-analysis of the correlations was performed to determine the relative likelihood of FT4, T3/FT3and TSH levels correlating with the clinical parameters.

**Results:** We identified 58 suitable articles and a total of 2439 correlations. In general, thyroid hormone levels associated with clinical parameters statistically significantly more often than with TSH levels – for no clinical parameter was the converse true. In the 2439 considered associations, FT4 levels correlated significantly with clinical parameters in 50% of analyses. The respective frequencies for T3/FT3 and TSH levels were 53% and 23% (p<0.001 for both FT4 and T3/FT3 vs TSH). FT4, T3/FT3 levels were correlated with clinical parameters equally strongly. More sophisticated statistical analyses suggest that the T3/FT3 associations are not as robust as the FT4 associations.

**Conclusions**. Thyroid hormone levels, and in particular FT4 levels, have stronger correlations with clinical parameters than do TSH levels. Correlations of clinical parameters with TSH levels can be explained by the strong negative population correlation between thyroid hormones and TSH, whereby TSH levels are an indirect measure of thyroid hormone levels.

Clinical and research components of thyroid medicine currently based on the measurement of TSH levels, including thyroid function testing, the monitoring of thyroid replacement therapy, and the concepts of subclinical thyroid dysfunction and isolated (or euthyroid) hypo/hyperthyroxinemia warrant reconsideration.

**Introduction**

Thyroid function testing is based on the measurement of thyroid stimulating hormone (TSH) levels [1, 2]. Patients are thereby classified as having euthyroidism (normal TSH and thyroid hormone levels), overt thyroid dysfunction (abnormal TSH and thyroid hormone levels), subclinical thyroid dysfunction (abnormal TSH/normal thyroid hormone levels) and isolated hyper/hypothyroxinemia (normal TSH/abnormal thyroid hormone levels).

This classification of thyroid function is based on the concept of TSH levels being the most sensitive indicator of thyroid function such that subclinical thyroid dysfunction as currently defined is thought to be more significant than isolated hyper/hypothyroxinemia[2], as indicated by the alternative term ‘euthyroid hyper/hypothyroidism’ [3].

Subclinical thyroid dysfunction, so defined, is common, and comprises most cases of thyroid dysfunction with a population prevalence of approximately 5% [4-8], increasing to 15% in the elderly [8]. Even though it is generally asymptomatic or associated only with non-specific symptoms, subclinical thyroid dysfunction has been associated with many adverse outcomes across a variety of organ systems [4-8]. Therefore, despite the lack of convincing evidence of significant benefit, treatment for subclinical thyroid dysfunction has been recommended in certain circumstances [5, 8-11].

It has previously been suggested by some authors that the above definition of subclinical thyroid dysfunction is overly simple and that its diagnosis should not be based solely on the TSH level being outside of a general population range [12, 13]. Rather, it is claimed that more accuracy may be achieved by defining a normal range for the combination of thyroid hormones and TSH.

However, any model whereby judgement of the thyroid status includes consideration of the TSH level is anomalous, in that the levels of other physiological parameters are not judged by the levels of their controlling hormones. For example, whether or not an individual has hypoglycaemia or hypercalcemia is not determined by reference to insulin [14] or parathyroid hormone levels [15] respectively. ACTH levels, though helpful in diagnosing adrenal autonomy are not considered diagnostic for Cushing’s syndrome [16]. In general the level of a controlling hormone is used to determine the cause of a disturbance rather than identifying whether or not there is a disturbance [14-16].

We therefore aimed to determine whether or not a systematic review of the literature might indicate the relative merits of thyroid hormone levels and TSH levels, in terms of correlations with a broad range of clinical parameters. Because of the strong negative population correlation between FT4 and TSH [17, 18] we expected to find correlations between both TSH and FT4 levels and the clinical features of thyroid dysfunction. We further reasoned that if the clinical features correlated better with TSH levels the current rationale for thyroid function testing and the current definition of subclinical thyroid dysfunction would be supported, but, if the clinical features correlated better with thyroid hormone levels, these concepts would warrant review. In this latter circumstance the previously noted correlations of clinical features with TSH levels could be attributed to the aforementioned strong negative population correlation between FT4 and TSH.

