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Original Research Article

Establishing the Physiological Range of Various Thyroid Hormones in Ethnic Healthy Adult Kashmiri Population of Himalayan Region - A Hospital Based Study

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Abstract

Introduction: Thyroid hormones are secreted from the thyroid gland, an important endocrine organ. These hormones are important in regulating metabolism, growth, weight, and thermogenesis. Kashmir is a part of the Himalayan belt of India, where the soil is deficient in iodine. The prevalence of thyroid disorders in Kashmir Valley are rising at an alarming rate. The study was carried out to determine the normal physiological range of thyroid hormones (TSH, T3, and T4) in normal, euthyroid subjects of ethnic Kashmiri origin. This would aid in the screening, diagnosis, and treatment of various thyroid disorders.

Methods: In this study, 400 healthy volunteers falling in the age group 20-60 years were enrolled and their serum TSH, T3, and T4 levels were assessed after taking proper history and general physical and systemic examination.

Results: We found that the TSH levels ranged from 0.27-4.20μIU/ml, T3 levels were 0.50-1.80 ng/ml, and T4 levels were 5.30-13.60 μg/dl in the study subjects. There was no significant difference in thyroid hormone levels with respect to the age and sex of the study participants.

Conclusion: the results show that the range of serum TSH, T3, and T4 levels in the Kashmiri population is in close agreement with the range established in the other populations. Larger sample sizes of studies need to be carried out to better understand the reference range in the population. Also, we recommend including free T3, and free T4 levels to be assessed.

Keywords: Thyroid Hormones, Reference Range, Kashmiri Population, Iodine Deficiency.

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Introduction

The thyroid (Greek- thyreoeidoús, meaning shield), name was coined by Thomas Wharton in 1656. [1] The thyroid gland is a vital endocrine organ that is responsible for major metabolic, growth, and developmental processes in our body. A regulated amount of thyroid hormones are released from the gland into the blood. [2]. The thyroid gland is responsible for the production of 90% of the inactive thyroid hormone i.e., Thyroxine (T4), and 10% of active hormone i.e., triiodothyronine (T3). The inactive hormone in the periphery is converted to the active form by type 1 deiodinase in the liver and kidneys. Type 2 deiodinase produced by glial cells in the brain leads to the conversion of T4 to active T3. The third iodothyronine is called reverse T3, or rT3. rT3 is inactive and forms by type 3 deiodinase activity on T4. The rT3, the third form of iodothyronine present in small amounts, is inactive and is formed by the action of type 3 deiodinase on T4 [3]. A trace element iodine is essential for thyroid hormone synthesis. Sodium-iodine symporter transports iodine actively from the blood into the iodine-storing organs including the thyroid. The increase in iodine storing capacity is necessary for individuals in whom the dietary intake of iodine is low or for people living in mountainous regions where the iodine concentration in the local food is low. Iodine transport into the thyroid is regulated by Thyroid Stimulating hormone (TSH). TSH stimulates the transcription of Sodium Iodide Symporter (NIS) and its placement on the thyroid cell membrane. TSH is secreted from the anterior pituitary and its secretion is regulated by negative feedback from T3 and T4 as well as TRH from the hypothalamus. Persistent low levels of iodine lead to increased expression of NIS and abnormal growth of the thyroid gland under the influence of raised TSH

leading to the development of Goiter [4]. The recommended dietary allowance (RDA) of iodine is 150 μg in adults (age 19+). A slightly higher intake of iodine is recommended for pregnant (220μg) and lactating (290μg) women. Soil contains variable amounts of iodine, which results in varied content of iodine in the crops grown in it. In certain areas of the world, the soil is deficient in iodine thus leading to the risk of iodine deficiency in the population living there. Among such areas is the Himalayan belt of India, which includes the Kashmir province of Union Territory of Jammu and Kashmir [5]. Apart from the goiter, other forms of thyroid illnesses are also prevalent in significant amounts in the Kashmiri population. Particularly in the last 10 years, these disorders have shown a significant rise in the region [6]. The current study was undertaken to evaluate the levels of Thyroid hormones (T3 and T4) and TSH levels in the Kashmiri healthy adult population and define the physiological variations of the same. Estimation of T3, T4, and TSH levels in serum form the fundamental tests for evaluation of the functional status of the thyroid gland and are hence the first line of investigation in various thyroid disorders.

