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Thyroid Function Status by Paired Test-A Mini Review

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ABSTRACT

We classified a population of 34159 paired FT_4 & TSH test results by combination of their reference ranges. This defined 9 classes with class specific hormonal ranges and the correlation between them. FT_4 of a case alone can identify its class because the FT_4 of a class has significant mean difference from all the rest 8 classes (sig $\leq$.002) except in 2 specific situations which can be solved by their TSH (sig.000). There is no strong association between FT_4 and TSH in any of our class(r $\leq$ .445) and so it warns not to use TSH alone in diagnostic or follow-up settings. We opine to use of the reference of FT_4 of euthyroid class as the treatment target for all cases with abnormal functional status and it has the potential to resolve some pitfalls in thyroid medicine.

INTRODUCTION

To narrate a background of the article I may flashback to my won carrier. I joined in the department of Endocrinology of Bangladesh Institute for Research and Rehabilitation in Diabetes, Endocrine & Metabolic Disorders (BIRDEM) in 1988 (as a Medical Officer) after completing my diploma DEM (Diploma in Diabetes Endocrine Metabolic Disorders) from BIRDEM. I worked there till my retirement in 2017 as a Professor of Endocrinology. One of the major bulks of my works was with the people having thyroid problems. I witness many pitfalls while I was trying to breech the gaps between clinical (symptomatology) and biochemical data as a clinician. During these 3 decades many changes or developments has occurred in the field of thyroidology some of which I should mention here. They are a) implementation of universal iodinization of table salt (since 1987 in Bangladesh), b) our endocrine laboratory was doing thyroid hormone assay by RIA since 1978 included ELIZA in 1985 and thereafter CIMA in 1995; free fraction of thyroid hormones (FT_4 & FT_3) assay begin in 1996 and use of 3rd generation kits for thyrotrope (TSH) assay in 2010. Other labs in our institute and also in Bangladesh have come up with newer versions of radiostopic & sonograph, immunocytochemistry for thyroid study. But recent incorporation of molecular diagnosis in thyroid medicine is yet to be available in our country.

Like elsewhere, the major bulk of tests in our Endocrinology laboratory are Thyroid Function Tests. This is due to increased loads from three different areas - namely a) lifelong follow-up of thyroid patients; b) increasing pull of diagnostic tests for new clinical cases and c) screening protocols of thyroid function status of apparently asymptomatic people as in i) routine workup of growth and development, infertility services, ii) health checks of increased number of cancer survivors and senior citizens.

Initially with T_4 and or T_3 and then FT_4 and or FT_3 value the people under investigation could be grouped into 3 functional status - euthyroximia (normal), hypothyroximia (hypofuncting) or hyperthyroximia (hyperfuncting). Subsequently with the introduction of TSH measurement it was found that the majority but not all people with euthyroximia, hypothyroximia and hyperthyroximia were coupled with normal, high and low TSH respectively. This concordance between hormones from thyroid and pituitary gland has enlightened us on the status of thyropituitary axis in disease state. A conclusion was made - hypothyroximia and hyperthyroximia in concordance states are due to abnormality at thyroid level without any abnormality at pituitary (Thyrotrop) level or above. They were named as primary hypothyroidism and primary hyperthyroism respectively. On the other hand, the discordant population consists of diverse pathology at and/or above pituitary and which may even encompass abnormality at thyroid level.

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This subset, though relatively rare, became the real challenge in thyroid medicine.

THE STUDY

In our present study, we used the existing reference ranges together (paired) to classify biochemical status. In total there are 9 classes of which 3 (including the normal) have with concordance and rest 6 with discordance pair of FT_4 and TSH **(Figure 1)**. This system of classification has the capacity to put any paired value into its class and so can be said to have 360° capability. The mean difference (MD) between the hormones of classes in all the 36 possible pairs was determined. This proved, FT_4 of a class is distinct from all the rest 8 classes with significant MDs (sig $\leq$ 0.002); but two exceptions - namely.

1) Between primary hypothyroid and isolated hypothyroximia classes; MD sig .228.
2) Between secondary hyperthyroidism and Isolated Hyperthyroximia classes; MD sig .872.

