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TREND OF THYROID DYSFUNCTION ASSOCIATED WITH VISIBLE GOITER

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Summary: This study was conducted with a view to evaluate the association of goiter size with thyroid disorders in females of reproductive age (20-45 years) residing in Lahore, a mild iodine deficient area. The thyroid gland was scanned and FT4, FT3, and TSH were determined in 1614 goiterous women attending Centre for Nuclear Medicine (CENUM) located inside Mayo Hospital during the year 2006. Among studied patients 866 (53.7%) had palpable and remaining 748 had visible goiter. Visible goitrous patients were mostly nodular (63.0%) and rest had diffuse enlargement. Low iodine deficiency, repeated pregnancies and late presentation may be the reasons of high prevalence of goiter and nodularity in these women. A comparative data of thyroid dysfunction in palpable and visible goiterous patients showed hyperthyroidism was most common thyroid dysfunction in visible than palpable goiterous patients (10.4% Vs 2.6%; $p<0.05$). Its incidence increased in parallel to goiter size. In contrast incidence of hypothyroidism, decreased in patients with large goiter although this decrease was not significant. Besides high nodularity in visible goitrous patients, incidence of hyperthyroidism was significantly higher in patients with diffuse goiter (17.3% Vs 6.4%; $p<0.05$). Overall thyroid dysfunction was significantly more prevalent in goiterous women as compared to women with normal thyroid size (24.8% Vs 19%; $p<0.05$). Comparison of mean values of FT4, FT3, and TSH in euthyroid patients with diffuse visible and palpable goiter showed only a significant difference in TSH levels. However the role of other factors like family history, thyroid autoimmunity and use of iodized salt need elucidation in these women.

KEYWORDS: Visible Goiter, Thyroid disorders, Thyroid Hormones, Hypothyroidism, Hyperthyroidism.

Introduction

Thyroid is an important endocrine gland in human body. The main function of the thyroid gland is to synthesize thyroid hormones which are essential for the regulation of metabolic processes throughout the body. Thyroid hormone plays its role in cellular metabolism, growth and development. They act through specific receptors to selectively regulate the gene expression in target tissues, particularly liver, muscles and developing brain. Iodine is the essential component of the thyroid hormone-T4 and T3. The recommended amount of dietary iodine is 150ug/day for adults. The iodine deficiency disorders include goiter, hyperthyroidism, hypothyroidism,

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mental retardation, reproductive impairment and decrease child survival (Dunn 1998).

Among all clinical thyroid disorders goiter is the most visible and important. Goiter is a slowly developing diffuse or nodular enlargement of thyroid gland due to an excessive replication of follicular epithelium with subsequent generation of new follicles of widely differing structure and function. It may result from hormonal and immunological stimulation of gland growth or the presence of inflammatory, proliferative and metabolic disorders (Langer 1999). In an iodine deficiency community prevalence of goiter increases progressively up to 20-30 years. The morphological condition of goiter indicates that iodine deficiency is the ultimate cause of its formation. In biochemical perspective during iodine deficiency the production of T3 is increased while that of T4 is decreased. It is an adaptive way to compensate the actual iodine deficiency. So an overall picture of a goiterous patient of iodine deficient area is increase in plasma TSH level and decrease in FT4 with an overall increase in T3. If T3 increased from reference range then it leads towards hyperthyroidism. However if the deficiency of iodine is continued even after goiter formation then it leads towards the decrease in plasma T3 and causes hypothyroidism. It is observed that the first functional consequence of iodine deficiency is an increase in the uptake of iodine by the thyroid on supplementations. To increase the iodide trapping the thyroid must have greater vasscularization by increasing number of cells. This process is enhanced by the increasing level of plasma TSH. However the sensitivity of thyroid gland for TSH is much more important than the increased plasma TSH level.

