A STUDY OF GOITER AMONG FEMALE ADOLESCENTS REFERRED TO CENTRE FOR NUCLEAR MEDICINE, LAHORE

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ABSTRACT:

Objective: To study goiter and thyroid dysfunction in female adolescents residing in Lahore referred to Centre for Nuclear Medicine (CENUM), Mayo Hospital for thyroid scanning and thyroid function tests.

Design: Retrospective study of thyroid size, thyroid scan patterns and serum FT_4 and TSH levels.

Setting: Centre for Nuclear Medicine (CENUM), Mayo Hospital, Lahore

Patients: 350 female adolescent referred during September 2002 to April 2003.

Main outcome measures: adolescent goiter, thyroid nodules, hyperthyroidism, hypothyroidism, Graves' disease, toxic multinodular goiter.

Results: Among 350 adolescents 212(60.6%) had goiter of various grades mostly visible. Among goiterous patients 136(64.2%) had diffuse and 76 (35.8%) had nodular presentation. The number of patients with solitary nodular goiter (20.7%) was more than multinodular goiter (15.1%) and number of patients with solitary cold nodule (16.5%) was more than functioning nodule (4.2%). The incidence of biochemical thyroid dysfunction, both overt and subclinical, was detected in 42(19.8%) patients and was significantly more frequent in patients with nodular than diffuse presentation (29% VS 14.7%; $p<0.001$) and in multinodular than solitary nodular goiter ($p<0.005$). More than 80% of the patients with solitary nodular goiter were euthyroid. Simple goiter was detected in 116(54.7%), Graves' disease in 5(2.4%) and toxic multinodular goitre in 4(1.9%) patients. Overall incidence of hypothyroidism was more than double as compared to hyperthyroidism. Incidence of nodularity and hypothyroidism was more in large goiter but duration of goiter was not significant in promoting nodularity.

Conclusion: Goiterous adolescents need urgent attention because they don't have just diffuse hypertrophy with normal thyroid function. Many are afflicted with dysfunction and nodularity, particularly solitary cold nodule bearing risk of thyroid malignancy.

KEY WORDS: adolescent goitre, iodine deficiency, thyroid nodules, thyroid dysfunction, iodized salt, thyroid malignancy.

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INTRODUCTION

All forms of thyroid disorders like nontoxic goiter, Graves' disease, Hashimoto's thyroiditis and thyroid neoplasm are more common in females than males[1]. The evidence from community studies is that general testing of the population detects only a few cases of overt thyroid disease and is therefore unjustified except for certain high risk groups[2]. Among females the high risk groups are adolescents, pregnant and lactating women. Puberty is a crucial period of hormonal interactions in a human life cycle[3]. Marked changes in thyroid function occur during puberty as an adaptation to body and sexual development[4]. That is why disorders affecting the thyroid gland are

common in adolescents occurring, according to an estimate, in 3.7% of adolescents between the ages of 11 and 18 years[5]. Thyroid disorders in adolescents may present as goiter, a nodule or a general cluster of abnormal symptoms and physical findings. The etiology and clinical presentation of thyroid disorders in adolescents substantially differ from that in adults[6].

There is a well known geographical dependency in thyroid diseases because of the different amounts of alimentary iodine intake that occur in different geographic locations[7]. Pakistan, a developing country, faces a number of health and nutritional problems. About 50% of the population is at risk of iodine deficiency disorders[8]. Female adolescents need special care as thyroid hormones play its role in the cellular metabolism, growth and development. Thyroid disorders can adversely affect somatic and sexual growth and development during puberty[3]. Early recognition and treatment of these problems can help to minimize their adverse effects. Physicians treating the female adolescents should be aware of the various thyroid problems that their patients can face. There have been a few cross-sectional studies on thyroid hormone profile among adolescent females[9]. This study was planned to find out the prevalence of goiter and biochemical thyroid dysfunctions among female adolescents of Lahore attending Centre for Nuclear Medicine (CENUM), Mayo Hospital for thyroid evaluation. CENUM is one of the major referral centers for thyroid disorders in the city and surrounding areas.