Class 2 **Primary Hypothyroid** FT_4(6.82 – 7.09)** TSH(61.23 – 66.59) r = -.445(.000) N 783	**TSH H**	**Class 4** **Compensated Hypothyroid** FT_4(13.54– 13.70)* TSH(7.29 –7.57) r = -.031(.028) N 4872	**TSH H**	**Class 7** **Secondary Hyperthyroid** FT_4(23.41– 33.86)** TSH(6.67 –7.77) r = -.232(.218) N 30
FT4 L		**FT4 N**		**FT4 H**
Class 8 **Isolated Hypothyroximia** FT_4(5.97– 7.32)** TSH(1.73 –2.74) r = -.019(.885) N 63	**TSH N**	**Class 1** **Euthyroid** FT_4(14.83 – 14.90)* TSH(2.40 – 2.43) r = -.056(.000) N 24722	**TSH N**	**Class 9** **Isolated Hyperthyroximia** FT_4(24.20– 32.04)** TSH(2.02 –3.78) r = -.030(.884) N 45
FT4 L		**FT4 N**		**FT4 H**
Class 6 **Secondary Hypothyroid** FT_4(7.70– 8.69)* TSH(0.22 –0.26) r = +.283(.090) N 37	**TSH L**	**Class 5** **Compensated Hyperthyroid** FT_4(16.96– 17.22)* TSH(0.26 –0.28) r = -.207(.000) N 3043	**TSH L**	**Class 3** **Primary Hyperthyroid** FT_4(35.59– 38.45)* TSH(0.12 – 0.13) r = -.386(.000) N 564

N.B: FT_4 & TSH N, L & H means normal, low & high respectively. FT_4(95% CI in pmol/ml) ; TSH(95% CI in µIU/ml); r = bivariate correlation coefficient between FT4 & TSH [expressed in r value (2 tail significance) N]

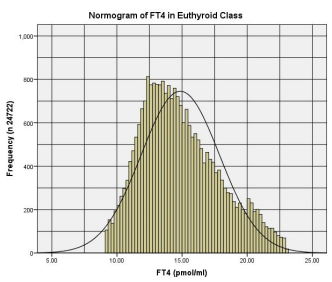
There are nine classes. * Significant Mean Difference of FT_4 from rest 8 classes (sig. $\leq$ .002). **Significant Mean Difference of FT_4 from all classes excepting one but have Significant Mean Difference of TSH from that (sig. .000). There is no strong correlation between FT_4 & TSH in any class (r $\leq$ .445) and there is no correlation in ethyroid class(r = -.056).

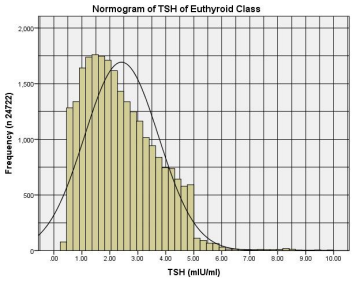
Figure 1. Paired test based classification of thyroid function status (data of 34159 paired tests)

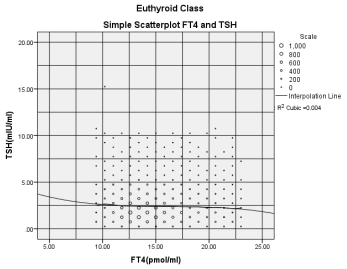
And both the pairs have distinct TSH (MD, sig.000). So, this system of classification is capable of defining functional status (class) of an individual by his/her FT_4 result only except for 2 specific pairs and in those situations a TSH value resolves the issue (see **Figure 3** of the original article).

The reference population for normal thyroid function (euthyroidism) in this study consists of 24722 cases. The normograms of their FT_4 and TSH are of almost bell shape and 95% CI of means are (14.83-14.90 pmol/ml) and (2.40 – 2.43µIU/ml) respectively (see **Figures 1 and 2**) and by Cohen's standard there is no association between the two hormones (r -0.056; sig.000) in it. We did cohort analysis to verify this nature of association. Cohorts are as follows with their correlation coefficients expressed as r value (2 tail significance) (pupation):

1) Cohorts on time of data collect (3 series), series 1(first 12 months) -0.041(.000) (n-8694), series 2 (next 6 months) -0.028(0.013) (n-7772) and series 3(last 6 months) -0.090(.000) (n-8256);
2) Cohorts on age groups adult-0.102(0.000)(n-19240), Children-0.051(0.001) (n-3950), Infants-0.041(0.170) (n-1147) & Neonates-0.066(0.198) (n-385) and
3) Cohorts on sex - male-0.010(0.373) (n-7708) & female-0.088(0.000) (n-17014). See **Figure 2**.