As per American Thyroid Association guidelines (2017), the establishment of reference intervals (RI) based on specific populations and specific assays is necessary for diagnosing thyroid dysfunction accurately. The RIs do not consider the influence of the environment or ethnicity on thyroid hormone levels, which may affect the clinical diagnosis. Various studies done previously have shown that normal thyroid hormone levels differ among various ethnic groups. This is beautifully exemplified by Lanzhou, a multi-ethnic city located in Western China, with an average elevation of 1,500 meters above sea level, The nutritional iodine status of residents there was repleted only after the implementation of universal salt iodization (USI) program to correct iodine deficiencies about 20 years ago. This study hypothesized that the reference intervals (Ris) established based on the local population in Lanzhou and Abbott chemiluminescence apparatus (Abbott, Santa Clara, CA, USA) would be inconsistent with the RIs supplied by the equipment manual due to the differences in source population characteristics. Thus there is a need for establishing reference range/reference intervals based on local populace

The data should exhibit a normal distribution or can be then transformed into a normal distribution using various mathematical methods [7].

Materials and Methods

The present study was designed to measure the serum levels of T3, T4, and TSH in a normal Kashmiri adult population. This cross-sectional study was conducted in the Department of Physiology, GMC Srinagar for which healthy volunteers were recruited. We excluded all people who were suffering from any thyroid disorder or any other comorbidity that might affect the serum levels of thyroid hormones. The serum T3, T4, and TSH levels of all healthy subjects were assessed using the Non-competitive Immunometric assay (IMA) method which uses fluorescence or chemiluminescent molecules as signals. This method is considered to be ten times more sensitive than the Radio Immunoassay (RIA) method.

The study population consisted of a sample of 400 healthy subjects, aged 20-60 years of both sexes from various districts of Kashmir valley. After obtaining proper consent from the subjects, a detailed history was taken which was followed by a general and systemic clinical examination to exclude subjects known to suffer from any significant non-thyroidal illness or any thyroid-related illness. On detailed clinical examination, only those subjects were selected who were ambulatory, in apparently normal nutritional status, and without any abnormality. A history of any thyroid disorder in the past was ruled out. The subjects selected for the study were not having any history of thyroid disorders in the past, were not taking any drugs known or suspected to influence thyroid hormone measurements and were not attending any hospital or requiring any institutional care. The subjects were classified into two groups according to their age:

Group A: 20-39 Years.

Group B: 40-60 Years.

After obtaining proper consent, venous blood sample was collected from anterior cubital vein and the principle applied for the estimation of serum T3,T4 and TSH levels is called as the Sandwitch Principle in Roche Elecsys 1010 Analyser, manufactured by Roche Diagnostics GMBH, Germany. The analyser measures the hormone levels by non-competitive immunometric assay method by using fluorescence or chemiluminescent molecules as signals. The manufacturer certifies that the analyzer is suitable for testing the thyroid hormone levels and is capable of producing valid results.

Statistical Analysis: The statistical analysis of the data was done by using Chi-square test so as to compare the observed results with expected results. Student t-test was also used to compare the means between two groups. A P-value less than 0.05 was taken as significant. The analysis of the data was done by statistical package SPSS version 10.0 Chicago, U.S.A. for Windows.

Results

The present study consisted of 400 healthy subjects divided into two groups (Group A, 20-39 Years, and Group B, 40-60 Years). The minimum age of the volunteers was 20 years and the maximum age was 60 years with an average of 37.65±13.97 years. The minimum weight was 40 kgs and the maximum was 85 kgs with an average weight of 59.36±9.62 kgs. The minimum height of subjects was 141cm and maximum was 183 cm with an average of 163±9.43cms. (Table1).

Table 1: Distribution of age (years), weight (kgs), and height (cms) of the studied subjects

Variables	Range	Mean±S. D
Age (years)	20-60	37.65±13.97
Weight (Kgs)	40-85	59.36±9.62
Height (cms)	141-183	163±9.43

Group A consisted of 102 males (45.10%) and 124 (54.90%) females, while as group B consisted of 76 males (43.70%) and 98 females (56.30%). The distribution of sex with respect to two groups was not significant. (Table 2)

Table 2: Comparison of age (years) and sex of studied subjects

Age	No. of cases	Males	Females		P-Value
20-39	226	102 (45.10%)	124 (54.90%)	χ^2 =0.084 1.d.f	0.772 (non-significant)
40-60	174	76 (43.70%)	98 (56.30%)		
Total	400	178 (44.5%)	222 (55.5%)		

The serum level of T3 ranged from 0.50ng/ml to 1.80ng/ml with mean±SD as 0.97±0.19ng/ml. The serum level of T4 ranged from 5.30ug/dl to 13.60ug/dl with mean±SD as 8.49±1.77ug/dl, and serum level of TSH ranged from 0.27µIU/ml to 4.20Uiu/ML with mean ±SD as 2.27±0.96Uiu/ml (Table3) (figure 1).

