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Research Article

Thyroid Function Status by Paired Test

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ABSTRACT

Aim and methods: To understand the utility of paired FT_4 and TSH test in determining functional status of Thyroid in diagnostic and follow up settings, we studied 34159 test results. We divided the population into all 9 nine possible classes by using the reference values of the FT_4 and TSH. Then we determined class frequency, reference ranges of FT4 and TSH for each class, their Mean Differences (MD) between classes and pattern of association between them within a class.

Results: Euthyroid population has FT_4 and TSH (14.83–14.90 pmol/ml) and (2.40–2.43 μIU/ml) respectively as 95% Confidence Interval and there is no association between them (r=-0.056; sig. 0.000). Major bulk of abnormal thyroid function (98.15%) is constituted by 4 classes namely Primary Hypothyroid, Primary Hyperthyroid, Compensated Hypothyroid and Compensated Hyperthyroid. The MDs of hormones between groups/classes are significant (sig.<0.009) in 91.67% (66 of 72) equations and documented FT_4 alone can identify 5 classes (Euthyroid, Primary Hyperthyroid, Compensated Hypothyroid, Compensated Hyperthyroid and Secondary Hypothyroid) as their FT_4 are significantly different from those of all rest 8 classes and for TSH it is true in only 2 classes (Primary Hypothyroid and Primary Hyperthyroid). Correlations between FT_4 and TSH in all 9 classes with abnormal functions are different and none is strong (r<-0.5) therefore only TSH should not be used in diagnostic or follow-up setting.

Conclusion: Paired Test can defines 9 classes with class specific FT_4 or/and TSH ranges and their correlation pattern. We opine, to use this tool to determination of functional status and utilize reference range of FT_4 of Euthyroid as the treatment target for cases with abnormal function.

Keywords: Thyroid Function Tests; FT_4; TSH; Paired test; Correlation; Classification

INTRODUCTION

Thyroid health is a recognized public health issue for its magnitude and also for its impact on physical and mental health. There is lacks of consensus in use of unified tools for assessment of Thyroid Function Status in diagnostic and follow up stings. We design our present study to assess feasibility of paired FT_4 and TSH test as a tool for determination of functional status. We utilized both FT_4 and TSH hormones from single sample and classify a population of 34159 tests of our laboratory into all possible classes by permutation combination of test results according to their reference ranges. As both the tests are widely available and in use by physicians for quite long time, our new reference ranges surrogated on them therefore this tool is a valid one. If our tool–paired test can define classes with distinct biochemical character then this will be an unambiguous common tool for assessment of Thyroid Function Status.

STUDY DESIGN

Aim and objective

Primary aim: To understand the utility of Paired Test of FT_4 and its tropic hormone TSH in assessment functional status of Thyroid of population with or without treatment.

Specific aim: A. To define classes of thyroid functional status and their frequency by Paired FT_4 and TSH Test in our laboratory.

B. To determent the reference ranges FT_4 and TSH for all classes defined Paired Test.

C. To compare FT_4 and TSH of different classes.

D. To evaluate the correlation between FT_4 and TSH in each class.

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MATERIALS AND METHODS

We have studied 34159 paired tests in the Endocrine Laboratory of BIRDEM done by Chemiluminescent Micropartical Immunoassay (CIMA) from 01/01/2017 to 31/12/2018.

The primary variables used in the study are age, sex; FT_4 and TSH.

A. Age is grouped in

a. Neonate (<1 month);

b. Infant (1 month to 12 months);

c. Child (>1 year to 18 years) and

d. Adult (>18 years).

B.Values of FT_4 and TSH are grouped into

a. Normal (within reference range);

b. Low (bellow reference range)

c. High (above reference range).

1. The reference range of FT_4 is 9.14 to 23.18 (pmol/ml).

2. The reference range of TSH (Age group based) is for

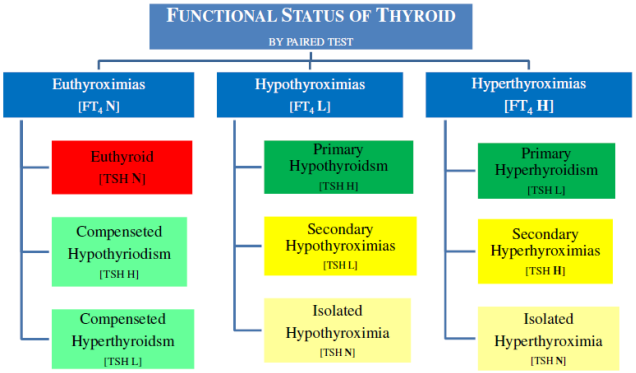
i. Adult 0.47 to 5.01;

ii. Child 0.37 to 6.0;

iii. Infant 0.52 to 16.0 and

iv. Neonate 1.30 to 16.0 (μIU/L).

