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PJBS

ISSN 1028-8880

Pakistan Journal of Biological Sciences

ANSInet
Asian Network for Scientific Information
308 Lasani Town, Sargodha Road, Faisalabad - Pakistan

Pakistan Journal of Biological Sciences 13 (17): 862-865, 2010
ISSN 1028-8880

The Children Reference Range of Thyroid Hormones in Northern Iran

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Abstract: Hypothyroidism is associated with mental and growth abnormality in children. The aim of this study was to determine the reference range of thyroid stimulating hormone (TSH). Thyroxin (T4) and triodothyronine (T3) of children in Northern Iran. The sample population for this study consists of subjects of 4 age groups up to 21 years. The subjects were selected randomly from people referred to Danesh Medical Diagnostic Laboratory in Gorgan Northern Iran. Thyroid hormone level were investigated with Radio immunoassay. The mean concentration for T4, T3, TSH for the sample population of 4 groups were as follow (113.5, 107.4, 102.9, 99.2 nmol L^{-1}), (1.9, 1.7, 1.9, 1.6 nmol L^{-1}) and (2.1, 3.5, 2.9, 2.7 mIu L^{-1}). The mean value of T3, TSH were higher for females but the mean value of T4 was slightly higher in males. The findings of this investigation indicated that there is an inverse age correlation in particular for T4 in all age groups. On the bases of the results from this study, we conclude that reference range, in all age groups and lower, upper limits of our reference range are not universally similar; therefore determination of reference range in each region is a critical need for clinical practice.

Key words: Children, thyroid hormones, reference range

INTRODUCTION

If the physician want to assess the thyroid function they should do that on the bases of reference range (Zurakowski *et al*., 1999). Reference range in each region should be assayed and established through the population of that areas and even in one country each province should have its own reference intervals due to the epidemiological, nutritional habits ethnicity and socioeconomic climate and various other factors in that region. Also, it should be remembered that there are many factors are responsible for the well being of thyroid function and its ultimate laboratory tests results. The adequate nutritional substances such as iodine due to the requirements of iodine in the structure of thyroxine (T4) and Triidothyronine (T3) and even body mass index are important elements in producing enough thyroid hormones. There are many studies and reviews indicating the iodine requirement for the proper functioning of thyroid gland (Mansourian *et al*., 2007, 2010a). The body mass index and its relation to thyroid function tests among adolescents also was investigated (Eftekhari *et al*., 2007). The other abnormalities is the correlation of thyroid malfunction with many metabolic alteration with catastrophic changes of lethal consequences. There are various studies reporting on the metabolic abnormalities, including free radical generations and cardiovascular damages due to thyroid disorders (Marjani *et al*., 2008; Masourian, 2010b). Not only dietary intake but many other autoimmune diseases such as Graves diseases and Hashimato thyroiditis and even some physiological alterations such as pregnancy cause thyroid abnormalities problems in the routine measurements of thyroid function tests (Mansourian *et al*., 2010; Mansourian, 2010c), which should have been taken into account when the thyroid reference ranges are evaluated. Thyroid function tests provide information about hormone metabolism and thyroid dysfunction. The clinicians enable to evaluate thyroid function tests on the bases of reference intervals (Soldin *et al*., 1997). There has been much interest in using clinic-databases to extract large volumes of patient's data for medical research (Solberg, 1996; Lezzoni, 1997). Databases provide a sufficient number of subjects for evaluating age and gender differences and for establishing age and gender based references intervals.

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The American thyroid association has classified thyrotropin (TSH) as the best single measurement of thyroid status because of high sensitivity (Surks *et al*., 1990) but, in this study, we report health-related reference intervals for serum thyroxine (T4). Triiodothyronine (T3) and Thyroid Stimulating Hormone (TSH) to be used as clinical guidelines for screening patients with suspected thyroid dysfunction in this region. These sample population are age and gender-specific and derived from a population of children and a adolescents referred to the Danesh Medical Diagnostic Laboratory in Gorgan, Northern Iran. The aim of this study was to investigate whether thyroid hormones are age and gender related for the children and adolescents of the South-East Caspian Sea of Northern Iran.