FT_4 in pmol/ml mean14.85, SD 3.01, SE .019, median 14.41,
95% Confidence Interval (14.83 – 14.90), range (9.14 – 23.16).
Have significant mean difference from all 8 abnormal classes (sig. ≤ .002).

TSH in μ IU/ml mean 2.42, SD 1.32, SE .008, median 2.19,
95%Confidence Interval (2.40 – 2.43), range (.32 – 15.34).
Have significant mean difference from all abnormal classes (sig.≤ 014) except with that of Isolated Hypothyroximia/Class 8(sig.2270).

Cohort	Total r -.056; sig. .000			
Age	Adult -.102(.000) (19240)	Children -.051(.001) (3950),	Infants .041(.170) (1147)	Neonates -.066(.198) (385)
Sex	M -.010(.373) (7708)		F-.088(.000) (17014)	
Time	1st -.041 (.000) (8694)	2nd -.028(.013) (7772)	3rd -.090(.000) (8256)	

Figure 2. Euthyroid class characters.

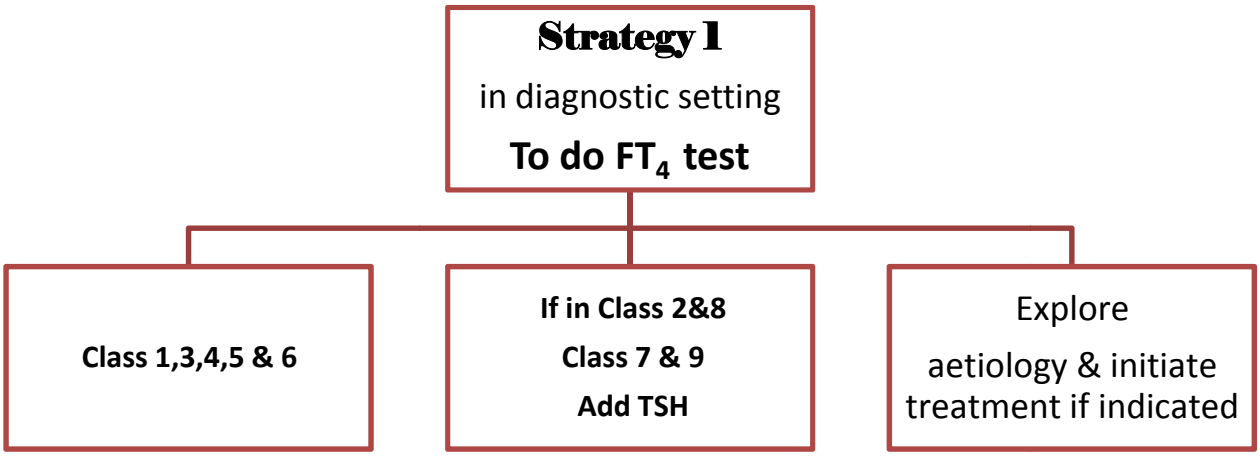


Figure 3. Strategy 1: Two steps test policy for functional status determination.

So, in all our cohorts there is no association between the 2 hormones (r ≤. 088) and only except in adult age cohort where r value is 0.102 which is just on the cut point between no association and weak association. We therefore, hypothesized that there exist a silent phase of Thyro-pituitary axis during the state of metabolic equilibrium (euthyroidism) and it starts operating in a negative feedback fashion when equilibrium is lost. The FT_4 of our primary hypothyroid and primary hyperthyroid classes are (6.82-7.09 pmol/ml) & lead to discontinuation of replacement therapy and lost from follow-up. This is not an uncommon finding in practice by non thyroidologist. To my experience it happens more with hypothyroid pregnant ladies [1].