METHOD

Search strategy

Up to 9 October 2019 a systematic search was performed of PubMed/MEDLINE using the following terms: thyroxine/T4, free thyroxine/ FT4, total triiodothyronine/T3, free triiodothyronine/FT3, TSH/thyroid stimulation hormone and subclinical. No restrictions were placed on language, country, or publication date. resulting

On account of the results of this first examination of the literature (see below) we studied atrial fibrillation (AF) and other cardiac parameters, bone density and fracture, cancer, death, frailty, dementia and associated pathology, obesity, features of the metabolic syndrome, and pregnancy outcomes. We specifically sought studies which addressed the correlations of both TSH and thyroid hormone levels, determined simultaneously in the same individuals, with any of the above clinical parameters.

Initially the titles of the articles were screened for relevance and then the abstracts, with full-text reports of potentially relevant reports reviewed. Additional relevant articles were searched for in the reference lists of the retrieved full-text studies. If repeated study was made of the same cohort the latest only was included. The literature search was performed by one author (HF), Data extraction, identification of additional relevant articles and critical appraisal were conducted independently by two of the authors (SPF and HF), and any discrepancies were resolved by consensus with reference to the criteria described in the next section. Should consensus regarding any article not have been achieved the default position was that the article would be included. No study which contradicted the results of our work was knowingly excluded.

Studies reporting on correlations of levels of FT4, T3/FT3, and TSH with clinical features related to thyroid dysfunction were included. We included both T3 and FT3 as there were relatively few studies of FT3. We also included analyses comparing correlations with subclinical hypothyroidism and euthyroid hypothyroxinemia, reasoning that this is a comparison of low thyroid function defined on the basis of TSH levels or thyroid hormone levels respectively. Reports were excluded if the studied population was less than 100 individuals. Review articles, editorials, meta-analyses, and meeting abstracts were also excluded.

The following information was extracted from each such study: first author, country, number of individuals, sex, age intervals, nature of the study and the relevant clinical parameter. We recorded any correlations with thyroid hormones and/or TSH, in addition to the statistical techniques and degrees of significance of any correlations (p values and /or confidence limits). We also recorded the presence of ‘incongruent’ correlations, i.e. correlations in the opposite direction to that normally expected (e.g. obesity correlating with high thyroid function), or correlations of thyroid hormones in the same direction as correlations with TSH, as indicators of reverse causation [19].

As our study was not directed at a collection of works addressing therapeutic outcomes of an intervention, the use of a quality assessment (the Newcastle-Ottawa Scale; available at: www.ohri.ca/ programs/clinical\_epidemiology/oxford.asp) was adjusted to suit this setting. In the main this adjustment consisted of allowing for continuous, as well as binary quantifications, of clinical outcomes and exposure to thyroid hormone levels. Articles were scored according to the representativeness of the subjects, the similarity of the subjects apart from differences in the parameter of interest, the reliability of the classification of thyroid status and parameter status, control for confounding factors, and for prospective studies, the demonstration that outcome was not present at study onset, the adequacy of length and completeness of follow-up. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were followed [20].

Statistical Analysis

To determine whether thyroid hormone levels or TSH levels correlated better with the examined clinical parameters we analysed the above studies as to the relative frequencies of significant correlations of thyroid hormone and TSH levels with the clinical parameters. We then performed further analyses to confirm that these findings did not result from any systematic bias.

We classified each result in a paper as showing a significant result or a non-significant result. By a significant result, we mean that a given thyroid test has been shown to be associated with a given condition at a 5% significance level. We treated the result as a binary response variable with the levels success (significant) and failure (non-significant).

The predictors considered were the type of thyroid test; the clinical parameter under consideration; the number of subjects in the analysis; and the number of covariates in the model. To account for the repeated analysis within each paper, we also incorporated a random intercept term. We considered random intercepts for the paper, the cohorts nested with each paper, the type of analysis nested within the paper; and the complexity of the models nested within the papers.

