Comparison of TSH, T4 and T3 Levels in Primary Hypothyroidism in relation to Gender and age in a Tertiary Care Hospital

Objectives: To compare the TSH, T4 and T3 levels in primary hypothyroidism, with respect to age and sex. Study Design Cross sectional descriptive study.

Study and duration: Chemical pathology laboratory Benazir Bhutto Hospital (BBH), Rawalpindi from September 2004 to February 2005.

Material and Methods: The study comprised of 96 subjects including 79 females and 17 males from 5-80 years of age. History and physical examination of each patient was taken according to the predesigned Performa. The thyroid profile was tested by ELISA technique to find out the values of TSH, T4, and T3. The normal range of TSH 0.4 -- 4.5 mU/L, T4 4.6 -- 11.4 ug/dl, and T3 72 – 180 ng/dl. The results were analyzed statistically by applying independent samples t- test at 5% level of significance and ANOVA test after entering data in SPSS version 14.

Results: In primary hypothyroidism the mean value of TSH, T4 and T3 were lower in females as compared to that in males; the difference was statistically highly significance with P-value of 0.002, for TSH and 0.0001 for T3 but not for T4.

On further analysis according to the age groups in males and females in primary hypothyroidism the mean values of TSH showed persistently decreasing trend in both sexes. Whereas the mean values of T4 showed increasing trend as the age advanced in males, however in females the mean T4 levels decline after 40 years of age. The highest level of TSH and the lowest level of T4 were observed in the age group of 0-15 years in both male and female. The statistical test ANOVA showed highly significant P-value in different age groups among the total population (including both sexes) for TSH, T3 and T4 in primary hypothyroidism.

Conclusion: The TSH, T4 and T3 levels in hypothyroidism exhibit different pattern according to the gender and age. The age wise distribution of thyroid profile in primary hypothyroidism amongst males and females showed that most severe form was found in age group of 0-15 year in both sex, and severity decreased as the age progressed. The primary hypothyroidism was more pronounced in males compared to females except in age group of above 40 years. The TSH values were inversely correlated well with T4 levels however the values of T3 were variable.

Key Words: Tri-iodothyronin (T3), Thyroxin (T4), Thyroid stimulating hormone (TSH), Primary hypothyroidism, Secondary hypothyroidism, Subclinical hypothyroidism.

Introduction

Thyroid disorders are amongst the most common endocrine dysfunctions. The total prevalence of these disorders estimated to be 200 million world wide. Some researchers reported 42 million Indians to be suffering form thyroid disorders. Similarly high frequency of occurrence have been reported in other countries as well.

The thyroid gland is the master gland to control the body metabolism, growth, development and maintenance of the internal environment. The gland works under the control of thyroid stimulating hormone (TSH) from pituitary gland which in turn is under the control of thyrotropin hormone (TRH) from hypothalamus. It secretes 93% of thyroxin(T4) and 7% tri-iodothyronin (T3), T3 is almost 10 times more active than T4 and produced mainly by the conversion of T4 in
the peripheral tissues. These hormones increase transcription of several genes, known to affect catabolism. Thyroid hormone initiate a chain of molecular events or gene expressions when the active form of the hormone interacts with specific cell receptors and subcellular components of various organs. Hypothyroidism is the most common thyroid disorder and is often over looked. It is 5-10 times more common in females as compared to males. The clinical presentation of hypothyroidism may vary from asymptomatic to, rarely, with multi-systems organ failure leading to myxedema coma. Hypothyroidism occur due to under activity of thyroid gland, which is further grouped as primary, secondary and tertiary due to thyroid gland, pituitary gland and hypothalamic dysfunctions respectively. Primary hypothyroidism is indicated when TSH level is high >10mU/L with decreased T3 and T4 levels. Secondary hypothyroidism is diagnose when TSH is low <0.4 mU/L with decreased T3 and T4 levels. Whereas the diagnosis of subclinical hypothyroidism is mainly based on increased TSH level between (4.5-10mU/L) with T4 and T3 within the normal range. The laboratory testing and practices guidelines for the detection and management are available from a number of organizations to diagnose overt and subclinical hypothyroidism. However problems with interpretation of serum TSH, T4 and T3 have been recognized. Various studies reported that thyroid disorders vary according to age, genders, ethnic and geographical areas. Therefore a study was planed to compare the TSH, T4 and T3 levels in primary hypothyroidism with respect to different gender and age groups in the population of Rawalpindi and Islamabad.