SUBJECTS AND METHODS

Female adolescents (age 10-19 years), newly referred during September 2002 to March 2003 were selected for this study. Those having thyroid surgery, medication or any illness affecting thyroid profile were excluded. Goiterous adolescents without thyroid scan were also excluded. The patients were interviewed by a qualified physician of CENUM regarding necessary information pertaining to thyroid. They underwent clinical assessment, thyroid scanning and determination of thyroid related hormones according to recommendation of referring physician. Each patient history was noted on a Performa. It included age, sex, thyroid size, thyroid age and signs and symptoms associated with thyroid dysfunction. Local examination of thyroid gland included inspection and palpation of the thyroid and neck. Goiter size was graded according to World Health Organization (WHO) criteria[10] (grade 0: absent goitre, grade I: goiter palpable but invisible with the neck in a normal position, grade II: goiter visible with neck in a normal position and grade III: large goiter perceptible at a distance).

Thyroid scanning was carried out by injecting 3 to 5 mCi of $^{99m}TcO_4$. Thyroid scans was acquired on a gamma camera (Toshiba, model GCA-40A) 20 minutes post injection. The thyroid image was obtained on clear base X-ray film and was visually interpreted. A 5ml blood sample was drawn from each patient. Serum was separated by low speed centrifugation (2000x g) for 5 minutes at room temperature. Serum samples were stored at -20C until analysis. FT_4 was estimated by radioimmunoassay (RIA) and TSH was estimated by IRMA techniques, described elsewhere[11] using commercial kits of Immunotech Inc. (Beckman, Czech Republic). Measurement of radioactivity, fitting of the standard curve and analysis of samples was carried out using a computerized gamma counter (Cap-RIA 16, CAPINTEC; Inc. USA). Assay reliability was determined by the use of commercially derived control sera of low, medium and high concentrations which were included in every run. All assays were carried out in duplicate. RIA and IRMA results were expressed at less than 10%CV of imprecision profile. Normal ranges for FT_4 and TSH, as standardized in our laboratory, were 11-22pmol/L and 0.3-4.0 mIU/L respectively.

Final diagnoses were based on scanning features of the thyroid and laboratory studies. A *solitary nodule* was considered if it could be readily distinguished from surrounding thyroid and/or extra thyroidal tissue on a scintigram.

The functional status of a nodule, commonly termed functioning and non-functioning (cold), was established by assessing the amount of radioactivity within the nodule. A goiter was considered *multinodular* when more than one functioning and/or non-functioning (cold) nodules were present in it. *Subclinical hypothyroidism* was diagnosed if serum FT_4 level was normal and serum TSH was elevated(>5.0 mIU/L), whereas *subclinical hyperthyroidism* was diagnosed if low TSH (<0.1mIU/L) level was detected in the presence of normal FT_4 concentration. *Overt hypothyroidism* was diagnosed in patients with low FT_4 (<11.0 pmol/L) and high TSH (>5.0 mIU/L) and *overt hyperthyroidism* by high FT_4 level(>22.0 pmol/L) and low TSH level(<0.1 mIU/L). *Adolescent or simple goiter* was diagnosed in patients with a diffusely enlarged thyroid and normal thyroid function. Graves' disease was suggested by diffuse thyroid enlargement associated with hyperthyroidism with or without ophthalmopathy. A *Toxic multinodular goiter* was the one having a single functioning nodule within an enlarged thyroid that also contained cold nodules to multiple functioning areas scattered throughout the gland with biochemical status of hyperthyroidism.

The analysis of scanning results and thyroid hormones levels distribution was carried out using Microsoft Excel program on a personal computer. Chi-Square test was applied to test the significance of difference between two arbitrary groups. A value of $p<0.05$ was considered significant.