Pairwise comparisons of the thyroid tests were performed at a 5% overall significance level for those models where a significant effect of thyroid test was found. We calculated the Tukey pairwise comparisons between the thyroid tests using the multcomp package [21].

As a final attempt to account for dependency within each paper we performed a simple logistic regression analysis using only a single randomly chosen analysis from the series of nested models in each paper. We performed this for each of the following strata:

* smallest number of subjects, simple model;
* smallest number of subjects, complex model;
* largest number of subjects, simple model; and
* largest number of subjects, complex model.

We performed a sensitivity study minimising the contribution of possible reverse causation, analysing only the prospective analyses from papers that were free of incongruent correlations.

All modelling was performed using the lme4 [22] and lmerTest [23] packages in R [24], and all code is available at <https://github.com/jonotuke/TSH_2019>

RESULTS

We found, in our first examination of the literature, that though the findings were not unanimous, there was general consistency of the data. In general, consistent with prior work [8], atrial fibrillation (AF) [23-29], osteoporosis , [ 30-37], and cancer [38-41] correlated with higher thyroid function defined using TSH and/or thyroid hormone levels, across and beyond the normal range, and steatohepatitis[42-44] and other features of the metabolic syndrome [19, 45-64] correlated with lower thyroid function .Both high and low thyroid function, as compared with mid-range thyroid function, were associated with clinical and pathological features of cognitive decline [24, 65-73], frailty [74-77], total /cardiovascular mortality [24, 78-87] , heart disease (apart from atrial fibrillation) [24, 29, 65, 81-83,-86-89 ] and pregnancy outcomes [90-97].

There were many series finding the above correlations in the context of subclinical thyroid dysfunction. Many of these studies [23, 48, 49, 65, 81-83, 85-87] however did not address the relative correlations of clinical parameters with TSH and thyroid hormone levels, the focus of our study.

In the end we identified 58 studies which addressed this question (Figure 1, Table 1). We found no previous synthesis of the data on the effect of thyroid function, as measured by TSH in comparison to thyroid hormone levels, across a range of organ systems. One meta-analysis restricted to atrial fibrillation [25] . was not included in our analysis. Many of the studies addressed multiple parameters summarised by those indicated in Table 1.

We found 22 studies [19, 24, 28, 29, 32, 33, 37, 39, 42, 43, 46, 53, 58-60, 63, 64, 69, 73, 76, 77, 89] that examined correlations with FT4, T3 ( or FT3) and TSH and a further 36 studies [26, 27, 31, 34-36, 38, 40, 41, 44, 45, 47, 50, 51, 52, 54, 61, 62, 67, 71, 72, 74, 75, 78-80, 84, 88, 90-97] that examined correlations with only FT4 and TSH levels.

These 58 studies included cross-sectional and prospective cohort studies, diverse populations and both sexes. They were contemporary and of high quality (Table1). The study populations comprised strictly euthyroid subjects [24, 27, 28, 32, 37, 43, 46, 50-53, 53, 60, 67, 79, 80, 84, 88, 89], subjects either euthyroid or with subclinical thyroid dysfunction [19, 31, 33, 34, 36, 38, 40, 45, 47, 58, 63, 69, 71, 73-76, 78, 90, 91, 93, 94, 96, 97], and subjects euthyroid or with subclinical/overt thyroid dysfunction [26, 29, 35, 39, 41, 42, 44, 45, 54, 59, 61, 62, 64, 72, 77, 92]. In some studies different subsets were examined separately.

The 58 articles included in our meta-analysis yielded 2439 results of correlation analysis. The supplement Table 1 catalogues all of these correlations in terms of clinical parameters, subgroups, number of participants, statistical methods, statistical significance, and p values/confidence limits.

The number of subjects for each analysis ranged from 18 to 10990 with a mean of 3071. The number of results in each paper ranged from 3 [58] to 180 [90]. Analysis of all this data confirmed the superiority of correlations with thyroid hormone levels (FT4, T3/FT3) as compared to TSH levels. (Figure 2).

FT4 had a significant association with a clinical parameter in 50% of the articles’ analyses. T3/FT3 had a significant association in 53% of the analyses whereas TSH had a significant association in only 23%. FT4 levels associated with clinical parameters statistically significantly more often than with TSH levels, p<0.0001, as did T3/FT3, p<0.0001. The difference between FT4 and T3/FT3 was not significant.