**Materials and Methods**

This cross-sectional study was conducted at the Pathology Department of Chemical laboratory Benazir Bhutto Hospital a tertiary care health facility affiliated with Rawalpindi Medical College, Rawalpindi. The study was conducted from September 2004 to February 2005. The object was to compare the differences of TSH, T4 and T3 levels in primary hypothyroidism in relation to age and sex. Purposive sampling was done. Every consecutive patient presenting to the pathology department of BBH for the thyroid profile within specified study period, fulfilling the following specified criteria was included in this study.

**Inclusion criteria:** Those patients visiting hormone clinic at Benazir Bhutto Hospital (BBH), Rawalpindi with derangement of even single parameter including TSH, T4 andT3 level suggesting under-activity of thyroid gland were selected irrespective of age and sex.

**Exclusion criteria:** Patients without any derangement of even single parameter in thyroid profile and negative clinical history with no sign and symptoms suggestive of hypothyroidism were excluded.

2. Patients taking medicine for hypothyroidism one month prior or any other drug effecting thyroid status were also excluded. Performa was applied to collect the data regarding the history and clinical examination. The written consent of patient or their guardians was taken. The laboratory investigations included the whole thyroid profile TSH, T4 and T3.

3-5 ml of venous blood was collected and centrifuged to separate serum from the cells as soon as the clot was formed. Serum aliquots were stored at 4oC to be run in batches. Bi-level i.e. high and low controls were run with each batch after standardizing. CV was within the expected range. Test was performed with ELISA (Enzyme-linked immuno-sorbent assay) kit, manufactured by Biotecx, based on the principle of “solid phase sandwich” technique for TSH and “competitive binding” technique for T3 and T4. Analysis was performed on the plate reader.

All the data collected were entered and analyzed in Statistical Package of Social Sciences version 14. Descriptive analysis was carried out to determine frequencies and proportions of categorical variables like various types of hypothyroidism, gender group and age groups. Mean values of the three hormones TSH, T3 and T4 along with Standard Deviations (SD) were calculated for all participants with each diagnosis, and with respect to gender and age groups. Independent sample t-test at 5% level of significance, was applied to determine any statistically significant difference exist between the mean values of the thyroid hormones according to gender groups in patients with primary hypothyroidism. To determine any statistically significant difference between the mean values of thyroid hormones in patients with primary hypothyroidism in relation to three age groups, ANOVA was applied at 5% level of significance. The graphs were constructed using Microsoft Excel program.

**Results**

The study sample comprised of 96 subjects within the age limits of 5-80 years. Among 96 subjects 79 (82.29%) were females and 17 (17.70%) were males. The results are presented in following tables and graph.

The result of the study showed that primary hypothyroidism is much more prevalent than secondary hypothyroidism as shown in table-I. As the number of individuals in secondary and sub-clinical was quite less as compared to primary hypothyroidism, the statistical analysis was done only on the individuals with primary hypothyroidism.
Table-I: TSH, T4 and T3 Levels In Various Types of Hypothyroidism in the Total Study Participants (n=96)

<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
<th>n</th>
<th>(%)</th>
<th>MEAN VALUES (±S.D.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>TSH (mIU/L)</td>
</tr>
<tr>
<td>Primary Hypothyroidism</td>
<td>88</td>
<td>(91.66)</td>
<td>37.19 (±8.61)</td>
</tr>
<tr>
<td>Secondary Hypothyroidism</td>
<td>2</td>
<td>(2.08)</td>
<td>0.12 (±0.03)</td>
</tr>
<tr>
<td>Sub-clinical Hypothyroidism</td>
<td>6</td>
<td>(6.26)</td>
<td>7.34 (±1.62)</td>
</tr>
</tbody>
</table>

The gender wise analysis was done to compare any statistically significant difference exist between the thyroid hormones mean levels in patients with primary hypothyroidism table II.