Table-I: Patients age, goiter prevalence and goiter size

Age Group	*Number of Patients*	*Goiterous Patients*	*G I (n)*	*G II (n)*	*G III (n)*
10-15 Years	154	79 (51.3%)	18 (11.7%)	35 (22.7%)	26 (16.9%)
16-19 Years	196	133 (67.9%)[b]	21 (10.7%)	82 (41.8%)[a]	30 (15.4%)
Total	350	212 (60.6%)	39 (11.2 %)	117 (33.4%)	56 (16.0%)

a= p<0.001
b= p<0.005

RESULTS

Three hundred and fifty consecutive female adolescents were studied for this investigation. The average age of patients was 15.6±2.7 years. Goiter of various grades (palpable, visible and large) were observed in 212(60.6%) adolescents whose number according to goiter size was 39(18.4%), 117(55.2%) and 56(26.4%) respectively. To see the effect of patient age on goiter prevalence and size, patients were divided, according to age, into early (10-15 years) and late (16-19 years) adolescents. The number of patients in each group and distribution of goiter size is shown in Table-I. A significant difference was observed in goiter prevalence between early adolescents (51.3%) and late adolescents (67.9% p<0.005). Point prevalence of palpable and large goiter was almost same in both groups. However, small goiter was more prevalent in late adolescents (p<0.001).

Table-II shows the scanning patterns. Diffuse goiter was found in 136(64.2%) patients and 76(35.8%) patients had nodular presentation. Among patients with nodular goiter, 44(20.8%) had solitary nodule (35 cold and 9 functioning) and 32(15.1%) had multinodular goiter. Thus number of patients with solitary cold nodule was more than patients with solitary functioning and multinodular goiter. The percentage of nodular goiter slightly increased from palpable to visible goiter (33.3% to 34.2%) but was significantly more (41.1%; p<0.005) in large goiter among whom more than

Table-II: Scan findings among goiterous adolescents

Goitre Size	*Number of Patients*	*Diffuse Goiter(n)*	*Solitary Nodular Goiter(n)**	*Multi Nodular Goiter(n)*
G I	39	26(66.7%)	13(33.3%) **11**	-
G II	117	77(65.8%)	30(25.6%) **21**	10(08.6%)
G III	56	33(58.9%)	01(01.8%) **01**	22(39.3%)
Total	212	136(64.2%)	44(20.8%) **35**	32(15.1%)

*= Bold figure indicate no. of patients with solitary cold nodular goiter.

two-thirds were multinodular.

Table-III and Table-IV show the relation of goiter size and scan findings respectively with functional status of thyroid. Thyroid dysfunction was detected in 42(19.8%) patients. Among them 13(31%) were hyperthyroid (11 overt and 2 subclinical) and 29(69%) were hypothyroid(16 overt and 13 subclinical). Thus overall incidence of hypothyroidism was more than double as compared to hyperthyroidism. The prevalence of both hyper- and hypothyroidism increased with increase in goiter size. Comparing diffuse and nodular goiters, overall thyroid dysfunction was doubly frequent in nodular than diffuse presentation (22/76 or 29% VS 20/136 or 14.7%). This difference was highly significant for hypothyroidism ($p<0.005$): among 16 overt hypothyroid patients 6 had diffuse and 10 patients had nodular goiter and among 13 patients with subclinical hypothyroidism 9 had diffuse and 4 nodular goiter. Similarly, among 11 overt hyperthyroid patients 5 had diffuse goitre while 6 patients had nodular presentation and 2 patients with subclinical hyperthyroidism had nodular goitre only. Among nodular goiters, thyroid dysfunction was significantly more prevalent in multinodular than solitary nodular goitre ($p<0.005$): among 8 hyperthyroid patients 2 had functional and 6 multinodular goiter and among 14 hypothyroid patients 6 had solitary cold and 8 had multinodular goiter.

