ORIGINAL RESEARCH PAPER

Volume-8 | Issue-3 | March-2019 | PRINT ISSN No 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

PATTERN OF THYROID PROFILE WITH ADVANCING AGE IN SOUTH BENGAL: A CROSS SECTIONAL STUDY

Physiology

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ABSTRACT

Marked changes in thyroid hormone production, metabolism and action occur with increasing age. Increased prevalence of (subclinical) thyroid disease in the elderly and various morphological and functional changes of the thyroid gland during ageing process are well-known. In general, clinical course of thyroid diseases in the elderly differs essentially from that observed in younger individuals, because symptoms are more subtle and are often attributed to normal ageing. This study has been carried out in a tertiary care hospital of South Bengal to determine the pattern of thyroid functioning along with advancing age. Thyroid profile (Serum levels of TSH, free T4, and free T3) was analyzed in selected 456 healthy, euthyroid population (within 21-80 years, further stratified into 6 consecutive decade-long age-groups). All three parameters varied significantly in elderly individuals as compared to young ones and were found to be of significantly decreased overall value in the males. Thus need for further exploration to set new standards of normal ranges of thyroid profile in the elderly of both sexes is suggested.

KEYWORDS

Ageing, Euthyroid, Thyroid profile, Elderly

INTRODUCTION

Ageing is a progressive physiological process that is characterized by degeneration of organ systems and tissues with consequent loss of functional reserve of these systems [1]. Part of ageing process involving body composition might also be related to changes in the endocrine system. Ageing changes in particular endocrine organs, including the thyroid gland, may be due to changes in the amount of hormones secreted or the sensitivity of target organs or the rate of metabolism of hormones [2]. Likewise, numerous morphological and physiological changes of the thyroid during the process of ageing are well-known [3]. There has been increasing interest in thyroid function in the elderly because of association of thyroid status with disability, cognitive function, cardiovascular disease risk, and longevity [4]. Frequently, the interpretation of thyroid function tests is also difficult in ageing individuals, because true "physiological" age-associated changes cannot be easily distinguished from the alterations secondary to subclinical thyroid disease, to acute or chronic non-thyroidal illness and / or drugs often taken by elderly patients. The definition of "physiological" age-associated thyroid changes with ageing and the correct understanding of these modifications are not merely speculative, since it greatly helps in differentiating "physiological" alterations from subclinical thyroid disease and in resolving the question of treatment of uncertain clinical situations [5].

Thyroxine (T4) along with much lesser amount of Tri-iodothyronine (T3) is secreted by the thyroid gland under the negative feedback regulation of hypothalamic Thyrotropin Releasing Hormone (TRH) and anterior hypophyseal Thyroid Stimulating Hormone (TSH) [6]. The thyroid hormones play a critical role in cell differentiation during development and help maintain thermogenic and metabolic homeostasis. Inappropriate secretion of thyroid hormones may occur in many thyroid disorders. In primary hypothyroidism T3 and T4 is suppressed while TSH concentration is high. While in primary hyperthyroidism T3 and T4 concentration is high while TSH is suppressed [7].

There has been long standing controversy about the thyroid function test results in the elderly [8]. Serum TSH, free T4, and freeT3 concentrations change with aging [9,10]. Moreover, the value of thyroid profile may move outside the normal ranges applicable to younger age group [11]. Several researchers from different parts of the world have worked on establishing the relationship of thyroid profile and advancing age, but their findings were different with wide variations. Moreover very few studies are available on Indian population on this issue. On this background, the present study intends to have an idea about the pattern of thyroid functioning along with advancing age in a population of southern part of West Bengal, India. It will also observe whether gender difference affects the said pattern or not.