Table-II: Gender Wise Comparison of TSH, T4 and T3 Levels in Study Participants with Primary Hypothyroidism

<table>
<thead>
<tr>
<th>THYROID HORMONE</th>
<th>MALES Mean (±SD)</th>
<th>FEMALES Mean (±SD)</th>
<th>t-values</th>
<th>p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH (mIU/L)</td>
<td>43.71 (±8.46)</td>
<td>35.74 (±7.28)</td>
<td>3.82</td>
<td>0.002*</td>
</tr>
<tr>
<td>T3 (ng/dl)</td>
<td>65.41 (±4.24)</td>
<td>29.53 (±7.44)</td>
<td>18.42</td>
<td>0.0001*</td>
</tr>
<tr>
<td>T4 (ug/dl)</td>
<td>2.76 (±1.49)</td>
<td>2.19 (±2.13)</td>
<td>1.01</td>
<td>0.313</td>
</tr>
</tbody>
</table>

*p-values <0.05 are statistically significant.

The gender wise comparison showed that the mean value of TSH in primary hypothyroidism was higher in males with the difference in mean value of 7.97 mIU/L while the difference was also statistically significant. The levels of T3 and T4 were also higher in males as compared to the females with mean difference of 35.83 and 0.6 respectively, but the difference was statistically significant only for T3 but not for T4.

The mean values of thyroid hormones were also assessed based on three age groups of the total study participants: (including both sexes). The difference amongst the mean values for each hormone in the study participants with primary hypothyroidism was determined by applying ANOVA at 5% level of significance. The results of comparison showed that the differences in TSH, T4 and T3 levels in three age groups were statistically significant in patients with primary hypothyroidism as displayed in table III.

Table III: Comparison Based On Age Groups, of TSH, T4 and T3 Levels in Patients with Primary Hypothyroidism in study group of Male and Female Population

<table>
<thead>
<tr>
<th>THYROID HARMONES</th>
<th>0-15 years Mean (±SD)</th>
<th>16-40 years Mean (±SD)</th>
<th>41 years &amp; above Mean (±SD)</th>
<th>F STATISTIC</th>
<th>P-VALUES</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH (mIU/L)</td>
<td>77.07 (±4.16)</td>
<td>26.97 (±13.96)</td>
<td>11.42 (±2.57)</td>
<td>150.91</td>
<td>0.00*</td>
</tr>
<tr>
<td>T3 (ng/dl)</td>
<td>23.56 (±15.11)</td>
<td>41.4 (±14.7)</td>
<td>33.30 (±3.31)</td>
<td>13.83</td>
<td>0.00*</td>
</tr>
<tr>
<td>T4 (ug/dl)</td>
<td>1.44 (±0.24)</td>
<td>2.20 (±0.63)</td>
<td>2.68 (±0.38)</td>
<td>21.67</td>
<td>0.00*</td>
</tr>
</tbody>
</table>

*p-values <0.05 are statistically significant.
Similarly, figure III displayed gender wise distribution of T3 levels in primary hypothyroidism for each of the three age groups.

**Discussion**

The study comprised of 96 subjects within the age limits of 5-80 years. Among 96 subjects 79 (82.29%) were females and 17 (17.70%) were males. The result of the study showed that primary hypothyroidism is much more prevalent than secondary hypothyroidism it is in agreement with most of the literature.

In this study the mean TSH level in patients with primary hypothyroidism was 37.19± 8.61 ul U/ml whereas in another study it was reported to be 9.54 ± 6.69 ul U/ml.2 Another study found TSH level in overt primary hypothyroidism to be 25.1± 2.55ul U/ml, which is consistent with our study.

In the present study the mean value of TSH in subclinical hypothyroidism is 7.34 ± 1.62 ul U/ml whereas in another study conducted in India it was found to be 9.55 ± 7.7 ul U/ml.2

In the current study the mean T3 level was 36.05 ± 4.02 in primary hypothyroidism and 66± 3.2 in secondary hypothyroidism. Where as in an other study it is reported to be 77.6 ± 16.011.

In the present study there was statistically significant difference in TSH, T3 and T4 levels in different age groups in primary hypothyroidism. In present study the mean concentration of TSH decreased and that of T4 increased in primary hypothyroidism as the age progressed in males and as compared to males till age 40 in primary hypothyroidism whereas above 40 T4 was higher in males. Whereas other study showed the serum T3 and T4 levels decreased progressively with age with the highest levels being observed in children and lowest in the elderly. Another study revealed the serum T3 levels of male and female did not show any difference in any age group, whereas the mean serum T4 level in the adult females was more than that of adult male though the difference is statistically insignificant.