Combining both scanning and biochemical results, diffuse goiter with normal thyroid function (simple or adolescent goiter) was detected in 116(54.7%) patients, 5(2.4%) patients had Graves' disease, 4(1.9%) patients had toxic multinodular goiter. More than 80% of the patients with solitary nodular goiter were euthyroid and hypothyroidism was significantly more prevalent in patients with nodular particularly multinodular goiter.

Goiter duration was recorded in 141(66.5%) patients. Table-V shows the relation of goiter duration with size, nodularity and incidence of hypothyroidism. More than half of the patients (54.6%) had recently developed (less than one year) which were mostly palpable and visible (20.8% and 62.3% respectively). Old goiter (age one year or more) was mostly visible and large (56.3% and 39.1% respectively). Prevalence of nodularity and hypothyroidism was same in recently developed and old goiter. However, incidence of subclinical hypothyroidism was more among recent as compared to old goitres.

TABLE-III: Thyroid dysfunction among patients of various goiter grades

Goiter Size	*No. of Patients with Thyroid Dysfunction*	*No. of Hyperthyroid Patients*	*No. of Hyperthyroid Patients*
G I	05(12.8%)	02 (5.1%)	03 (7.7%)
G II	24(20.5%)	07 (6.0%)	17 (14.5%)
G III	13(23.3%)	04 (7.2%)	09 (16.1%)
Total	42(19.8%)	13(6.1%)	29(13.7%)

TABLE -IV: Goiter type (based on scan finding) & biochemical status of adolescents

Goitre Type	*Euthyroid Patients (n)*	*Hyperthyroid Patients (n)*	*Hypothyroid Patients (n)*
Diffuse	116(85.3%)	05(3.7%)	15(11.0%)
Nodular	54(71.1%)	08(10.5%)	14(18.4%)
Cold	29	00	06
Functional	07	02	00
Multinodular	18	06	08

TABLE-V: Relation of goiter duration with size, nodularity and hypothyroidism

Goiter Duration	*Number of Patients*	*G I (n)*	*G II (n)*	*G III (n)*	*Nodularity (%)*	*Hypothyroid Patients(n)**
< 01 Years	77	16 (20.8%)	48 (62.3%)	13 (16.9%)	32 (41.6%)	13[8] (16.9%)
>01 Years	64	3 (4.7%)[a]	36 (56.2%)	25 (39.1%)[a]	27 (42.2%)	12[2] (18.8%)

a= $p<0.001$

*= Number in bracket shows patients with subclinical hypothyroidism.

DISCUSSION

The higher prevalence of goiter (60.6%) among our study patients was because of the patient selection method. They were all referred patients suspected of having thyroid abnormalities. However, high prevalence of goiter among adolescents is not surprising. Studies conducted in two large cities of India have reported a 40% and 56% incidence of goiter among adolescents[12,13]. Similarly, in northern western part of Tunisia, 49.5% adolescents had goiter[14].

Minimal diffuse enlargement of the thyroid gland is found in many teenage boys and girls and is almost a physiological response to the complex structural and hormonal changes occurring at that time[3-5]. It usually regress[1] but occasionally it may persist, enlarge and become nodular depending on many factors like sex, family history, iodine intake and thyroid autoimmunity[3,4,12-15]. Low iodine intake enhances the TSH sensitivity and positive influence of growth factors involved in the physiological regulation of thyroid growth. The outcome of such stimulation may be substantial in girls with mild iodine deficiency leading to the development of goiter during mid to late puberty[4]. According to a recently conducted study mild iodine deficiency is prevalent in Lahore[11]. It seems a major reason of goitrogenesis in our patients might be the limited amount of iodine available in food and goiter was a physiological event by which the thyroid gland had adapted to an insufficient iodine supply. However, an adolescent goiter in such an environment should generally be a diffuse one with normal thyroid function but our results showed that only 55% of the adolescents had such goiters while nodularity and hypothyroidism was detected in a number of patients (35% and 13.7% respectively).