Table 3: Distribution of T3, T4, and TSH values of all study subjects

Variable	Range	Mean±S.D
T3 (ng/ml)	0.50-1.80	0.97±0.19
T4 (µ/dL)	5.0-13.60	8.49±1.77
TSH (µIU/ml)	0.27-4.20	2.27±0.96

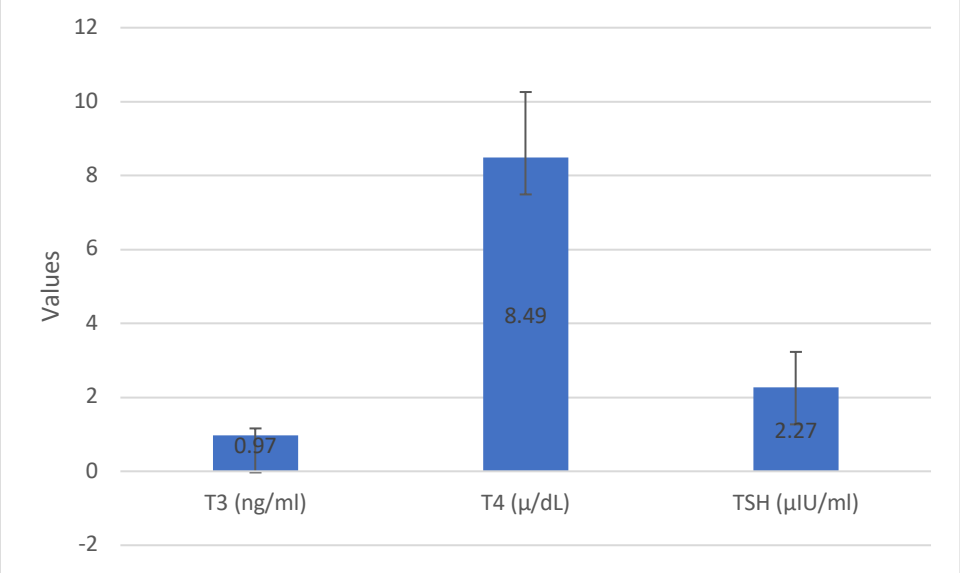

Figure 1: Distribution of T3, T4, and TSH values of all study subjects

There was no statistically significant difference in mean values of T3, T4 and TSH between groups A and B. (table 4) (figure 2).

Table 4: Comparison of T3, T4, and TSH Values with respect to age

Variable	Group A	Group B	T Value	P Value	Result
	Mean±S.D.	Mean±S.D.			
T3 (ng/ml)	0.99±0.19	0.95±0.18	1.63	0.104	Not significant
T4 (µ/dL)	8.74±1.92	8.48±1.51	1.73	0.092	Not significant
TSH (µIU/ml)	2.19±0.93	2.37±1.00	1.33	0.185	Not significant

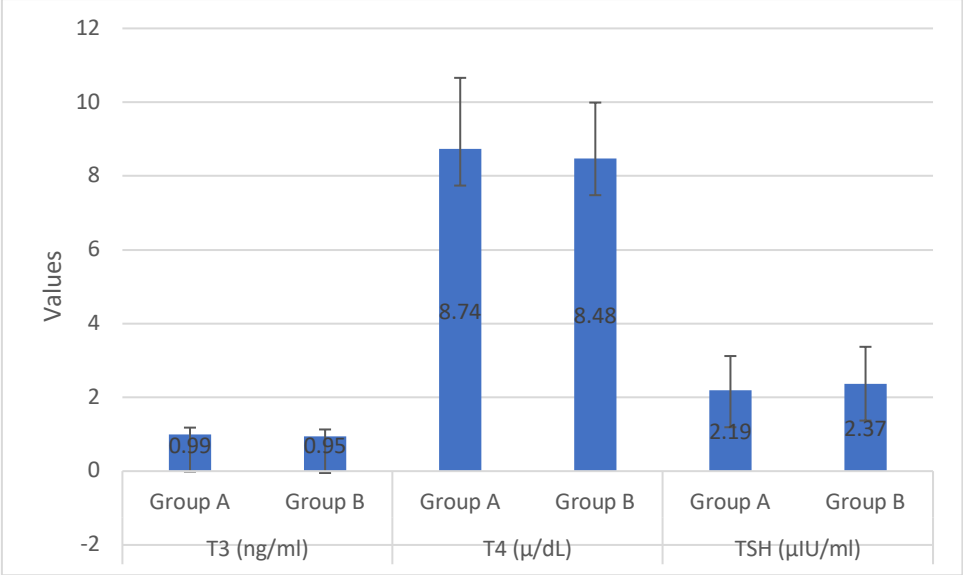

Figure 2: Comparison of T3, T4, and TSH Values with respect to age

There was no statistically significant difference in mean level of T3,T4 and TSH with respect to sex.(Table 5) (figure 3).