Different studies showed conflating results. Some of the studies showed increasing trend of TSH with age.7, 8, 12, 13

However a study conducted in Puducherry showed that there was no significant difference in free T4 in relation to age, where as free T3 value decline with age2. In an other study there was no significant difference between different age group in free T3 and free T4 levels.5, 14 In contrast some studies are consistent with our study and have revealed similar pattern of decreasing trend of TSH level and compensatory increasing level of T4 level with increasing age. such as Hoogendom et al reported a decrease in TSH with age15 and Kundsen et al have reported an increase in free T3 with age.16 The difference in different studies may be due to different populations, iodine intake, genetic factors etc.

In our study the TSH level correlated well inversely with T4 levels but the levels of T3 were variable. It was supported by other studies which reported the same co-relation17, 18. Elevated TSH level directly reflects impaired thyroid hormone production.19 The better co-relation of TSH with T4 may be due to the reason that T4 is mainly produce from pituitary gland and only 7% of T3 is secreted. The rest of the T3 production is dependent on the peripheral conversion of T4 to T3 which in turn dependent on many factors including bioavailability of enzyme deiodonase, drugs, disease in which inactive rT3 form instead of T3. Similarly age, gender ethnic distributions have been reported to be additional contributing factors by many studies.

During diagnosis, most doctors use the TSH test to evaluate thyroid function and determine the optimal course of treatment. The circulating levels of actual thyroid hormones T4 and T3 may not be able to detect more subtle thyroid problems, or conditions that are resulting from improper peripheral conversion of thyroid hormones. However early in the disease process of primary hypothyroidism compensatory mechanisms may maintain T3 levels to some extent. Decreased production of T4 causes an increase in the secretion of TSH by the pituitary gland. This in turn, causes the thyroid to release more T322 by increasing thyroid T4 -5 deiodinase activity in hypothyroidism leading to higher efficiency of the thyroid gland to secrete the more biologically active fraction of the hormones.5 T3 estimation is not very useful in hypothyroidism hence T3 testing may be avoided in primary hypothyroidism because the levels are frequently normal and when decreased non-thyroid illness needs to be excluded.6

It was found that during a normal human life span, serum T3 is low at the time of birth, increase markedly during early infancy, remains high during childhood, is reduced (during) after adolescence, then remains stable until late middle age and ultimately decreases in old age. Some studies reported stable T4 levels for men throughout life, and T4 values lower in females older than 60 years.21

In the present study in females the TSH level in the age group of 16-40 years was 40. 84mIU/ml compared to TSH 14.0 mIU/ml in the age group above 40 years, whereas the T4 level was 2.83 and 2.30 respectively. It may be because with increasing age, a decrease in the sensitivity of the pituitary to slight deficiencies of thyroid hormone occur, so that more marked deficiency than younger individuals would be required to elicit hyper- secretion of TSH. Thyroid function probably decreases with senescence and the
decrease is probably the result of the aging process.\textsuperscript{21}

Hypothyroidism in adults if left untreated can cause hyper-lipidemia\textsuperscript{23}, hypertension, infertility, osteoporosis\textsuperscript{24}, dementia and depression\textsuperscript{3} etc, and in children permanent retardation and other congenital abnormalities.\textsuperscript{24}

It has been reported that 4\% of subclinical hyperthyroidism progress to overt hypothyroidism per year 10 TSH level greater than 10 mU/L could progress to overt hypothyroidism\textsuperscript{6} Hence it is suggested that follow up of subjects with high TSH value is important to prevent progress to overt hypothyroidism.

The screenings with TSH have been recommended in pregnancy\textsuperscript{25}, neonates\textsuperscript{24} and other vulnerable population such as elderly women\textsuperscript{10} to prevent serious outcome. The study revealed that the TSH T4 and T3 levels vary according to the age sex and various types of hypothyroidism. This knowledge will be helpful for proper interpretation of the results, diagnoses and treatment of such patient.

**Conclusion**

The TSH, T4 and T3 levels in primary hypothyroidism exhibit different patterns according to the different gender and age.. The age wise distribution of thyroid profile in primary hypothyroidism amongst males and females showed that most severe form was found in age group of 0-15 year in both sexes, and severity decreased as the age progressed. The primary hypothyroidism was more pronounced in males compared to females except in age group of above 40 years. The TSH values were inversely correlated with T4 values however the values of T3 were variable.

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