MATERIALS AND METHODS

Our study was a prospective cross-sectional hospital-based non-interventional one & was carried out in the semi-urban population of South Kolkata (a city of West Bengal, lying within the eastern part of India) and neighbouring areas. The study population consisted of the randomly chosen subjects attending the General OPD of Institute of Post Graduate Medical Education & Research (IPGMER), Kolkata with minor complaints during the period of December, 2017 to November, 2018 and were primarily screened based on a predesigned questionnaire survey. The following strict criteria were applied in selecting the test subjects:

Inclusion criteria:

a) Healthy ambulatory individual.
b) Age between 21- 80 years as per last birthday.
c) Resident of South Kolkata.

Exclusion criteria:

a) Present or past history of thyroid gland disorder.
b) At present acutely ill, or having chronic diseases like diabetes, liver disease, renal failure.
c) History of radiation therapy.
d) Pregnant women.
e) Clinical evidence of infective, inflammatory, or neoplastic diseases.
f) Alteration of one or more laboratory parameters - like Hemoglobin %, FBS, Serum Urea, Serum Creatinine, Liver function test.
g) Presently taking any of these medications-Glucocorticoid, Amiodarone, Carbamazepine, Phenytoin, Aspirin, NSAIDS, Oral contraceptive pills(female candidates), Levothyroxin, Carbimazole, iodine containing drugs.

The questionnaire-based data collection (regarding history of past illness, present illness, medications etc.) was done along with basic clinical examination and routine blood examinations (Hemoglobin concentration, fasting blood sugar, serum urea, serum creatinine, liver function tests), keeping in mind the inclusion and exclusion criteria specified for the study population. Prior informed consent was taken from all the study subjects. Approval (in prescribed format) from the concerned Institutional Ethics committee (IEC) was also obtained before conduction of this study.

Fasting venous blood samples were collected from 550 subjects primarily selected for the study and were analysed for thyroid profile (Serum levels of TSH, free T4, and free T3) using standard commercial enzyme linked immunosorbent assay (ELISA) kits (ELISCAN - manufactured by RFCL Limited, Uttarakhand, India). Reference ranges (for Adult) derived from concerned kit-manufacturer standards were as follows: TSH = 0.39-6.16 μIU/ml; free T4 = 0.8 -2.0 ng/dl and free T3 = 1.4 - 4.2 pg/ml.

Only euthyroids were to be included in the final step of the study and thus 94 (17.09%) individuals were excluded as they were found to be either hypothyroid or hyperthyroid as their serum levels of the said hormones were out of the reference range. Remaining 456 individuals (who were euthyroid and thus found to be fit for the final steps of the study) were stratified into six groups by their age in the following manner.

Group 1: age 21-30 yrs
Group 2: age 31-40 yrs
Group 3: age 41-50 yrs
Group 4: age 51-60 yrs
Group 5: age 61-70 yrs
Group 6: age 71-80 yrs

Each group contains both male and female individuals. The data obtained was then computer-analyzed using 'Prism 5' (Graphpad Software Inc., San Diego, 2012) statistical package for Windows. Calculation & comparison of Mean and Standard Deviation (SD), independent samples t-test, one-way ANOVA test and Pearson's two-tailed correlation study were done (wherever applicable) for the data analysis. The results were of statistical significance when the p-value was less than 0.05.

OBSERVATION AND RESULTS

In this study, a population of total 456 euthyroid subjects (comprising of 231 males and 235 females) within the age-range of 21 to 80 years (with mean 48.64±17.29 years), were selected and stratified into six age-groups (as shown in **Table 1**). Their thyroid profiles were subsequently analyzed and compared as per plan of the study to meet the objectives.

Table 1: Distribution of effective study population according to age group and gender:

Age group	Population		Gender wise population & %			
	Total	%	Male	%	Female	%
21-30 yrs	78	17.11	45	57.7	33	42.3
31-40 yrs	84	18.42	42	50	42	50
41-50 yrs	84	18.42	36	42.8	48	57.2
51-60 yrs	81	17.76	42	51.9	39	48.1
61-70 yrs	69	15.13	36	52.17	33	47.8
71-80 yrs	60	13.16	30	50	30	50
Total	456	100	231	50.65	225	49.35

The mean serum TSH level & mean serum free T3 level significantly varies in different age-groups **(Table 2 & Table 3)**, but the variation of mean serum free T4 level in different age-groups is not statistically significant **(Table 4)**.