As the number of subjects in the analysis increased, the superior correlations with thyroid hormones did not diminish (Figure 3) and similarly system did not play a significant role (Figure 4). In an analysis including the number of covariates in the original result, T3/FT3 levels are no longer statistically significantly different from TSH at higher numbers of covariates (Figure 5).

The above is a basic analysis that ignores the many sources of dependence between the results reported in each paper. To account for this, it was necessary to incorporate a random intercept for paper in the model (P-value ). There is still then a statistically significant effect of thyroid test in predicting a result’s significance (P-value ). Post-hoc pairwise comparisons show that there is a statistically higher proportion of significant results for FT4 compared to TSH (P- value ), and also a statistically higher proportion of significant results for T3/FT3 compared to TSH (P- value ). These results confirm those illustrated in the earlier-mentioned confidence interval plots. We found that the additional main effects of system, cohort size, and number of covariates again did not improve the predictive effect of the model, compared to one with just thyroid test (based on minimising the Bayesian Information Criterion). We found that a nested random effects structure of cohort within paper was a statistically valid addition to the model, but did not change the observed effects of thyroid test to that given above.

The results from addressing the issue of dependence of results using a sampling methodology found a statistically significant effect of thyroid test on the proportion of statistically significant results. Pairwise comparisons reveal that the only significant results in all four models were for FT4 having more significant associations than TSH (Table ?).

|  |  |  |
| --- | --- | --- |
| Model description | thyroid test | FT4 v TSH |
| smallest number of subjects, simple model | p = 0.0001891 | p = 0.000202 |
| smallest number of subjects, complex model | p = 0.0007730 | p < 0.001 |
| largest number of subjects, simple model | p = 0.0112600 | p = 0.00905 |
| largest number of subjects, complex model | p = 0.0006587 | p = 0.000638 |

The results of our sensitivity analysis aimed at minimising any effect of reverse causation showed no significant change in the likelihoods of FT4 and TSH levels correlating with clinical parameters. As in the immediately above results and as seen in Figure 5, the association of T3/FT3 levels with clinical parameters was not significantly different than with TSH levels. The proportion of associations with T3/FT3 was only 13% in this analysis as compared with 53% in the full analysis.

Only a few of the studies included patients on thyroxine therapy. In these studies the proportion of patients on thyroxine was very low such that separate analyses of these patients were not undertaken. Analyses of cohorts with removal of these patients did not affect the results.

DISCUSSION

We believe this is the first systematic review studying TSH and thyroid hormone correlations with various clinical parameters. The results went beyond not finding evidence to support the current paradigm of the superiority of TSH. They indicated that the reverse applies i.e. thyroid hormone levels correlate better than TSH levels with clinical parameters.

In our sample we found no indication of, or reference to any work, that suggested that TSH levels consistently indicate thyroid status more strongly than thyroid hormone levels.

Our meta-analysis methodology differs from traditional meta-analysis in that we pooled all statistical results rather than pooling all original data for re-examination of significance. This latter technique is used to determine an overall effect when individual studies (usually of a therapeutic effect) are conflicting and/or do not achieve convincing statistical significance.

Potentially the summation of statistically significant results can be unreliable [20], but we have accounted for the possibilities of bias on account of, imbalance in the size of the studies, the nature of the parameters and the possibility of reverse causation. As in all of the studies each subject was his/her own control, and the study populations of many of the studies were unselected members of a community, the risk of bias from these considerations was obviated. The convincing degree of superiority of thyroid hormone levels as compared with TSH levels also provides a buffer against the possibility of some unidentified bias influencing our results.

