Are we using Thyroid Function Tests Appropriately?

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Abstract Thyroid function tests are very important for the diagnosis and monitoring of patients with thyroid dysfunction. The guidelines recommend serum thyroid stimulating hormone (TSH) as the single most reliable test to diagnose all common forms of hypothyroidism and hyperthyroidism. The aim of this study was to analyze the ordering pattern for thyroid function tests by physicians and the analysis of results based on the clinical history. The mean age of the patients was 32.5 ± 6.5 years. Majority of samples (87.7% of total) were received from the departments of Medicine and Gynae. Thyroid profiles (47.5%) were ordered more frequently as compared to TSH only (46%). There was no significant difference in the percentage of normal reports for both types of tests. 77.8% of TFT and 76.6% of TSH samples had results within the reference range. The percentage of abnormal results was 13.7% in the patients who were screened for thyroid disorders. There is a need to redefine the case definition for thyroid dysfunction and order the appropriate test in a rational and cost effective manner.

Keywords Thyroid function test · TSH · Hypothyroidism · Hyperthyroidism

Introduction

Thyroid dysfunction is common in adults [1–3] and can be diagnosed accurately by laboratory tests [4, 5]. Commonly done tests to diagnose thyroid disorders include estimation of thyroid stimulating hormone (TSH) along with thyroid hormones, tri iodothyronine (T3) & tetra iodothyronine (T4) either in total or free form. The guidelines of American thyroid association and American Association of Clinical Endocrinologists recommend serum TSH measurement as the single most reliable test to diagnose all common forms of hypothyroidism and hyperthyroidism particularly in the ambulatory setting [6, 7]. Thyroid stimulating hormone confirms or excludes the diagnosis in all patients with primary hypothyroidism, an elevated concentration being present in both overt and mild hypothyroidism [4]. Patients with hyperthyroidism have serum TSH concentration less than 0.1 mIU/ml and usually less than 0.05 mIU/ml. A serum TSH within the euthyroid reference interval almost always eliminates a diagnosis of hyperthyroidism [8]. Free T4 levels can be ordered when TSH level is abnormally high or low. This TSH centered strategy for initial evaluation of thyroid function is both cost effective and medically efficient [9, 10].

The appropriate use of these tests remains controversial and medical practice may vary from the guidelines. The various studies done to evaluate the ordering pattern of thyroid function tests indicate that frequency of order of TFT is much higher than that of only TSH [11–13]. Similar studies have not been reported from India. There is a need to analyze the use of biochemical tests for diagnosis of thyroid disease so that they can be used in a more rational and cost effective manner.

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Materials and Methods

This study was designed to analyze the ordering pattern of thyroid related tests referred by clinicians to the endocrine lab of our 500 bed tertiary care teaching hospital in Punjab. This was a retrospective observational study. The samples referred to biochemistry lab from 1st July 2009 to 31st May 2010 for thyroid function tests were analyzed for the different combinations of tests ordered. Analysis of results was done to find out the percentage of abnormal reports. The criteria for abnormal reports were results higher or lower than the reference interval and thus included sub-clinical cases also.

Thyroid stimulating hormone, T3, T4, FT4 and FT3 were the assays performed in our lab. Estimation was done on automated immunoassay analyzer AIA 360 which works on the principle of fluoroimmunoassay. The reference ranges for variables were as follows:

T3 = 0.6–1.65 ng/ml, T4 = 4.4–11.0 µg/dl, FT3 = 2.0–4.0 pg/ml, FT4 = 0.7–1.7 ng/ml, TSH = 0.25–5.25 µIU/ml.

Results and Discussion

During the study period starting from July 2009 to May 2010, endocrinology lab of biochemistry department of our hospital received 1683 samples in which 3415 thyroid related tests were done. 1529 (90.8%) of these samples were of female patients and 154 (9.3%) were of the male patients. This significant difference may be due to the bias of clinician in suspecting thyroid disorder in female patients as these are common in females as compared to males [14]. Higher rate of testing of thyroid hormones in females has been reported in previous studies also [15, 16]. Analysis of age wise distribution of samples was done to know about the susceptibility to thyroid disease among people of different age groups. There were nine neonatal samples and four samples were received from infants. These 13 samples were excluded for the calculation of mean age. Maximum samples were received from the patients in third decade of life (40.4%) followed by those in fourth decade (23.6%) (Table 1). Mean age of patients was 32.5 ± 6.5 years. High prevalence of thyroid disorders has been reported in age groups of 21–35 and 20–55 respectively in previous studies from India [15, 17].