C. By combining laboratory reference values of FT_4 and TSH the study population is divided into 9 classes (nomenclature is on biochemical consideration only) (Figure 1).



3.: N = normal: L: low and H: high

Figure 1: Nomenclatures of paired TSH with FT_4 based classification of functional status.

Class 1: (FT_4 normal+TSH: normal)/Normal or euthyriod

Class 2 (FT_4 low+TSH high): Primary Hypothyroidism

Class 3 (FT_4 high+TSH low): Primary Hyperthyroidism

Class 4 (FT_4 normal+TSH high: Compensated Hypothyroidism

Class 5 (FT_4 normal+TSH low): Compensated Hyperthyroidism.

Class 6 (FT_4 low+TSH low): Secondary Hypothyroidism

Class 7(FT_4 high+TSH high): Secondary Hyperthyroidism

Class 8 (FT_4 low+TSH normal): Isolated Hypothyroximia

Class 9(FT_4 high+TSH normal): Isolated Hyperthyroximia.

D. The reference range FT_4 and TSH are determine as the 95% Confidence Interval and compared between the classes by independent sample t tests.

E. Correlation between FT_4 and TSH with of total and 9 class are determined by bivariate correlations and association is expressed by Cohen's standard (r value<0.1 means no association between the 2 variables, 0.1 to<0.3 weak association; 0.3 to<0.5 moderate association and>0.5 strong association).

F. Inclusion and exclusion criteria: All paired test done in our laboratory during the period 01/01/2017 to 31/12/2018. These included samples from same person but in different time points for follow-up are included. And test results those are above or below the detection range of assay kit are excluded.

G. Hormone assay methods: The ARCHITECTURE Free T4 and TSH assay kit of Abbott were used. They determine Free T4 and TSH in human serum and plasma by two-step immunoassay by CMIA technology.

H. SPSS (Version IBM 24) is used for data analysis (Figures 2 and 3)

RESULTS

We studied 34159 tests results. For all cases age group distribution is

a. Neonate 1.48%;

b. Infant 3.71%;

c. Child 14.07%

d. Adult 80.73%. Male: Female: 2:5 (approximately). Mean and 95% Confidence Interval for Mean of FT_4 (pmol/ml) and TSH (in μIU/L) are 15.08 (15.02–15.13 and 4.31 (4.19–4.43) respectively (Table 1).

Paired test classification systems can classify al test results (360° capability) into one of the 9 classes. Each has distinct reference ranges of FT_4 and TSH and their correlation pattern.FT_4 of 5 classes (Class 1 and 3 to 6) and TSH of Class 2are significantly different from that of rest 8 classes. But both FT_4 and TSH are required for diagnosis of Class 7, 8 and 9 (Figures 2 and 3).

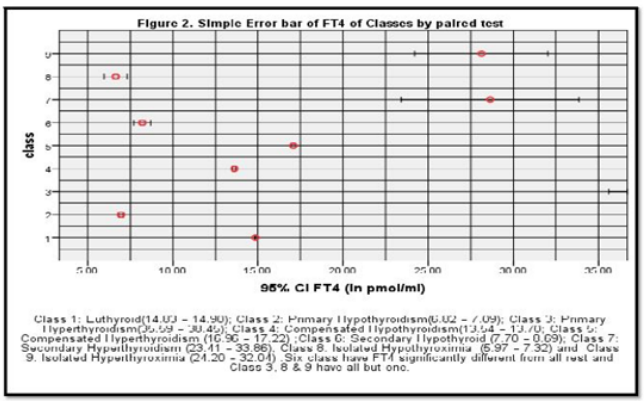


Figure 2: Simple error bar of FT_4 of classes by Paired test.

Only FT_4 result divided the population in to 3 groups

1. Euthyroximia 32637 (95.5%),

2. Hypothyroximia 883 (2.6%),

3. Hypothyroximia 639 (1.9%).

Table 1: Paired based classification of thyroid functional status class, definition, nomenclature, frequency with sex and age distribution.