Our research question differed from many research questions too in its breadth. We aimed to determine whether any of 2 or 3 valid measures of a whole body thyroid effect was/were superior to the other(s). Our analysis encompassed therefore, multiple studies covering various clinical outcomes, using different methodologies, different assays and statistical methods. It would not have been appropriate to combine all of these factors into a traditional meta-analysis. Theoretically one could do such a meta-analysis of each clinical parameter but still these individual meta-analyses would need to be combined using a method akin to ours (i.e. summing the meta-analyses in some way) to determine whether levels of thyroid hormones or TSH are more likely to be associated **in general** with clinical parameters. Furthermore, in using such a technique of analysis, the information from many of the studies in our sample would be lost as the parameter /population/ statistical method might not be amenable to pooling [ ].

The results of the individual patient meta-analysis of atrial fibrillation [25] do in fact support our conclusions, showing superior correlations with FT4 levels than with TSH levels. Also supportive is a recently published similar meta-analysis of pre-term delivery [98], showing that FT4 levels correlate at least as well as TSH levels. One could even argue that the results of these two conventional meta-analyses alone disprove the general hypothesis that TSH levels provide a better guide to thyroid status than FT4 levels.

Our results indicate that the results of the atrial fibrillation and pre-term delivery meta-analyses can almost certainly be generalized. They indicate that, in general, whatever clinical parameters, assays or statistical methods are chosen, thyroid hormone levels, rather than TSH levels, are more likely to indicate thyroid effect.

Reverse or bi-directional causation may have underlain some of our correlations. Obesity and insulin resistance may lead to increases in TSH and thyroid hormones in some populations, perhaps as a thermogenic response [99], to the increased weight itself [100] or to caloric intake [101]. TSH enhanced secretion of FT3 might affect the lipid profile adversely [55, 56, 102]. Whatever the cause of such reverse causality, in such populations, as these particular correlations concern a low thyroid state, the associations between clinical features and high TSH would be artifactually enhanced whilst the association with low levels of thyroid hormones would be attenuated.

We are not aware of any factors that would artifactually preferentially increase the association of high FT4 with atrial fibrillation, osteoporosis and cancer. If anything, any component of the sick euthyroid state associated with these conditions, by lowering TSH and FT4 [103], should again favour an association with TSH rather than FT4.

The sensitivity of T3/FT3 levels to the sick euthyroid state, generated by altered deiodinase activity [104], may also explain some of the correlations with T3/FT3. In particular, mortality and frailty may be associated with low T3/FT3 levels via reverse causation. As the TSH would also be expected to be low in this situation one might expect incongruent correlations between clinical parameters, and T3/FT3 (and possibly FT4) and TSH.

Mendelian randomization studies can provide evidence as to the direction of causation [105]. Because genetic polymorphisms may affect TSH levels more than FT4 levels [106] such studies, whilst indicating the direction of causation between the thyroid state and the parameter, cannot add to the discussion as to whether thyroid hormone or TSH levels correlate better with any parameter. There is evidence from such studies that the relationship between increased thyroid function and atrial fibrillation is causal [107,108], but that reverse causation applies with higher BMI/fat mass (i.e. there is an increase in FT3 levels caused by increasing BMI [109]).

Our sensitivity studies also indicate that thyroid hormone levels reflect the thyroid state rather than reflecting reverse causation. Other indicators supporting a causative relationship between thyroid function and at least some of the parameters we examined include, relationships similar to those seen in overt thyroid disease [110-122], basic science evidence of causative mechanisms [123], animal intervention studies indicating causation [124], the relationships being seen in otherwise healthy individuals [89-97]), and the prospective nature of many of our included studies.

There was a consistent as well as a strong association of clinical parameters with FT4 levels. Correlations of FT4 and TSH levels with clinical parameters were concordant in terms of being in the opposite directions (e.g. AF is associated with a high thyroid state- with higher FT4 levels and lower TSH levels). Any discordance only occurred when the clinical parameter was associated with both relatively high and low thyroid states (e.g. death). In such a situation there might be an association with both high FT4 and high TSH levels.

We found T3/FT3 level correlations with fewer parameters than we found for FT4. Although T3/FT3 levels correlated better than TSH levels, and as well as FT4 levels, with clinical parameters, some of these correlations were, as previously mentioned, incongruous or paradoxical, i.e. they appeared in studies where the direction of association was aberrant as compared with other studies or were in the same direction as simultaneous correlations with TSH levels. These results were suggestive of reverse causation. Our sensitivity study showing the fall in the frequency of correlations with T3/FT3 levels confirmed this impression. Overall, T3/FT3 measurement added little to the assessment based on FT4 levels.