Table 2: Distribution of serum TSH (in µIU/ml) according to age-group

Age Group	Mean ± SD	p-value
21- 30 yrs	4.17 ± 0.74	< 0.0001 (significant)
31 – 40 yrs	4.17 ± 0.69	
41 – 50 yrs	4.10 ± 0.72	
51 – 60 yrs	3.4 ± 0.73	
61 – 70 yrs	2.9 ± 0.79	
71 – 80 yrs	1.9 ± 0.74	

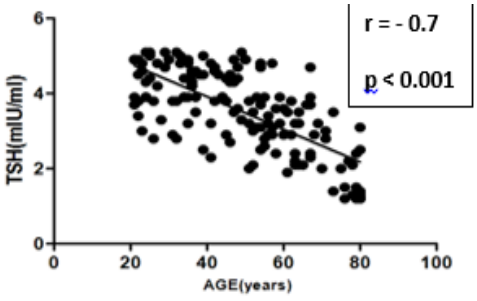

Figure 1: Scatterplot showing correlation of seum TSH Levels with advancing age

There exist a significant negative correlation (r = - 0.7, p<0.001) between serum TSH Level and advancing age (**Fig 1**). Significant negative correlation (r = - 0.8, p <0.001) is also seen between serum free T3 level and advancing age (**Fig 2**), whereas serum free T4 level is found to be negatively correlated (r = - 0.09) with advancing age (**Fig 3**), but it is not significant (p = 0.27).

Table 3: Distribution of serum free T3 (in pg/ml) according to age-group

Age Group	Mean ± SD	p-value
21- 30 yrs	3.62 ± 0.39	< 0.0001 (significant)
31 – 40 yrs	3.15 ± 0.56	
41 – 50 yrs	3.00 ± 0.30	
51 – 60 yrs	2.72 ± 0.44	
61 – 70 yrs	2.24 ± 0.32	
71 – 80 yrs	1.88 ± 0.36	

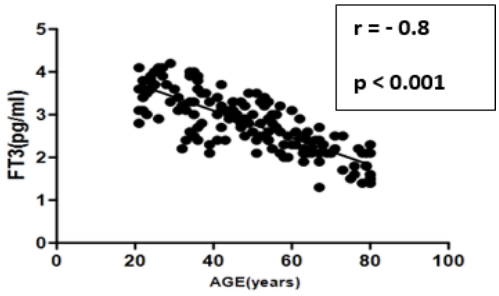

Figure 2: Scatterplot showing correlation of serum free T3 Levels with advancing age

Table 4: Distribution of serum free T4 (in ng/dl) according to age-group:

Age Group	Mean ± SD	p-value
21- 30 yrs	1.57 ± 0.39	0.0201 (significant)
31 – 40 yrs	1.49 ± 0.24	
41 – 50 yrs	1.50 ± 0.24	
51 – 60 yrs	1.43 ± 0.27	
61 – 70 yrs	1.53 ± 0.15	
71 – 80 yrs	1.45 ± 0.27	

Thus in the study-population of clinically healthy euthyroid subjects, it is found that serum TSH level & serum free T3 level gradually decreases along with advancing age, but the variation of serum free T4 level with age shows no such definite trend.

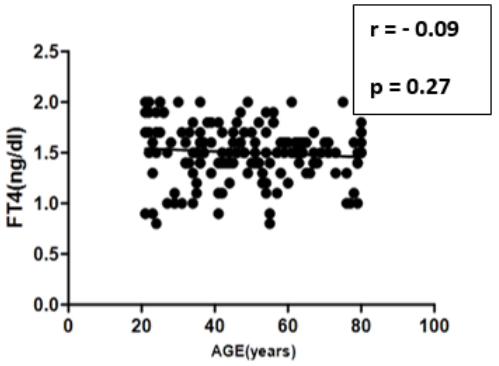

Figure 3: Scatterplot showing correlation of serum free T4 Levels with advancing age

Table 5 shows that although there was no significant variation of age among the male & female population, mean of all three tested parameters of thyroid profile (serum levels of TSH, free T3 & free T4) varied significantly between male & female subjects.