Category	Class	Nomenclature (Definition)	Frequency	Sex	Age distribution			
Age mean ± SD			% (N)	Male/Female (M:F)	Neonate (<1 month)	Infant (1 to 12 months)	Children (>1 to 18 years)	Adult (>18 years)
	Total		100% (34159)	3756/9158 2:05	507 (1.48%)	1268 (3.71%)	4807 (14.07%)	27577 (80.73%)
Reference	Class 1:	Normal/ Euthyroid [FT4 N+TSH N]	72.37% (24722)	2890/6630 2:5	385 (1.57%)	1147 (4.64%)	3950 (15.98%)	19240 (77.83%)
PRIMARY	Class 2:	Primary Hypothyroidism [FT4 L+TSH H]	2.29% (783)	104/200 1:2	11 (1.40%)	23 (2.94%)	99 (12.64%)	650 (83.01%)
	Class 3:	Primary Hyperthyroidism [FT4 H+TSH L]	1.67% (564)	64/156 1:3	5 (0.89%)	19 (3.37%)	30 (5.32%)	510 (90.43%)
	Class 4:	Compensated Hypothyroidism [FT4 N+TSH H]	14.26% (4872)	277/1258 1:5	3 (0.06%)	0	476 (9.77%)	4393 (90.17%)
	Class 5:	Compensated Hyperthyroidism [FT4 N+TSH L]	8.91% (3043)	296/875 1:3	91 (2.99%)	64 (2.10%)	238 (7.82%)	2650 (87.09%)
SECONDARY	Class 6:	Secondary Hypothyroid [FT4 L+TSH L]	0.10% (37)	43559 1:1	0	1 (2.70%)	1 (2.70%)	35 (94.59%)
	Class 7:	Secondary Hyperthyroidism [FT4 H+TSH H]	0.09% (30)	43588 3:5	0 3:5	0	2 (6.67%)	28 (93.33%)
	Class 8:	Isolated Hypothyroximia [FT4 L+TSH N]	0.20% (63)	44166 3:5	0	1 (1.58%)	6 (9.52%)	56 (88.89%)
	Class 9:	Isolated Hyperthyroximia [FT4 H+TSH N]	0.13% (45)	43744 3:5	12 (26.67%)	13 (28.89%)	5 (11.11%)	15 (33.33%)

N.B.: N=Normal; L=Low and H=High.
Major bulk (98.15%) of abnormal thyroid function is constituted by 4 classes (class 2 to 5) of primary category the rest 4 classes (class 6 to 9) are rare (1.85%), belong to secondary category.

But when FT_4 is paired with TSH each of them sub grouped into three and total population turned into 9 classes/groups. The frequency of cases in classes are shown as Class number, nomenclatures (definition) with % (n) are:

Class 1: Normal/Euthyroid (FT_4 N+TSH N) 72.37% (24722);

Class 2: Primary Hypothyroidism (FT_4 L+TSH H), 2.29% (783);

Class 3: Primary Hyperthyroidism (FT_4 H+TSH L), 1.67% (564);

Class 4: Compensated Hypothyroidism (FT_4 N+TSH H), 14.26% (4872);

Class 5: Compensated Hyperthyroidism (FT_4 N+TSHH), 8.91% (3043);

Class 6: Secondary Hypothyroid (FT_4 L+TSH L), 0.1% (37);

Class 7: Secondary Hyperthyroidism (FT_4 H+TSH H), 0.09% (30);

Class 8: Isolated Hypothyroximia (FT_4 L+TSH N), 0.2% (63) and

Class 9: Isolated Hyperthyroximia (FT_4 H+TSH N), 0.13% (45). So the major bulk of abnormal thyroid functional classes (98.15%) are Class 2 to 5, they are categorized as primary category. The remaining classes of secondary category and rare (Table 1).

The reference ranges of FT_4 (pmol/ml) and TSH (μIU/L) of class is shown as Class numbers, nomenclature with 95% Confidence Interval are as follows:

Class 1: Normal/Euthyroid (14.83–14.90) and (2.40–2.43);

Class 2: Primary Hypothyroidism (6.82–7.09) and (61.23–66.59);

Class 3: Primary Hyperthyroidism (35.59–38.45) and (0.12–0.13);

Class 4: Compensated Hypothyroidism (13.54–13.70) and (7.29–7.57);

Class 5: Compensated Hyperthyroidism (16.96–17.22) and (0.26–0.28);

Class 6: Secondary Hypothyroid (7.70–8.69) and (0.2–0.26);

Class 7: Secondary Hyperthyroidism (23.41–33.86) and (6.67–7.77);

Class 8: Isolated Hypothyroximia (5.97–7.32) and (1.73–2.74)

Class 9: Isolated Hyperthyroximia (24.20–32.04) and (2.0 2–3.78) (Table 2 and Figure 2).

Comparative Data of the between classes are as follows:

1. The reference population is class 1 or Euthyroid. The mean differences for FT_4 with all the 8 abnormal classes are significant (Sig. 0.000). The mean differences for TSH with the all but 1 abnormal classes are significant (Sig. 0.000) and the only one exception is with Class 8/Isolated Hypothyroximia (Sig. 0.277) (Table 3).

2. The mean differences for FT_4 in 28 equations between the 8 abnormal classes 26 are significant (Sig. 0.000). The 2 equations those are not significant (Sig>0.063); they are between Class 2/Primary Hypothyroidism and 8/Isolated Hypothyroximia and Class 7/Secondary Hyperthyroidism and 9/Isolated Hyperthyroximia (See Table 3).