It would therefore appear that clinical features in general result from the exposure of tissues to the combination of thyroid hormones, and that the previously emphasized correlations of clinical parameters with TSH levels are secondary to the strong negative population correlation between thyroid hormones (chiefly FT4) and TSH. As FT4 levels provide most of the information, and for reasons detailed below, these results may warrant a change of clinical practice such that levels of thyroid hormones and especially FT4 levels become the main determining parameter in the diagnosis of borderline thyroid function. Further studies may clarify the relative importance of FT4 and FT3 levels.

The above applies even though FT4 is not the active thyroid hormone at the cellular nuclear level [104]. The strong relationships of parameters, especially atrial fibrillation (risk increased up to 9x across the normal range [28]), to levels of FT4 indicate that the active intracellular T3 generated by thyroid hormone transporters and deiodinases [104] appears to be, in general, proportional to circulating FT4. Any discrepancy, indicating local regulation of thyroid effect may be more prominent in more severe pathophysiological circumstances [104], and therefore more relevant in the circumstances of multisystem entities such as frailty, death and metabolic disturbance.

Our results do not imply that no information can be gleaned from the presence of an abnormal TSH level with normal thyroid hormone levels. Such levels indicate that the thyroid gland physiology is abnormal and that normal range thyroid hormone levels are being achieved only by dint of the abnormal TSH levels. However, for the function of other tissues and organs, the TSH level required to maintain a given level of thyroid hormones appears generally not to be relevant.

It remains possible too, that additional analyses might find that TSH levels are providing an additional signal to FT4 levels, in some populations for some conditions. It has been suggested that TSH itself may have physiological effects apart from the stimulation of thyroid hormone levels [34, 125], and such effects rather than via the reflection of thyroid status might explain such a TSH signal. Empirically, thus far, the evidence suggests that any of these TSH effects are small.

The association of thyroid hormone and particularly FT4 levels, rather than TSH levels, with clinical features has been noted by many authors, covering many individual parameters [24-26, 28, 31, 33, 40, 42, 44-46, 46, 50, 51, 55, 67, 71, 74, 78, 79, 84]. In particular, the meta-analysis regarding atrial fibrillation noted the association with FT4 but not with TSH [25]. authors have also previously 4769, 7178,8447 We were not able to find authors concluding that there are strong associations of clinical parameters with TSH but not thyroid hormone levels.

Nevertheless this information from the individual studies showing the superiority of thyroid hormone levels as correlates with clinical parameters has not to date, to our knowledge, been synthesised into a general proposition.

It has been suggested that ‘despite TSH being considered a more sensitive indicator of thyroid status, FT4 may be a more sensitive indicator of ‘cardiac’ [26], or ‘tissue’ [45, 51] thyroid status. Our study strengthens and generalizes these propositions, indicating that FT4 **is** the more sensitive indicator of thyroid status **because** it is the better indicator of tissue and organ effects.

The superior correlation of clinical parameters with FT4 as compared to TSH levels has more often been attributed to a putative disturbance of set point physiology [24, 38, 44, 45, 74, 79, 84], to a significant difference between pituitary and peripheral sensitivity to FT4[25, 44, 46, 50, 67], or to statistical/other factors [31, 34, 42, 47, 56].

Such explanations are denied by, respectively, the evidence that thyroid set points do not exist (see below), and the evidence that, at a population level, TSH levels do indeed decrease with rising FT4 levels [17, 18]. Any such disturbance to pituitary sensitivity, in the absence of a corresponding change to peripheral sensitivity, would in any event provide another reason not to diagnose subclinical thyroid dysfunction on the basis of TSH levels.

It has been suggested that in elderly individuals the TSH may not be so suppressed by any given rise in FT4 [40, 74] but in this situation, though the range of TSH may change, any physiological association with greater or lesser TSH levels should remain intact. Furthermore, the greater correlation of clinical parameters with FT4 rather than TSH levels is apparent across a wide age range (Table 1).