Table 5: Comparison of T3, T4, and TSH values in comparison to sex

Variable	Male (Mean±S.D)	Female (Mean±S.D)	T value	P value	Result
T3 (ng/ml)	0.94±0.17	0.99±0.20	1.74	0.083	Not significant
T4 (µ/dL)	8.55±1.60	8.77±1.86	1.78	0.068	Not significant
TSH (µIU/ml)	2.34±0.95	2.21±0.98	0.97	0.329	Not significant

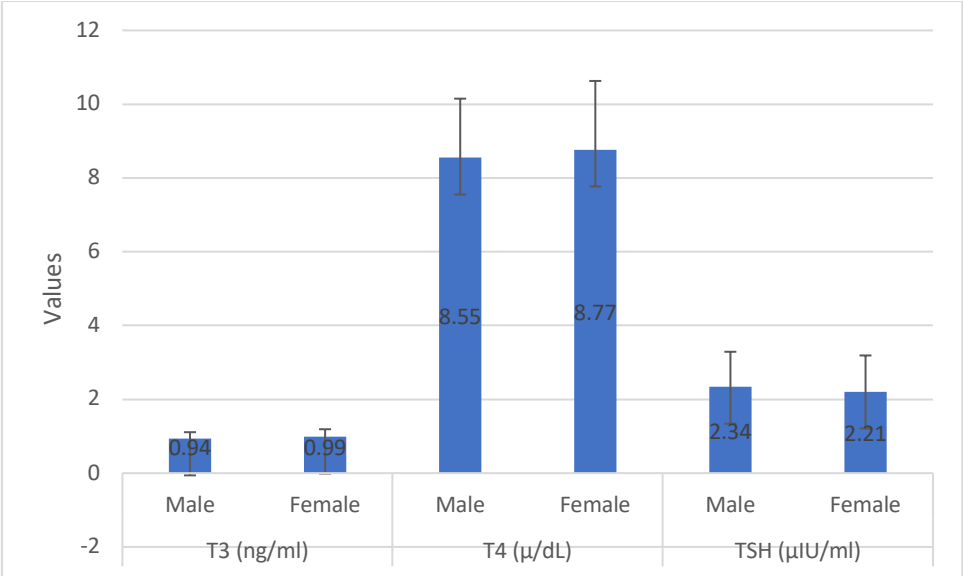

Figure 3: Comparison of T3, T4, and TSH values in comparison to sex

Discussion

Estimation of T3, T4, and TSH levels in serum form the fundamental tests for evaluation of the functional status of the thyroid gland and are hence the first line of investigation in thyroid function tests. These tests are vital to assess various thyroid disorders and also assess the treatment outcome of the same.

Considering the importance of the levels of these hormones in serum it is imperative to consider the factors that might influence the normal range of these hormones in various geographical regions. Studies have reported the variable range of thyroid hormones in different geographical areas, [8] and age, gender, race, and iodine intake also play a role. [9] Due to all these reasons the International Federation of Clinical Chemistry (IFCC) and Clinical and Laboratory Standards Institute (CLSI) promote the testing laboratories to set their own range, [10] so that diagnostic errors can be avoided. Kashmir being the part of Himalian Goiter Belt,

being situated at a high altitude and with peculiar food habits of the population it becomes imperative to establish a well-defined range of values of serum T3, T4, and TSH levels. After obtaining proper consent, venous samples were obtained from the volunteers in non-fasting state as fasting is known to cause rapid fall in serum T3 levels [11].

In the present study the TSH, T3 and T4 values in Group A, i.e., age group of 20-39 years, were 0.27μIU/ml to 4.20 μIU/ml (mean value 2.19±0.93 μIU/ml), 0.60ng/ml to 1.80ng/ml (mean value was 0.99±0.19ng/ml) and 5.30μg/dl to 13.60 μg/dl (mean value was 8.74±1.92 μg/dl).