3. The mean differences for TSH in 28 equations between the 8 abnormal classes 24 are significant (Sig. 0.000). The 4 equations those are not significant (Sig>0.063); are between Class 1 and 8/Isolated Hypothyroximia; Class 4/Compensated Hypothyroidism and 7/Secondary Hyperthyroidism, Class 5/Compensated Hyperthyroidism and 6 Secondary Hypothyroidism and Class 8

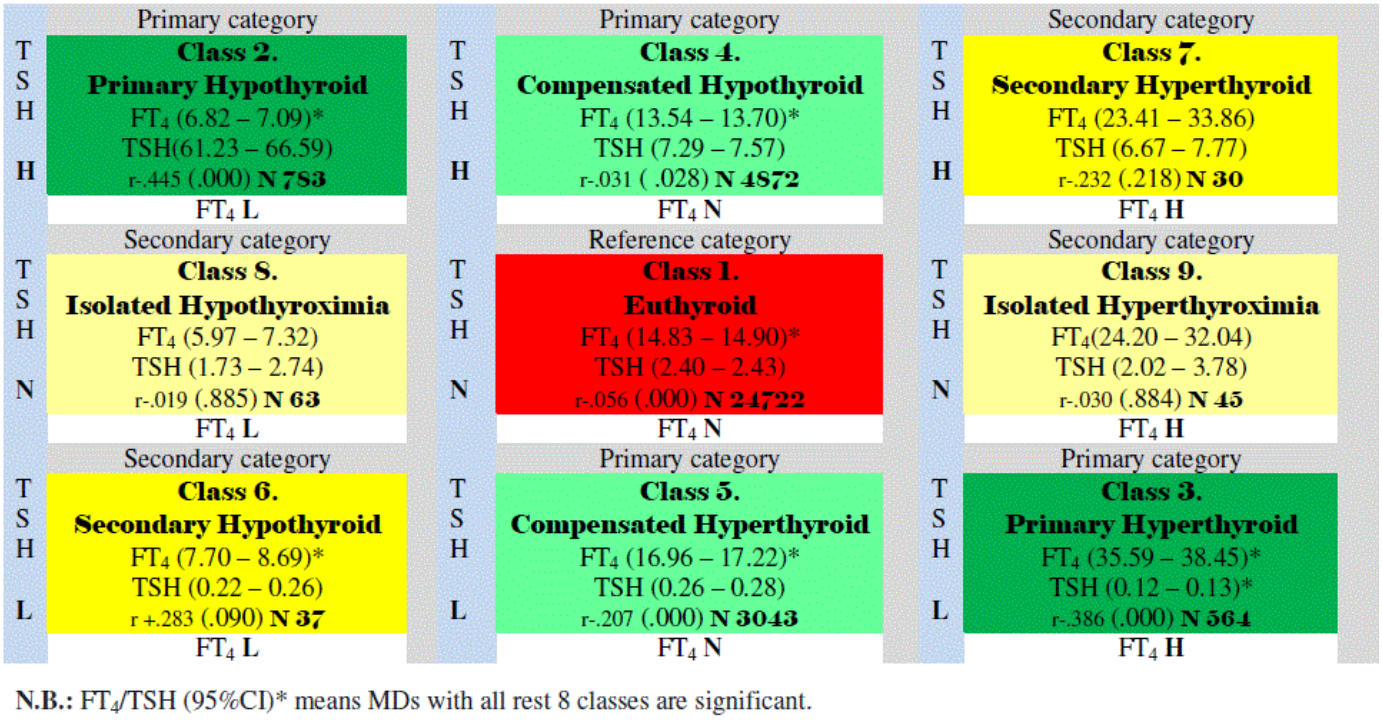


Figure 3: Paired test based thyroid function status of 34159 cases three categories and 9 classes. Reference: Class 1, primary: Class 2 to 5 and secondary: Class 6 to 9.
Paired test classification system can classify all test results (360° capability) into one of the 9 classes. Each has distinct reference ranges of FT_4 and TSH and their correlation pattern. FT_4 of five classes (Class 1 and 3 to 6) and TSH of Class 2 are significantly different from that of rest 8 classes. But both TSH and FT_4 are required for diagnosis of Class 7, 8 and 9.

Table 2: Paired based classification of thyroid functional status class, nomenclature, reference ranges of FT4 and TSH and correlation between them.