The evidence also suggests that, regardless of the method used, the classification of thyroid function into normal, subclinical disease and overt disease is arbitrary. Thyroid hormones, as previously suggested [8, 24], like many other biological parameters, exert a continuum of effects across the normal range. There is no clear border between normal and abnormal. There are advantages and disadvantages associated with all levels [8, 24, 126]. Individuals with relatively low levels of FT4 for example are less likely to develop atrial fibrillation but more likely to develop metabolic syndrome; the converse applies for individuals with higher FT4 levels. At the extremes the disadvantages clearly outweigh the advantages, and individuals are likely to become symptomatic.

On the other hand, any excursion from the middle of the range has an association with some pathology or other. Some individual pathologies, e.g. frailty, mortality and dementia may increase with deviations either side of the middle of the range. It seems likely that evolutionary mechanisms have arisen to minimize variation from the middle of the normal range of thyroid hormones [127].

Our work indicates that if any individuals are to be regarded as having subclinical thyroid dysfunction on the basis of a discrepancy between the normality of TSH and thyroid hormones, it would be more logical to so classify those with abnormal levels of thyroid hormones but with normal levels of TSH (i.e. euthyroid hypo/hyperthyroxinemia), rather than vice versa as currently recommended. We would suggest that it would be more logical still if the TSH level were not a determinant at all, and that borderline thyroid function was defined by borderline levels of thyroid hormones alone. With the current paradigm of screening for thyroid dysfunction by measurement of TSH levels the above patients may well not be identified.

None of the above denies the possibility that some individuals (for example individuals with paroxysmal atrial fibrillation), with thyroid hormone levels within the normal range might have improved outcomes if their thyroid hormone levels were adjusted. It may also be that in some individuals, different levels of thyroid hormones within the normal range result in different senses of wellbeing. Furthermore, in some individuals, thyroid hormone levels may not provide the whole diagnosis, and considerations of hormone sensitivity may also apply. However, the fact that, at a population level, clinical features and TSH levels reflect FT4 levels, argues against central or peripheral sensitivity generally being an important factor in the pituitary or peripheral response to thyroid hormones.

The above conclusions are consistent with, and reinforce, contemporary understanding of thyroid regulation. The conventional TSH - based definitions of thyroid disease on the other hand appear to have arisen and persisted on account of the perpetuation of misunderstandings of thyroid regulation. These misunderstandings concern the set point hypothesis and the greater sensitivity of TSH as compared to FT4 with changes in thyroid function.

The current consensus, despite evidence to the contrary [128], still confirms the set point hypothesis of thyroid regulation [1]. This hypothesis proposes that each individual has a set point or target, ideal level of a given parameter defended by physiological mechanisms [129].

The presence of a set point is said to be supported by there being greater inter-individual variation than intra-individual variation in thyroid hormone levels [1, 130] and by ‘various studies showing that, despite normalized TSH and FT4 levels, approximately 15% of patients treated for hypothyroidism or hyperthyroidism still have significant thyroid associated complaints’[1].

The former argument represents a misreading of the work [131] that purportedly demonstrates this proposition. Illustrative empiric examples to the contrary abound [132,133]. Contradicting the latter argument is the observation that individuals with subclinical thyroid dysfunction, who would have thyroid function even further away from any putative set point levels than the above treated patients, have few if any symptoms [4, 5], i.e. their abnormality is indeed ‘subclinical’. Furthermore any residual symptoms in patients treated for hypo/hyperthyroidism may have another cause, and indeed, one study has suggested that thyroid surgery to remove the offending source of autoimmune inflammation may be helpful in this regard [134].

As there is no reason to believe that any individual’s particular thyroid hormone levels represent a set point, it follows that any deviation away from these levels, within the normal range, is not necessarily deleterious, regardless of the TSH level. Individuals do not so become ‘individually ‘dysthyroid’, and may in fact become more ‘normal’ if any change from baseline is towards the middle of the range. No individual needs to become ‘more hypothyroid’ [130] than other individuals to have hormone levels fall out of the normal range and enable diagnosis. By the same logic, there is no imperative with thyroid replacement therapy to attempt to recreate the exact pre-morbid thyroid status of an individual.