MATERIALS AND METHODS

Test results for T4, T3, TSH obtained retrospectively from outpatient records at Danesh Medical Laboratory Research Center in Gorgan, the Capital city of Golestan Province located in the South-East of Caspian sea of Northern Iran. the sample population including the infants, children and adolescents, during 2008-09. The anonymity of patients data was maintained. The patients names were driven out of the center record system by a test code. The age and thyroid test were recorded and a total of 243 patients were randomly chosen for this study. The hypothyroid and hyperthyroid cases based on standard kit references intervals range, were excluded from this study. The final sample size consisted of 72, 171 males and females respectively. The thyroid hormone measured using Radio Immunoassay technique (Moncayo *et al*., 2005).

Statistical analysis: The ANOVA Fisher test was used to assess the correlation normality of data for each thyroid test among age groups. Linear equation were used to determine reference range the mean value for each intervals. Reference range were determined as the 95% prediction reference intervals closely estimated value related to each mid points. Correlation coefficient was used to assess if there was any correlation within the each age groups. t-test was applied to check for any statistically sex significance correlation between the male and female subject.

RESULTS

The reference interval are presented in Table 1, the mean thyroid hormone concentrations and the number of subjects for each group and gender analyzed for this study was mentioned in the Table 1. The mean value for females and males of TSH, T4 and T3 of presented in Table 2. The ANOVA-Fisher test revealed inverse correlation for T4 with chronological age ($p<0.05$) Mean value for, T4 were shown to be higher for males than female in the same age group except age group of 11-15 years. In this study the mean value for TSH, T3 did not show significant relation with age. No significant gender differences were found for the TSH, T4 and T3. The lower limit of reference interval found in these studies for TSH, T4 and T3 are higher than those already reported, but the higher limits are lower.

Present result are not in agreement with other workers except for T4 which indicate in general that T4 indirectly related with age in all age groups ($p<0.05$). Our findings also indicated that generally the level of T3 and TSH not have any correlation with increasing age ($p>0.05$). Within the each group for the level of T4 there was a meamingful indirect correlation among group 1-5 years ($p<0.05$). In group 6-10 years it is not shown to have a significant correlation but still there is an indirect relation of T4 and age. In groups 3 and 4 there are not any meamingful correlation for age and T4 levels. For T3 there were not any significant differences between the level of T3 and age, but the reversible relation was found among the 6-10 year of age. Mean value for T4 was higher in females for all age groups except for 5-10 years. The mean value for T4 for female and males in groups 1-4 were as follow: 106.60 vs. 122.54, 105.95 vs. 113.37, 107.75 vs. 96.00 and 98.37 vs. 94.40 nmol L^{-1}. Mean value for T3 was higher for female in all age groups except for 5-10 year and were as follow: 1.92 vs. 1.7, 1.48 vs. 2.02, 1.89 vs. 1.84, 3.20 vs. 1.39 nmol L^{-1}. Mean value for TSH in group 1 and 4 was higher in female than male, but in groups 2, 3 the mean value of females was lower in male and were as follow: 2.98 vs. 1.91, 2.77 vs. 3.50, 2.65 vs. 3.93 and 4.62 vs. 2.34 mIu L^{-1} in groups 1-4, respectively. For TSH there were not any significant differences between the level of TSH and age but reversible relation was found among 1-5 years. Our findings indicated that in general there was

Table 1: The reference range intervals of TSH, T4, T3 for <21 years of males and females

Groups	Age (year)	No. of subjects	Mean of TSH (mIu L^{-1})	Reference range intervals TSH (mIu L^{-1})	Mean of T4 (nmol L^{-1})	Reference range intervals T4 (nmol L^{-1})	Mean of T3 (nmol L^{-1})	Reference range intervals T3 n (mol L^{-1})
1	1-5	41	2.14	1.53-2.75	113.50	97.54-129.45	1.86	1.65-2.18
2	6-10	38	3.52	2.85-4.19	107.38	90.16-124.54	1.71	1.27-2.15
3	11-15	39	2.86	2.13-3.59	102.92	95.28-110.56	1.87	1.64-2.10
4	16-21	123	2.73	2.25-3.22	99.21	92.38-106.04	1.65	1.44-1.86

Table 2: Mean value for female and male of TSH T4, T3

Hormone	Gender	No. of subject	Mean
T4	F	170	101.53
	M	72	103.23
T3	F	100	2.59
	M	41	1.67
TSH	F	167	3.73
	M	72	2.84

not any significant differences between the level of TSH, T4, T3 and sexes ($p>0.05$), but within each age group the following results were found: in group 1 the level T4 and T3 did not show ant significant changes with sex but the level TSH is higher in female ($p<0.05$). In group 2 there was not any significant differences among the level of TSH and sexes. In group 3, T4 and T3 did not show significant changes with sexes, but the level TSH was higher in male. In group 4, there was not any significant changes between the level of TSH and sexes.