Category	Class	Population (n)	FT4 (in pmol/ml) Mean (95%CI of Mean)	TSH(in µIU/L) Mean (95%CI of mean)	Association between FT4 and TSH	
					r value (sig.)	Cohen's standard pattern
	Total	All (n-34159)	15.08 (15.02–15.13)	4.31 (4.19–4.43)	-0.261 (0.000)	Weak negative
Reference	Class 1	Euthyroid (n 24722)	14.86 (14.83–14.90)*	2.42 (2.40–2.43)	-0.056 (0.000)	No
Primary	Class 2	Primary Hypothyroidism (n 783)	6.95 (6.82–7.09)	63.91 (61.23–66.59)*	-0.445 (0.000)	Moderate negative
	Class 3	Primary Hyperthyroidism (n 564)	37.02 (35.59–38.45)*	0.12 (0.12–0.13)*	-0.386 (0.000)	Moderate negative
	Class 4	Compensated Hypothyroidism (n 4872)	13.62 (13.54–13.70)*	7.43 (7.29–7.57)	-0.031 (0.028)	No
	Class 5	Compensated Hyperthyroidism (n 3043)	17.09 (16.96–17.22)*	0.27 (0.26–0.28)	-0.207 (0.000)	Weak negative
Secondary	Class 6	Secondary Hypothyroidism (n 37)	8.20 (7.70–8.69)*	0.24 (0.22–0.26)	+0.283 (0.090)	Weak positive
	Class 7	Secondary Hyperthyroidism (n 30)	28.64 (23.41–33.86)*	7.22 (6.67–7.77)	-0.232 (0.218)	Weak negative
	Class 8	Isolated Hypothyroidism (n 63)	6.64 (5.97–7.32)	2.24 (1.73–2.74)	-0.019 (0.885)	No
	Class 9	Isolated Hyperthyroidism (n 45)	28.12 (24.20–32.04)	2.90 (2.02–3.78)	-0.030 (0.884)	No

N.B.: (95% CI)* means mean differences (MDs) by independent sample t test for groups are significant with rest 8 classes. Correlation is determined by Pearson Bivariate coefficient with Sig. (2 tailed); association pattern by Cohen's standard r<0.1=no association, 0.1 to<0.3=weak, 0 .3 to<0.5 moderate and>0.5=strong association between 2 variables.

Note: A class has at least one of two reference range is significantly different from rest 8 classes with exception for Class 8 and 9. There is no strong linear relation between FT_4 and TSH in total or in classes. There are 4 different pattern of association suggesting it as a class character.

Table 3: Check board of Mean differences (MD) of FT4 and TSH between Paired test based nine classes.

FT_4 \ TSH	Class 8	Class 6	Class 4	Class 2	Class 1	Class 3	Class 5	Class 7	Class 9
Class 8	-	(1.33-2.65) Sig. 0.000	(3.99-6.40) Sig. 0.000	(52.23-71.12) Sig. 0.000	(-1.46-0.51) Sig. 0.277	(1.94-2.28) Sig. 0.000	(1.89-2.04) Sig. 0.000	(4.17-5.81) Sig. 0.000	(-0.27-1.61) Sig. 0.162
Class 6	(0.61-2.51) Sig. 0.002	-	(5.61-8.76) Sig. 0.000	(51.34-75.99) Sig. 0.000	(1.75-2.60) Sig. 0.000	(0.09-0.15) Sig. 0.000	(-0.02 -0.07) Sig. 0.209	(6.49-7.46) Sig. 0.000	(1.70-3.62) Sig. 0.000
Class 4	(6.24-7.71) Sig. 0.000	(4.46-6.37) Sig. 0.000	-	(55.36-57.60) Sig. 0.000	(4.94-5.08) Sig. 0.000	(6.90-7.71) Sig. 0.000	(6.98-7.33) Sig. 0.000	(-1.54-1.96) Sig. 0.816	(3.09-5.95) Sig. 0.000
Class 2	(-0.19-0.82) Sig. 0.228	(0.62-1.87) Sig. 0.000	(6.45-6.88) Sig. 0.000	-	(61.00-61.98) Sig. 0.000	(60.63-66.94) Sig. 0.000	(62.28-64.99) Sig. 0.000	(43.00-70.37) Sig. 0.000	(49.83-72.18) Sig. 0.000
Class 1	(7.48–8.97) Sig. 0.000	(5.69-7.63) Sig. 0.000	(1.15-1.34) Sig. 0.000	(7.69-8.12) Sig. 0.000	-	(2.18-2.40) Sig. 0.000	(2.09-2.19) Sig. 0.000	(4.33-5.28) Sig. 0.000	(0.09-0.88) Sig. 0.014
Class 3	(26.10-34.65) Sig. 0.000	(23.24-34.39) Sig. 0.000	(22.86-23.94) Sig. 0.000	(28.85-31.28) Sig. 0.000	(21.83-22.48) Sig. 0.000	-	(0.14-0.16) Sig. 0.000	(.6.97 – 7.22) Sig. 0.000	(2.54-3.02) Sig. 0.000
Class 5	(9.57-11.33) Sig. 0.000	(7.74-10.03) Sig. 0.000	(3.33-3.62) Sig. 0.000	(9.88-10.39) Sig. 0.000	(2.11-2.34) Sig. 0.000	(19.25-20.61) Sig. 0.000	-	(6.88-7.02) Sig. 0.000	(3.16 – 5.47) Sig. 0.000
Class 7	(18.38-125.61) Sig. 0.000	(15.82-25.05) Sig. 0.000	(13.89-16.15) Sig. 0.000	(20.49-22.87) Sig. 0.000	(12.68-14.86) Sig. 0.000	(2.09-14.68) Sig. 0.009	(10.18-12.90) Sig. 0.000	-	(3.16-5.47) Sig. 0.000
Class 9	(18.13-24.83) Sig. 0.000	(15.62-24.22) Sig. 0.000	(13.57-15.44) Sig. 0.000	(20.10-22.23) Sig. 0.000	(12.37-14.15) Sig. 0.000	(3.73-14.06) Sig. 0.001	(9.89-12.16) Sig. 0.000	(-5.79-6.82) Sig. 0.872	-