Pakistan is an iodine deficient country. Typical Pakistani diet contains low iodine content (40 μg/day) which is 3.8 times lower than recommended (150 μg/day) for adult subject (Fatima et al., 2002). Three percent of the population has some grade of goiter. Goiter is much more common in females of reproductive age as the women of reproductive age experiences more physiological, hormonal and nutritional stress in Pakistan (UNICEF 2001). Keeping these facts in view, this cross sectional study is planned to investigate the relation of goiter size and thyroid dysfunction in females of reproductive age (20-45) attending CENUM located inside Mayo Hospital. To compare the different biochemical thyroid dysfunction associated with goiter of various sizes in referred women of age 20-45 year.

Material and Methods

Records of goitrous women of reproductive age (20-45y), residing in Lahore and referred to CENUM during the calendar year 2005 were reviewed. Patients having thyroid surgery or taking thyroid medication were excluded. Goiter size was determined by the Tc-^{99} scanning that was carried out by injecting 3 to 5 mCi of $^{99}TcO_4$. Thyroid scans was acquired on a gamma camera (Toshiba, model GCA-40A) 20 minutes post injection. A 5ml blood sample was drawn for each patient and serum was separated by low-speed centrifugation (2000×g) for 5 minutes at room temperature. Serum samples, stored at minus 20°C, were analyzed for FT4, FT3 and TSH. FT4 and FT3 were estimated by radioimmunoassay (RIA) and TSH was estimated by IRMA techniques 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 percent coefficient of variation (CV) of imprecision profile. The analysis of FT4, FT3 and TSH levels distribution was carried out using SPSS program (SPSS Inc., Chicago, IL) on a computer. Patients were categorized as normal (euthyroid), hyperthyroid or hypothyroid according to normal ranges for FT4, FT3 and TSH standardized at CENUM. Hyperthyroidism was diagnosed if serum TSH was < 0.1 mIU/L and FT4 > 22 pmol/L. Hypothyroidism was considered if serum TSH was > 4.0 mIU/L and FT4 < 8.0 pmol/L (Hoogendoorn et al 2006). Chi-Square test was applied to know the significance of difference between proportions in arbitrary groups. A value of $p<0.05$ was considered significant.

Results

We consecutively selected 1614 goiterous women of **reproductive age** from our data base. Their age range was aged 20-45 years (average 30.8 $\pm$ 7.7 years). Among them 866 (53.7%) had palpable and remaining (n= 748) had visible goiter. Goiterous patients were selected according to goiter size based on WHO classification (WHO 2001). Among visible goiterous patients more than 60% had nodular and rest had diffuse enlargement. Mean age of palpable and visible goiterous patients was almost same.

A comparative data of thyroid dysfunction in palpable and visible goiterous patients is shown in Table 1.

Table 1: Thyroid Dysfunction in Patients with Visible and Palpable Goiter*

Group	No. of Patients	Hyperthyroidism N (%)	Hypothyroidism N (%)
Visible Goiter (G2)	748	78[a] (10.4%)	23 (3.1%)
Palpable Goiter (G1)	866	23[b] (2.6%)	42 (4.8%)

* WHO 2001

Hyperthyroidism was more frequent in visible than palpable goiterous patients (10.4 % Vs 2.6%; $p<0.05$). In contrast to this no significant difference was detected in incidence of hypothyroidism in both groups of patients (3.1% Vs 4.8%; p=NS).

Among visible goiterous patients more than 60% patients had nodular enlargement. Table 2 shows the incidence of hyper- and hypothyroidism in diffuse and nodular visible goiterous patients. Incidence of hyperthyroidism was significantly higher in diffuse as compared to nodular goiterous patients (17.3% Vs 6.4%; $p<0.05$). However, there was no significant difference in

Table 2: Thyroid Dysfunction in Patients with Diffuse and Nodular Visible Goiter*

Goiter Size	No. of Patients	Hyperthyroidism N (%)	Hypothyroidism N (%)
Diffuse	277 (37.0%)	48[a] (17.3%)	12 (4.3 %)
Nodular	471 (63.0%)	30[b] (6.4 %)	11 (2.3 %)

Table 3: Thyroid Hormone concentrations in euthyroid Patients

Euthyroid Group	No. of Patients	FT4 (pmol/L)	FT3 (pmol/L)	TSH (mIU/L)
Visible Goiter (Diffuse)	186	15.0 ± 3.2	3.0 ± 0.9	1.5 [a] ± 0.8
Palpable Goiter	716	15.2 ± 3.0	3.0 ± 1.0	1.7 [b] ± 0.9

incidence of hypothyroidism among diffuse and nodular visible goiterous patients.