Table 5: Overall Comparison of Age, serum TSH, serum Free T3 & serum Free T4 according to the gender of the study population:

	Male (n = 231)	Female (n = 235)	p-value
	(Mean ±SD)	(Mean±SD)	
Age (years)	48.44±17.94	48.85±16.73	0.799
TSH (µIU/ml)	3.21±1.12	3.88±0.94	<0.001
Free T3 (pg/ml)	2.75±0.72	2.89±0.66	0.029
Free T4 (ng/dl)	1.43±0.29	1.57±0.25	<0.0001

DISCUSSION

This study revealed a progressive decline of serum TSH level and serum free T4 level along with advancing age and such variations in the elderly population when compared to young age-groups was statistically significant. At the same time, the present study shows that although significant change of serum free T4 level occurs with advancing age, there is neither any definite trend of such variation nor any significance in the said correlation. Earlier studies done on similar issue in different geographical locations and on different study populations showed varying results [2, 4,11,13,14].

A highly significant decrease of serum TSH and serum free T3 concentrations were recently found in healthy and ambulatory elderly subjects [15, 16], which supports our finding. The physiological explanation of such reduced levels of TSH with ageing is currently unknown. Whether there is age-related decrease of TSH secretion by the Pituitary [13] or increased sensitivity of the thyrotropes to the negative feedback by free T4 [2] or reduced hypothalamic TRH secretion [4], is still a topic of debate.

Almost unaltered serum free T4 level with ageing and absence of any significant relationship between serum free T4 level with advancing age is found recently [15,17], which largely corroborates our results. The probable explanation of this is age-related decline of Deiodinase enzymes (type 1 & type 2), which is responsible for the conversion of T4 to T3 and for the clearance of the inactive metabolite rT3 [15,2]. It is still unknown whether an increased inner ring deiodination by type 3 Deiodinase enzyme (D3), which would result in an increased clearance of T4 and T3 along with increased production of rT3, also contributes to these changes or not [12].

Our study also showed an overall and significant increase of the mean serum levels of TSH, free T3 and free T4 in females as compared to their age-matched male-counterparts. The gender difference may be due to difference of lean body mass between male and female [8]. Gonadal hormones may also have a significant role for this difference in hormonal level, as it has been observed that the difference between serum FT3 and TSH level in male and females are obvious after 60 years, i.e. after female menopause [18]. Moreover, age-related changes in Pituitary-Thyroid function [2,4] and its probable variation in both sexes [12] should also be taken into account to explain the said findings.

Thus a lot are yet to be answered for proper understanding of these observations, which calls for further studies on this issue. At the same time, certain limitations of this study are worth to be mentioned. To come to a proper conclusion regarding the correlation between thyroid function and advancing age in concerned geographical location, a relatively larger sample size should have been selected including elderly population up to 100 years of age. Also a more detailed screening of the study population and additional estimation of serum rT3 levels would have been instrumental in ruling out the effect of nonthyroidal illness and various drugs on thyroid function.

CONCLUSION

This study suggests the existence of significant alteration of thyroid function with advancing age. The age-associated physiological variations of thyroid profile in both sexes should also be considered while interpreting the results of thyroid function test in the elderly. But this study is not large enough to conclude the normal range of thyroid profile in different age group and sex. Thus a more planned and elaborate study with greater control over the confounding variables should be undertaken to generate stronger evidence for the derived correlations, to explore mechanisms behind the alteration of thyroid profile with age and to set new parameters of normal ranges of thyroid hormone levels in the elderly population.

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