N.B.: Class 1=Euthyroid; Class 2=Primary Hypothyroid; Class 3=Primary Hyperthyroid; Class 4=Compensated Hypothyroid; Class 5=Compensated Hyperthyroid; Class 6=Secondary Hypothyroid; Class 7=Secondary Hyperthyroid; Class 8=Isolated Hypothyroximia; Class 9=Isolated Hyperthyroximia. MD: Mean difference calculated by independent sample t test expressed as (95%Confidence interval of the difference); Sig (2-tailed). Note: Sixty six of total 72 (91.67%) MDs are significant (sig.<0.009). Five classes (Class 1 and 3 to 6) are having FT_4 significantly different from all the rest 8 classes. The Class 2 has TSH significantly different from all the rest 8 classes. The three remaining classes (Class 7, 8 and 9) are having FT_4 significantly different from all but one of the rest 8 classes. Therefore, FT_4 is better indicator than TSH for a class in this system of classification.

Isolated Hypothyroximia and 9/Isolated Hyperthyroximia (Table 3).

Five classes (Class 1 and 3 to 6) are having FT_4 significantly different from all the rest 8 classes, one class (Class 2/Primary Hypothyroid) is having TSH with all of the rest 8 classes and none of the rest 3 classes (Class 7/Secondary Hyperthyroid, 8/Isolated Hypothyroximia and 9/Isolated Hyperthyroximia) are having FT_4 or TSH significantly different from all of the rest 8 classes. So in 34 out of 36 (94.44%) occasions a class can be diagnosed by only FT_4 but this figure drops to 86.11% if use only TSH. So, in this classification system FT_4 of maintains a class character more than that of their TSH.

Correlation between FT_4 and TSH of the all and individual sub groups are as follows:

By Cohen's standard the association between FT_4 and TSH in all the 34159 test is a weak negative (r=-0.261; Sig. 0.000). But in class setting association became of 4 different patterns. There is no association (r<0.1) class 1: Euthyroid (r=0-0.056; Sig. 0.000), Class 4: Compensated Hypothyroidism (r=-0.031; Sig. 0.028), Class 8: Isolated Hypothyroximia (r =-0.019; sig. 0.885) and Class 9: Isolated Hyperthyroximia (r=0.030; sig. 0.884). Weak negative association(r>0.1 to<0.3) in class 5: Compensated Hyperthyroidism (r=-0.207; sig. 0.000) and Class 7: Secondary Hyperthyroidism (r=-0.232; sig. 0.218) Moderate negative association (r>0.3 to<0.5) in class 2: Primary Hypothyroidism (r =-0.445; Sig. 0.000) and Class 3: Primary Hyperthyroidism (r =-0.386; Sig. 0.000). And weak positive association is Class 6: Secondary Hypothyroidism (r =+0.283; Sig. 0.090), r values are significant in all classes except for the classes of secondary category (Table 2).

So, in this classification system the correlation between FT_4 and TSH is a class character and in healthy status (Euthyroid) there exist no correlation.

DISCUSSION

The thyroid medicine is facing some pitfalls of thyroid function tests interpretations [1–5]. We explore the features of classes defined by combining FT_4 and TSH tests results from same blood sample in diagnostic and follow up settings together. If classes defined by this system can show significantly different hormone profiles from one another, than the paired test will be a valid tool to determine the functional status. The TSH test gained much attention soon after its assay kits became available. A preexisting concept of a negative feedback control between Thyroid and Pituitary has contributed to place TSH test over Thyroxin test. Still the debate of "Which one is better -TSH or FT_4?" is going on. Now a day's, some groups' uses TSH test as a screening test for all thyroid dysfunctions and also to judge the adequacy of replacement and antithyroid drug treatment [6–9]. Ideally, a perfect negative linear relationship between FT_4 and TSH can only rationalize such a dictum. Therefore, we also looked into the association between FT_4 and TSH of the class defined by the test.