Epidemiological studies has shown that pattern of thyroid dysfunction in a community is largely determined by iodine intake level[7]. In iodine deficient communities incidence of hypothyroidism is low while nontoxic goiter and hyperthyroidism due to toxic nodular goiter is common and increases with age. On the other hand, in iodine sufficient areas thyroid autoimmune diseases like Graves' disease and Hashimoto's thyroditis are common reason of thyroid enlargement and etiologic factors for hyperthyroid and hypothyroid presentation respectively among children and adolescents[3,13,14]. In areas where iodine deficiency is severe they are of limited importance in the development of goiter[16]. The lower incidence of hyperthyroidism due to Grave's disease among our patients (2.4%) confirms the low iodine intake status of our patients but low incidence of toxic nodular goitre (1.9%) is not consistent to this. Similarly, prolonged TSH stimulation as a reason for increased nodularity[8,17] is not in agreement with our data (Table-V) according to which older goiters had not significantly more incidence of nodularity as compared to recent ones. This shows other factors like autoimmunity and family hitory were also operative in this malady.

Higher incidence of hypothyroidism particularly subclinical hypothyroidism[15] in recently developed goiter points towards a definite role of thyroid autoimmunity in goitrogenesis and nodularity among our patients. This assumption is in accordance to a study according to which 19.5% of goiterous adolescents are thyroid antibody positive in Lahore[9]. A potential reason for thyroid autoimmunity may be the consumption of excess iodized salt as a therapy to regress goiter. Iodized salt is being promoted and marketed in the country since a decade[8,18] and according to a report 26% marketed samples contain excess iodine[19]. In previously iodine-deficient populations where iodized salt was introduced to combat iodine deficiency autoimmune thyroditis and thyroid antibodies had been detected in a number of goiterous adolescents[7,13,20,21]. According to recent national nutritional survey, 56.4 percent households are aware of iodized salt benefits[22]. So in a self medicated culture of our society, it can be suspected that iodized salt was used by a number of our patients as a first line therapy to cure goiter and its excess use may have resulted in increased nodularity and autoim-

mune hypothyroidism. However, this conclusion needs confirmation.

Thyroid nodules, although common in general population (5-7%)[23], but less so in children or adolescents[24,25]. If present, however, the likelihood of malignancy is increased. Iodine deficiency, thyroid autoimmunity, infection and previous irradiation are the common etiological factors of nodules[24]. The incidence of malignancy in solitary thyroid nodule is approximately 5 percent[23]. According to a study 25.5% cold nodules in children and adolescents were found malignant[25]. Large cold nodule is particularly associated with malignancy. The incidence of cold nodule among our female adolescents was 16.5%. Among those, two-third had developed to a visible size at the time of presentation (Table II). This higher incidence and large size of cold nodules is alarming. The prevalence of thyroid cancer is three times more in female than in male and 80% of thyroid cancers are of papillary type[9]. According to a local study based on Fine Needle Aspiration Cytology (FNAC) of thyroid nodules, the incidence of papillary carcinoma was 57.1 percent[26] which is the commonest thyroid cancer in childhood and adolescent age group[1,3,9].

This study, although not carried out on general adolescent population of the city, bear certain implications. First, adolescents with nodular goiter harboring cold nodule are at risk of thyroid cancer which need immediate attention. Second, goiterous adolescents need follow up because requirement of iodine increases during pregnancy and its deficiency during gestation causes a lot of reproductive complications[28]. Third, magnitude of iodine deficiency warrants urgent quantification in the country because it varies from place to place[8] and iodine content in iodized salt should be according to its need in a particular area. Moreover, physician should educate the patients that iodized salt is not a medicine to cure goiter but is a preventive measure to avoid its deficiency. Patients should be prohibited from using iodized salt when goiter becomes enlarged or nodular because it promotes further nodularity[27].

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