The samples included both outpatient and inpatient samples. Majority of these samples, 1510/1683 (89.7%) were received from outpatients. Ordering of few TFTs in inpatients is a good clinical practice because as many as 3% of hospitalized patients on admission have subnormal TSH values often associated with the acute phase of illness or with glucocorticoid or dopamine therapy, known as the euthyroid sick syndrome. Assessment of thyroid function in ill patients is best postponed until the illness resolves, unless a diagnosis would affect patient outcome [8].

Data was analyzed for the distribution of samples from various clinical departments. Maximum number of samples were received from Medicine and Obstetrics & gynaecology (Obs & gynae) departments. 46.9% requests were received from the department of Medicine and 40.8% from Obs & gynae (Table 2). Distribution of ordering of TFT and TSH was studied for these departments. Obs & Gynae ordered for 52.2% & medicine for 43.3% of the total requests for estimation of TSH. 30.3 and 50.7% of the requests for TFT estimation were received from Obs & gynae and medicine departments respectively. The samples from Obs & Gynae included 43 samples from pregnant females. 35 of these requests were made for the estimation of TSH.

The samples were ordered for different combinations of thyroid function tests. 47.5% of total samples were ordered for complete thyroid profile which includes T3 + T4 + TSH. Thyroid stimulating hormone was the investigation requested in 46% of samples. FT3 + FT4 + TSH were the investigations marked in 2.4% of samples. 1.5% of samples required FT4 + TSH (Table 3).

Analysis of results was done after excluding the samples received from pregnant females, neonates & infants. There were 56 such samples in total.

Among the TFT profile samples, 77.8% had results within reference interval for all the three parameters and thus excluded thyroid disorder. 6.8% had high TSH with normal value for thyroid hormones which may be suggestive of subclinical hypothyroidism. The worldwide prevalence of subclinical hypothyroidism ranges from 1 to 10% [18, 19]. Since these patients develop overt hypothyroidism at the rate of 5% per year [19, 20], it is important to identify these patients [21]. Typical biochemical picture suggestive of hypothyroidism was observed in 1.6% of samples. Raised concentration of

Table 1 Distribution of patients according to age

Age (years)	1–10	11–20	21–30	31–40	41–50	51–60	61–70	71–80	81–90	Mean age
No	10 (0.6%)	145 (8.7%)	674 (40.4%)	394 (23.6%)	283 (16.9%)	127 (7.6%)	29 (1.74%)	6 (0.4%)	2 (0.1%)	32.5 ± 6.5 years

Table 2 Distribution of samples according to the clinical departments

Department	TFT requests	TSH requests	Others	Total
Medicine	405	335	50	790 (46.9%)
Obs & Gynae	242	404	40	686 (40.8%)
Psychiatry	64	7	10	81 (4.8%)
ENT	44	7	5	56 (3.3%)
Surgery	16	10	5	31 (1.8%)
Pediatrics	15	3	1	19 (1.1%)
Orthopedics	7	3	0	10 (0.6%)
Skin	4	3	0	7 (0.4%)
Eye	1	2	0	3 (0.2%)
Total	799	774	110	1683

Others include FT3 + FT4 + TSH, FT3 + FT4, T4 + TSH, T3 + T4, FT4 + TSH, T3 + TSH, FT3 + TSH, T3, FT3 or T4 requests. Due to their diversity and small number, department wise distribution is not displayed