We classified 34159 tests of our laboratory into all possible classes by permutation combinations of their FT_4 and TSH results. This system yields total of 9 classes. They are Euthyroid with normal thyroid function and 4 pairs of abnormal functions

a) Primary Hypothyroid and Primary Hyperthyroid;

b) Secondary Hypothyroid and Secondary Hyperthyroid;

c) Compensated Hypothyroid and Compensated Hyperthyroid

d) Isolated Hypothyroximia and Isolated Hyperthyroximia.

We determined frequency cases for class, their reference ranges of FT_4 and TSH, Mean Differences (MD) of them between classes and the pattern of their association within a class.

The study documented 5 classes (Euthyroid, Primary Hyperthyroid, Secondary Hypothyroid, Compensated Hypothyroid and Compensated Hyperthyroid) a have their FT_4 significantly different from that of all rest 8 classes. TSH of Primary Hypothyroid is significantly different from that of all rest 8 classes. The reaming 3 classes are Secondary Hyperthyroid, Isolated Hypothyroximia and Isolated Hyperthyroximia have their FT_4 are also significantly different from all but only one specific class-Isolated Hypothyroximia with Primary Hypothyroid and Secondary Hyperthyroid with Isolated Hyperthyroximia. So, we can consider FT_4 as a primary test to follow in a 2 step test protocol.

Step I. To do FT_4 test only.

Step II. To add a TSH test from same blood sample when the FT_4 value is in the reference ranges of Primary Hypothyroid, Secondary Hyperthyroid, Isolated Hyperthyroximia or Isolated Hyperthyroximia classes.

Therefore, the paired test based classification is a simple and cost-effective system of defining thyroid function status.

Our study documented that the patterns of association between FT_4 and TSH are class specific. Therefore, this system incorporates the functional status of thyro-putitary axis also. There are 4 different pattern of association between the hormones. There is no association in are 4 classes. The most remarkable finding is the no association between FT_4 and TSH in Euthyroid (r=-0.056 sig. 0.000). Could it be due to a silent phase in the negative feedback between thyroid and pituitary operated by on/off system determined by metabolic equilibrium. Compensated Hypothyroidism is also another class with no association (r=-0.031; Sig. 0.028). Both classes are having normal FT_4-(14.83–14.90) and (13.54–13.70) respectively. This hypothesis needs further evaluation. Some pitfalls with the present correlations studies between the two hormones will be solved if we classify the functional status a paired test first and then determine the correlation within the class.

Most of the nomenclatures of classes of this system are already in use in existing practice. But they are diagnosed by reference ranges were determined from data of untreated cases only and there is no mention whether the hormones are assay must be from a single blood sample or not. Moreover their class specific references values are not yet available. The two classes Compensated Hypothyroid and Compensated Hyperthyroid are popularly known as Sub-clinical Hypothyroid and Sub-clinical Hyperthyroid respectively. We avoid terminology 'Sub-clinical' because the tool we used is a biochemical one.

The FT_4 of Compensated Hypothyroidism and Compensated Hyperthyroidism classes are within euthyroxima and are on either side of that for Euthyroid class. On their adjacent other sides lay Primary Hypothyroid and Primary Hyperthyroid. This pair of class has moderate negative association between their FT_4 and TSH. The association pattern of Compensated

Hypothyroidism is similar to Euthyroid but that of Compensated Hyperthyroidism is similar to Primary Hyperthyroid (Figure 2). Therefore, it may be postulated that there exist a phenomenon of shift of cases from one functional class/status to another and which occurs more between specific pair of classes. For example, Compensated Hypothyroidism cases likely moves to and from euthyroid while Compensated Hyperthyroidism to and from Primary Hyperthyroid.

The Secondary Hypothyroidism and Secondary Hyperthyroidism are two well recognizes terminology/class of dysfunction of thyroid [9]. The first one is in fact historically represented by Sheehan's syndrome and now it include others cases such as post-surgery at sellar and parsellar regions, post radiation of head, head injury etc. [10,11]. The second one is loosely termed as Thyroid Hormone Resistance Syndrome now getting expansion with some rare challenging disorders like TSHomas, genetically determined hormone receptor abnormality [12–14].