The reference range of both FT_4 and TSH are calculated from data of clinically euthyroid population. There are 4 separate (age specific) ranges for TSH and but only one for FT_4. We used them in pair and they yield classes with class specific hormonal ranges and the correlation between them. So a class (35.59-38.45 pmol/ml) respectively. And their r values with TSH are (-.445, sig.000; n 783) & (-.386, sig.000; n 564) and so it supports the hypothesis.

There is no strong association between the two hormones in our total study population (r-0.261, sig.000; n 34159) or in any of its 9 class (r ≤ 0.445; sig.000). Therefore, any attempt to use value of one hormone to assume the status of the other one is not valid. Consequences of such an effort may even defined by this system exploits/incorporates status of the thyropituitary axis of the class. Such a system has ability to pick up biochemically more homogeneous cases than done by one hormone. In follow up setting this classification will provide data on phenomenon of shift of functional status of a case by therapeutic intervention and/or by the course of natural process. We expect that this system of classification will enable us to reduce pitfalls that exist in thyroid medicine [2-11].

CONCLUSION

In the present system of classification FT_4 alone is capable of determining the functional status/class of a person in 34 out total 36 paired settings between its 9 classes. And the rest 2 settings are solved by their TSH. We expect that all laboratories will publish their data using the new system of classification and that will enable us to adopt at least three simple strategies in thyroid medicine. They are:

1. Two step test policy for functional status determination. See **Figure 3**.
2. Single treatment goal (range of euthyroid class) for all cases with abnormal functional status. See **Figure 4**.
3. To document phenomenon of shift of functional status during follow-up for different aetiologies with or without therapeutic intervention(s). See **Figure 5**.