DISCUSSION

Due to problems of obtaining large number of healthy children in population based study the clinical data are used to establish a reference inference intervals for thyroid function tests, therefore laboratory clinical database contain large stores of clinical data that can be used to establish reference range intervals (Zurakowski *et al*., 1999; Djemli *et al*., 2004).

There are not any study that provide reference range for thyroid hormones levels of TSH, T4, T3 in our region for children and adolescent. The thyroid reference range in this region which routinely are used mostly come from the thyroid hormones kits manufactures references intervals, therefore, this research project was designed to establish the new reference intervals for thyroid hormones for children and adolescents of Gorgan, in the North-East of Iran located in the South-East of Caspian sea. There are various methods and technique for measurement of TSH, T4, T3. In this study the radioimmunoassay method was applied, the Gamma Counter technique was used to detect the hormones level which is a method used in many other studies (Moncayo *et al*., 2007). There are many studies and reports, on the reference ranges in various part of the world using different methods and techniques for the reference intervals of children and adolescents (Demers and Spence, 2003). The sample population in this study were Selected randomly from the people referred to Danesh medical diagnostic Laboratory of Gorgan in Northern Iran and therefore our subjects are not absolutely population based, which can be one of the limitation in this study, to combat it, we did not take into consideration all subjects that on the Standard Laboratory Kits, was labeled either hypothyroid or hyperthyroid subjects. In this study, the lower limit value for TSH, T4, T3 were higher and the higher limit of normal reference interval was lower than other study (Zurakowski *et al*., 1999). In establishing the reference range for any particular population, age, gender, are the main two key factors in the study, therefore our main concern in this research projects was the comparison of the whether hormones levels have direct or indirect correlation with age and sex. In this study, we found that the T4 levels are inversely age-relate, also the reference range for thyroid hormones directly related with various laboratory kits, but the results of this Study can confirm earlier Studies (Zurakowski *et al*., 1999; Djemli *et al*., 2004), that thyroid hormone levels are age related which explain the reason for determination of reference interval in different part of the world. The reference range for the TSH, T4, T3 in this Study, are not Similar to other reports (Zurakowski *et al*., 1999) the findings of thyroid hormones regarding gender Specific reference intervals and also age specific reference intervals are contradictory (Elmlinger *et al*., 2001), but the age and gender play an important role in the determination of reference intervals (Zurakowski *et al*., 1999; Kapelari *et al*., 2008) and it should be taken into consideration. We found in our study that there is a significant inverse-age correlation within our sample population in T4. Age and gender play an important role in the determination of correct reference intervals for any biochemical metabolite as well as for thyroid hormones, therefore the determination of relation between the thyroid hormone and either age or sex is critical for the clinical diagnosis. We found mostly T4 decline with age, but not with gender, which is in agreement partly with other study (Nelson *et al*., 1993; Kapelari *et al*., 2008) although, our data does not confirm a significant correlation between other thyroid hormones and sex but in some age groups the relations were as follow: the mean value T3, TSH were higher for females but the mean value of T4 was slightly higher in males, but it was not significant. The main finding of this study was the inverse correlation between T4 and age which in some part similar with others (Murthy *et al*., 1995). This observation physiologically is explainable due do the approaching adulthood and subsequent increasing level of sex hormone among male subjects and its effect on the metabolism of thyroid hormones (Smallridge, 1995) As general in this present study the mean level T3 and TSH in females was higher. The other disagreement of our findings with some other studies is the level of lower and higher range of reference intervals, which our data indicated generally our lower and higher range of intervals are higher and lower receptivity compared to others (Smallridge, 1995; Kapelari *et al*., 2008).

CONCLUSION

The lower and upper limit of reference interval for thyroid hormones in our study not universally similar with other studies, therefore the establishment of reference interval in one region is a critical need for clinical diagnosis, patients follow-up and management.

ACKNOWLEDGMENT

The authors sincerely thank the Danesh Medical Diagnostic Laboratory Research Center, for providing the data of this Research project.

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