The two new classes identified by this system of classification are Isolated Hypothyroximia and Isolated Hyperthyroximia. They are de novo classes of paired test based classification system and belong to secondary category. The reference ranges of their FT_4 are (5.97–7.32) and (24.20–32.04) respectively which do not differ from the respective primary (sig.>0.228) but from their secondary abnormal classes (Sig.<0.002). There is no association between their FT_4 and TSH. We may assume that their cases likely to move between their respective primary and secondary status. Their population sizes are small in our series and need more cases to validate the class features.

We observed the secondary category classes constitutes very small proportion of abnormal thyroid function (approximately 1.85%) and the correlation between FT_4 and TSH are not significant (sig.>0.090) which might me due to heterogeneity thyro-pituitary axis status of their population. We opine to follow a policy to perform a routine repeat assay of hormones for these small but important group/classes for his important group.

We found no strong linear negative relation between FT_4 and TSH in total(r =-0.261; Sig. 0.000) as well as in normal functioning thyroid population(r=-0.056; Sig. 0.000). So we are unable to support the current practice of only TSH test neither as a screening test for Thyroid dysfunctions and nor to judge the adequacy of replacement and antithyroid drug treatment [15]. Rather targeting to keep FT_4 within the range our euthyroid class (14.83 to 14.90 pmol/ml) will provide opportunity of doing only FT_4 test in follow up setting of all abnormal thyroid function classes. Such an approach will not only reduce many pitfalls but also make lifelong thyroid care cost effective.

We should study on aetiological distribution within these new biochemical classes. Such data will help us to understand the phenomenon of shift of cases that can occur with or without therapeutic intervention. This will help clinicians to take appropriate therapeutic action for a case in time (Figure 4).

Figure 4: CLINICAL RELEVANCE OF CLASSIFICATION DURING DIAGNOSIS AND FOLLOW UP SETTINGS

Status/class	Diagnostic setting	During follow up	
Euthyroid	Look for AITD (for High risk) If positive follow up to detect early (Compensated Hyper/Hyperthyroid)	1. In Hypothyoids – due to adequate thyroxine replacement. 2. In Hyperthyoids – due to adequate antithyroid drugs. 3. In Graves' disease or Thyroiditis due to remission of disease 4. Following radiotherapy or surgery in transition of hyper to hypo.	
Primary Hypothyroid	Initiate replacement therapy & look for cause	In Primary Hypothyroid 1. Inadequate dose of drug 2. Irregular intake of drug 3. Varying dose schedule	In Primary Hyperthyroid 1. Excess dose of drugs 2. Graves' on remission but continuing antithyroid drug 3. Post radio- ablation/post-surgery & 4. Transient/permanent hypothyroid phase of AITD/Thyroiditis
Primary Hyperthyroid	Look for cause & initiate replacement therapy	As in Primary Hypothyroid	As in Primary Hyperthyroid
Compensated Hyperthyroid	Look for AITD Coexisting systemic conditions – septicemia, CVD; -Medication like amidarone, heparin; -pregnancy & Pituitary/hypothalamic lesion (Imaging/TRH study) than initiate therapy	As in Primary Hyperthyroid	
Compensated Hypothyroid	Look for AITD & initiate replacement therapy	As in Primary Hypothyroid	
Secondary Hypothyroid	Look for Pituitary/hypothalamic lesion (Imaging/TRH study) than initiate therapy	Repeat test & reconfirm before looking for cause & test as in diagnostic setting.	
Secondary Hyperthyroid	Look for Pituitary/hypothalamic lesion (Imaging study for mass like TSHoma and genetic study for resistance syndrome) than Initiate therapy.	Repeat test & reconfirm before looking for cause & test as in diagnostic setting.	
Isolated Hypothyroximia/ Hyperthyroximia	Repeat test & reconfirm before looking for cause as in other 2 classes Hypothyroximia/ Hyperthyroximia	Repeat test & reconfirm before looking for cause & test as in diagnostic setting. If normal evaluate existing treatment.	

Figure 4: Clinical relevance of classification during diagnosis and follow up settings.

The importance of a dependable biochemical test is rising because there is a sharp increase in number of test with asymptomatic person. For example' executive heath checks programs and long term or lifelong follow-up for persons with thyroid dysfunction who are also mostly asymptomatic. Health checks for increasing population with growth or fertility problems and cancer survivor are also included in this list.

We like to propose that, all endocrine laboratories should publish their paired test based normograms of all the 9 sub-groups so that clinicians will be able to utilize them for diagnosis and will also be able use the FT_4 of euthyroid as the treatment target for all cases with abnormal thyroid function. Such an endeavor will bring down the investigation cost and improve Thyroid Medicine as whole.

CONCLUSION

Paired Test can defines 9 classes with class specific FT_4 or/and TSH ranges and their correlation pattern. We opine, to use this tool to determination of functional status and utilize reference range of FT_4 of Euthyroid as the treatment target for cases with abnormal function.

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