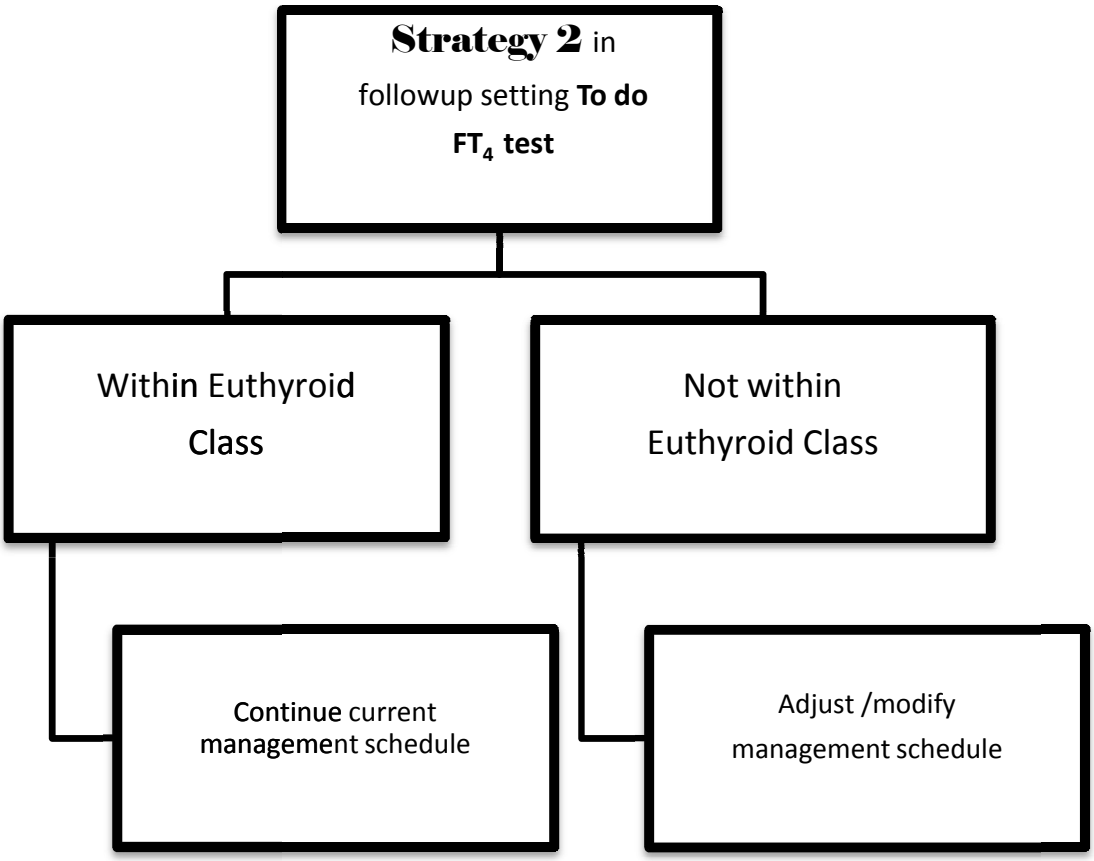


Figure 4. Strategy 2: Single goal / target of functional status correction.

Strategy 1 and 2 will make lifelong thyroid health care more cost-effective. Data generated by the strategy 3 will be valuable source to develop cost-effective management protocols for common, uncommon and rare cases with abnormal thyroid function in near future.

We believe that immediate useful output of our study is the target of single biochemical goal for all thyroid cases with abnormal function. We opine that future trends of research should focus on search of aetiology/cause(s) for individual class and the cumulative data of such studies will help us to understand the phenomenon of shifting of functional status of cases with particular aetiology, to simplify diagnostic and therapeutic workups and also to develop better management protocols for common as well as rare & emerging disorders in thyroid medicine.

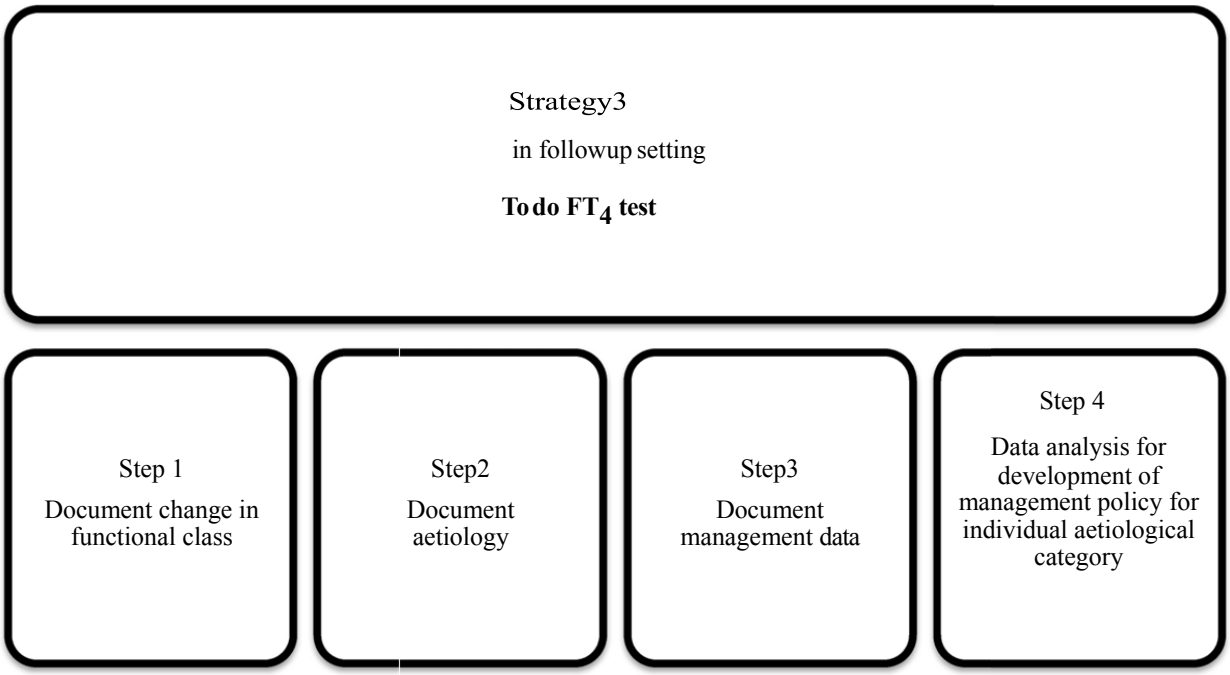


Figure 5. Strategy 3. Documentation of phenomenon of shift of functional status during follow-up for different aetiologies with or without therapeutic intervention(s).

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