It also does not follow that because TSH levels are more sensitive indicators than FT4 levels in the context of changes in thyroid function, that TSH levels are better indicators of thyroid function [1, 7, 130, 135]

There are proportionally greater changes to levels of the controlling hormones insulin [136], parathyroid hormone [137] and erythropoietin [138] in response to primary changes of levels of the parameters glucose, calcium and hemoglobin respectively, but this provides no justification to rely on the levels of the controlling hormones to define normality of these parameters [14, 15].

The fact that TSH levels reliably identify overt thyroid dysfunction can also be explained by the negative population relationship between TSH and FT4, i.e. its extension into the abnormal ranges of FT4 [17, 18]. This is due merely to the fact that nearly all overt thyroid dysfunction is primary rather than secondary [139]. This situation differs from other endocrine pathology, for example Cushing’s syndrome, where ACTH levels cannot be used as a screening test on account of the likelihood that Cushing’s syndrome may be secondary, i.e. be due to a disorder of ACTH regulation [140]. The fact that TSH levels are thereby very sensitive screening tests for thyroid dysfunction [135] does not imply TSH levels are very specific, i.e. that an abnormal TSH level implies thyroid dysfunction. Our work indicates that an abnormal TSH level per se is an imprecise indicator of tissue or organ hyper/hypothyroidism. Certainly an abnormal FT4 level is more indicative of a dysthyroid state. Testing for an abnormal FT4 would also lessen the chance of error in the circumstances of thyroid dysfunction of central origin [141].

This work addressed diagnosis alone. Randomized trials are necessary to determine whether additional considerations apply in the context of thyroid treatments. One study has reported that TSH levels are important in the treatment of thyroid insufficiency [142], but this was an observational study and it did not fully stratify FT4 levels or exclude factors that might interfere with the FT4/TSH relationship.

Our work has relevance for the interpretation and planning of interventional studies. It may well be that previous trials of the treatment of subclinical thyroid dysfunction have been negative on account of treatment being directed at TSH levels. Not only were these TSH levels inappropriate targets, but in addition, on account of the sensitivity of TSH levels to changing FT4 levels, only minimal changes (approximately 2 pmol/L [10]) in FT4 levels would have followed normalization of the TSH levels. If subtle improvements are to be sought within and at the edges of the normal range, FT4, and possibly FT3 levels, would appear to be better targets, with the aim being to bring them at least to the middle of the range; even at the cost of generating an abnormal TSH level.

As organ effects can be appreciated within the normal range however, it does not necessarily follow that even if treatment can be shown to have a beneficial effect that an abnormality was present in the first place. Improved understanding of which clinical states might have engendered compensatory or secondary changes in thyroid function, rather than having resulted from such changes, might explain any suggestion of a signal of harm with treatment of any borderline thyroid function state [143].

In summary there is now matching theoretical and empiric evidence from a variety of sources suggesting that the concept of subclinical thyroid dysfunction is flawed, and that if it does exist, it should not be diagnosed on the basis of TSH levels. The same applies for the concepts of isolated hypothyroxinemia and hyperthyroxinemia. The borderline thyroid hormone levels in these latter situations indicate borderline normal tissue exposure to thyroid effect, and increased potential for some adverse outcomes, just as they would if the TSH levels were not normal.

There is rather, a continuum of thyroid hormone effect along the continuum of thyroid hormone levels, with a possible optimum around the middle of the range. Though TSH levels remain good screening tests for overt thyroid dysfunction, it is theoretically and empirically more sound to rely on the thyroid hormone, and especially FT4, levels to classify the thyroid state. This applies in principle for all diagnostic, therapeutic, monitoring and research considerations.

This work should result in a simplification of the understanding of thyroid physiology and pathophysiology, and bring it more into line with the understanding of the physiology and pathophysiology of other parameters, whereby the status of a parameter is judged by **its** level rather than the level of any controlling factor. Reconsideration of the TSH-based diagnostic approach to thyroid function, the consequent definitions, and the dependent guidelines appears to be indicated.

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