Table 3 Analysis of different combinations of thyroid related tests ordered

Investigation ordered	No of samples (Total = 1683)
T3 + T4 + TSH	799 (47.5%)
TSH	774 (46%)
FT3 + FT4 + TSH	40 (2.4%)
FT4 + TSH	25 (1.5%)
FT3 + FT4	15 (0.9%)
T3 + T4	14 (0.8%)
T4 + TSH	3 (0.2%)
Others (T4/FT4/T3/T3 + TSH/FT3 + TSH)	13 (0.8%)

thyroid hormones with low TSH levels suggestive of hyperthyroidism was seen in 1.9% of samples. T4 toxicosis (T4 raised, T3 normal, TSH low) was seen in 1.6% of cases referred (Table 4). Another important category was of results which had T4 as the only abnormal parameter with other two lying within reference interval. 4.3% of the samples had this type of result. This may be due to rise in levels of thyroxine binding globulin which may occur due to pregnancy, neonatal age, infection, chronic active hepatitis, genetic factors and use of drugs e.g. estrogen, oral

contraceptive pills and tamoxifen [22]. Pregnancy and neonatal age have already been excluded as the causative factor for rise in total T4 levels.

Analysis of 43 samples received from pregnant females showed that TSH was the investigation done in 35 of these patients. There were six TFTs and one sample each for FT3 + FT4 + TSH and FT4 + TSH. The results of all these samples were within the reference range for pregnancy except one low TSH.

There were 40 requests made for estimation of FT3 + FT4 + TSH. One of these patients was pregnant and one was neonate. These two samples were excluded from analysis. 29 of the rest 38 (76.3%) had normal results for all the three parameters.

Analysis of results for TSH requests showed that the results of 76.6% samples were within the reference interval. 15.4% of samples had TSH results higher and 4.9% had values lower than the reference range (Table 5). Since the percentage of samples with normal results was around 77% in both thyroid profile and only TSH samples, it can be concluded that estimation of thyroid hormones does not offer any additional information in majority of patients.

Percentage of normal results did not have much difference when results for all the TSH tests done during this period were taken into account (only TSH + TSH included in thyroid profile or in other combinations). Out of total 1585 TSH done, 1256 (79.2%) had results within the reference interval.

After excluding 43 samples from pregnant females, there were 1,467 outpatient samples in the study. Out of these, 224 were diagnosed cases for thyroid dysfunction and were already on treatment. 190 of these 224 patients (84.8%) had a diagnosis of hypothyroidism. This finding again re-establishes the fact that incidence of hypothyroidism is more than that of hyperthyroidism in India [15, 23]. In other patients in which thyroid function tests were ordered to rule out thyroid dysfunction, 86.3% had no biochemical evidence of same. The probability of thyroid dysfunction was approximately one in every seven patients suspected for it.

An important conclusion from this study is that though the guidelines favour TSH as the screening test for thyroid dysfunction, use of thyroid profile is common. There is a

Table 4 Analysis of results for thyroid profile samples ($n = 784$)

T3/T4/TSH Normal (N)	T3 & T4N, TSH ↑	T3 & T4N, TSH ↓	T3 & T4↓; TSH ↑	T3 & T4↑; TSH ↓	T3N, T4↑, TSH ↓(T4 toxicosis)	T4↑, T3 & TSH N
610 (77.8%)	54 (6.8%)	20 (2.5%)	13 (1.6%)	15 (1.9%)	13 (1.6%)	34 (4.3%)

Normal refers to T3 = 0.6–1.65 ng/ml, T4 = 4.4–11.0 µg/dl, TSH = 0.25–5.25 µIU/ml

Results above or below these values are indicated by ↑ & ↓ respectively

25 samples with other combinations of results for these variable e.g. all ↑ or ↓, only T3 value ↑ or ↓ etc. are not showed in table due to many combinations & few samples for each type

Table 5 Analysis of results of TSH samples

	TSH normal (0.25–5.25 μ IU/ml)	TSH $\uparrow$ (>5.3 μ IU/ml)	TSH $\downarrow$ (<0.2 μ IU/ml)
TSH = 736	564 (76.6%)	114 (15.4%)	36 (4.9%)
Total TSH = 1585 (included in all combinations)	1256 (79.2%)	220 (13.8%)	94 (5.8%)

need to evolve a standard case definition based on some applicable clinical criteria with the involvement of the concerned clinical departments to rationalise the testing behaviour among physicians. Improving the appropriateness of ordering of tests related to thyroid function will definitely be more cost effective and help in achieving better patient satisfaction.

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