Discussion

The aim of this study was to know the trends associated with goiter size for biochemical thyroid dysfunction in goiterous female of reproductive age (20-45 year). The occurrence of goiter and thyroid diseases is determined by interplay between genetic, environmental and gender factors. The major environmental factor that determines goiter prevalence is iodine intake status (Hershman et al 1983, Supawan et al 1993, Osman et al 1995) while higher prevalence of goiter among female is attributed to proliferative effects of estrogens on thyrocytes (Knudsen et al 2002). In women of reproductive age pregnancy is not only a hyper estrogenic physiological condition but also increases the iodine requirement that is important for fetus brain development. In regions where iodine intake is inadequate pregnancy accentuates iodine deficiency which is a probable cause for the higher prevalence of goiter and thyroid nodules in women with previous pregnancies (Struve et al 1993). Knudsen et al (2002) found a higher thyroid volume among parous than among nulliparous women (P=0.007). The association between parity and thyroid volume was strongest in the youngest age groups and in the region with the most severe iodine deficiency. Pregnancy increases thyroid volume, particularly when combined with iodine deficiency. In a Recent study most of the women of reproductive age in Lahore were found having low iodine intake (Fatima 2003) which combined with high birth rate might have contributed to such a higher prevalence of goiter in them.

According to our results development of visible goiter was associated with increased incidence of thyroid dysfunction particularly hyperthyroidism. This increase in incidence of hyperthyroidism was independent of nodular formation. It seems that there was severe thyroid failure in women, so their thyroid gland could not simply adapt to the changes induced by pregnancy and had lost the ability to compensate for the iodine deficiency and became hypothyroid easily. The degree of nodularity is markedly increased in large goiters and gives rise to thyroid autonomy during longstanding insufficient iodine intake (Hoogendoorn et al 2006). Table 3 shows the concentration of thyroid related hormone in diffuse visible and palpable goiterous women. Compared to palpable goiterous women serum TSH was significantly decreased in diffuse visible goiterous women. This observation is in accordance to other studies (Bregengard et al 1987, Roti et al 1986). However elevated production rate of T3 was not observed in diffuse goiter patients as reported Bregengard et al (1987).

TSH secretion in the goiterous patients is more closely related to serum FT_3 levels than to serum FT_4 levels. The occurrence of goiter is not directly related to TSH

stimulation in mild iodine deficient area where maintenance of diffuse hyperplasia is independent of TSH level (Hu et al 2003). In reproductive age women higher incidence of hypothyroidism along with lower TSH level points to the role of gestational factors that might have contributed in development of autoimmunity (Wilder 1998; Muller et al 2001). So, our results provide a support for the concept of functional autonomy of the thyroid accounting for the finding of low serum TSH in patients with large goiters (Bachtarzi et al 1983, Fenzi et al 1985). Thyroid function is reported autonomous in nodular goiters (Toft et al 1976) but the concept of progressive autonomy of thyroid function related to increasing thyroid volume is supported as reported by Breghout et al (1990).

In summary, thyroid gland undergoes severe stress during pregnancy in women residing in areas with moderate to severe deficiency (Glinoer 1997). Goiterous female of reproductive age in Lahore had high prevalence of hyperthyroidism. Increased goiter size is related to further increase in autonomous functioning and/or nodularity that may be due to a long standing iodine deficiency and/or late presentation of patients. Role of family history and use of iodized salt in development of thyroid dysfunction in goiterous women of reproductive age needs further investigation. Keeping in view these facts, early diagnosis and preventing measures are urgently required in this age group of females.

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