While as in Group B, i.e., age group of 40-60 years, TSH, T3, and T4 values varied from 0.30 μIU/ml to 4.20 μIU/ml (mean value was 2.37±1.00 μIU/ml), 0.50 to 1.70 ng/ml (mean value was 0.95±0.18ng/ml) and 5.70 μg/dl to 12.80 μg/dl (mean value was 8.48±1.51μg/dl).

The overall serum TSH, T3 and T4 levels among 400 studied subjects were ranging from 0.27 to 4.20 μIU/ml), 0.50 to 1.80 ng/ml and 5.0 to 13.60 μg/dl. These results are in close agreement with various studies that showed the normal range of TSH, T3, T4 are 0.3–4 mU/l, 1.2–2.8 nmol/L, and 77–155 nmol/l [12]; 0.64 to 5.94 lU/mL, 0.91 to 2.47 ng/dL, and 5.53 to 12.48 g/dL [13]; 0.3–5.0mU/L, 1.2–2.7nmol/L, 60–140nmol/L [14].

A study from an iodine-deficient area in Germany showed a lower reference range (0.25 to 2.12 mIU/liter) for serum TSH in subjects who had no history of thyroid disease [15].

The minor differences observed among the established reference ranges for the serum T3, T4, and TSH levels as reported by various studies and the present study may be due to the involvement of various factors such as variation in techniques, use of different laboratory methods and influence of various physical factors like climatic conditions, dietary habits, anthropometric measurements, etc. of the studied subjects.

On comparing the mean T3, T4, and TSH values with respect to two age groups (20-39 years and 40-60 years), the difference observed was statistically non-significant (i.e., the P value for all the three levels T3, T4, TSH was >0.05), hence suggesting that the serum levels of T3, T4, and TSH do not vary significantly from 20-60 years of age. As per the Whickham survey, the levels of TSH did not vary with age in the case of males, but the females showed a significant rise in TSH levels after the age of 45 years [16]. The NHANESIII survey stated that the serum TSH levels rise in both men and women with increasing age [17]. A more recent study from Australia stated the TSH levels increase with age with no significant change in free T4 levels [18].

However, the studies from borderline Iodine deficiency have revealed that the serum TSH levels decrease with age and serum free T4 levels increase [19]. A study from Italy stated that there is a significant reduction in serum total and free T3 levels, especially in nonagenarians whereas serum total and free T4 levels remained unaltered in relation to age [20].

The serum levels of TSH, T3, and T4 were compared between males and females and the results shown were not significant. A study from China stated the TSH levels were lower in males as compared to females, whereas FT3 and FT4 levels were higher as compared to females [21]. Another study concluded that serum TSH levels increase with age in the Chinese population. The study also stated that the females and older adults have lower serum FT3 values and lower FT3/FT4 ratios, and serum FT4 values remain unaffected [22]. Various previous studies done in 11 countries like Asia, America and Europe have shown that thyroid hormone RIs differ among different ethnic groups, and these values may not be generalizable from one group to another. Variations in TSH RIs were found not only between different countries, but also between various ethnic groups in the same country. Studies have shown that Indian TSH RIs were higher than those in South Korea, Japan, China, and Turkey. India is a multi-ethnic country located in the South Asian subcontinent. Apart from ethnic differences, the prevalence of mild iodine deficiency disorder in India may be a probable reason for the significantly high TSH RIs.

The lower limit of the TSH RIs in seven European and American countries fluctuates between 0.3-0.64 mIU/L, and the upper limit ranged from 3.24-5.8 mIU/L. The reason for this variation might be related to ethnicity, geographical location, diet, and especially iodine intake, since even within a single country, like United States, the TSH RIs differ among Caucasians, Mexicans, and African Americans. Thus there is an unmet need for establishing the reference intervals/reference range of various thyroid hormones for diagnostic and therapeutic purposes, hence the aim and objectives of our present study [7].

Limitations of the study were the small sample size, hospital-based study and we have included only a single ethnic group i.e., the Kashmiri population. We recommend further large scale epidemiological studies where the sample size can be increased thus helping in the generalization of results. We also recommend testing for the levels of serum free T3 and free T4 levels and urinary iodine level assessment for future reference purposes.

Conclusion

The variation in the reference interval/reference range of various thyroid hormones in various studies in different continents of the world makes it mandatory to establish local population-based assays/levels for diagnostic and therapeutic purposes. Due to the geographic location of Kashmir Valley and a rising incidence of various thyroid disorders, this study was undertaken to establish the normal reference range of various thyroid hormones.

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