ORIGINAL ARTICLE

A Study of Thyroid Profile in Patients with Benign Breast Disease

*A Faruq[1], MNA Alam[2], F Afsana[3], M Haque[4]

ABSTRACT

Background: To observe the association between thyroid dysfunction and benign breast disease.

Methods: Prospective observational study conducted in the surgical outpatient department on female patients with benign breast disease from April 2017 to April 2018.

Results: Among the 208 female subjects included in the study 14.9% had hypothyroidism and 87.5% were completely symptom free when treated with Thyroxin replacement. Serum Prolactin level was also measured in all the subjects and hyperprolactinemia found in 4.8% with 50% associated with hypothyroidism.

Conclusion: Thyroid profile may serve as a useful investigation in the treatment of patients with benign breast disease.

Key Words: benign breast disease (BBD), hypothyroidism, hyperprolactinemia.

Introduction

A fairly large group of female patients attend outpatient department of hospitals with breast related complains, with an array from mastalgia, nipple discharge, lumpiness or definite lump. Whether this significant increase in patients can be attributed to awareness or cancer phobia or actual increase in breast disorders is yet to be evaluated. However this study was aimed to investigate whether thyroid hormone status had any relation to benign breast disorders. Few recent studies have suggested that there is a relation between carcinoma breast and hypothyroidism,[1] but that with benign breast disease has not been established.

Therefore

The objective of this study was to investigate patients with benign breast disease and

- Evaluate the percentage of thyroid dysfunction in patients with benign breast disease.
- See if Thyroxin replacement in hypothyroid patients had any impact on symptoms of benign breast disease.
- Observe if age has a relevance in the hormone levels and benign breast disease.

Materials and Methods

This is a prospective observational study conducted on patients attending outpatient department of Surgery (breast clinic) of BIRDEM General Hospital from April 2017 to April 2018 (one year).

Inclusion criteria

1. All patients with benign breast disease and with

[1]*Dr. Amreen Faruq, Assistant Professor, Department of Surgery, BIRDEM General Hospital, Shahbagh, Dhaka e-mail- dramreen78@yahoo.com

[2]Dr. MNA Alam, Department of Surgery, BIRDEM General Hospital, Shahbagh, Dhaka

[3]Dr. F Afsana, Department of Endocrinology, BIRDEM General Hospital, Shahbagh, Dhaka

[4]Dr. M Haque, Department of Surgery, BIRDEM General Hospital, Shahbagh, Dhaka

*Corresponding Author

Date of submission: 08.04.2019 Date of acceptance: 27.04.2019

no indications for surgery

Exclusion criteria

1. Patients with breast lumps benign or malignant.
2. Patients with breast abscess.
3. Patients with blood stained nipple discharge.
4. Patients with suspicious lesion on mammography or cytology requiring core or open biopsy.
5. Pregnant females.
6. Patients on oral contraceptives, ovulation induction, hormone replacement therapy.
7. Patients already on Thyroxine supplementation.
8. Patients on antipsychotic and antidepressant drugs.

All patients were evaluated with thorough history, clinical examination, and required investigations. In history patients were asked to grade there mastalgia in mild (occasional), moderate (tolerable/frequent), severe (disturbs daily activities). Whether nipple discharge was present or not and when presented the colour and amount of the discharge. Bilateral breast palpation was done for tenderness, lumpiness, nodularity, or definite lump. Investigations, ultrasound of both breasts was done in all patients below 45 years of age, and ultrasound and mammography in patients above 45 years. Any patient detected with SOL of breast on ultrasound or mammography but not clinically palpable, was also excluded from the study.

Thyroid profile- TSH, FT4 and FT3 were done in all patients. Thyroid antibodies and thyroid ultrasound done in patients with altered hormones. The normal reference range from our laboratories was as follows TSH adult 0.47-5.01 uIU/ml, FT4 9.14-23.18 pmol/L. Serum Prolactin level (PRL) was also estimated. (Normal value-non pregnant female: 59.0-619.0 mIU/L and postmenopausal female: 38.0-430.0 mIU/L).

Hypothyroidism was defined as TSH level above the defined upper limit of reference range. Patients with normal FT4 level but high TSH were considered subclinical hypothyroidism and those with FT4 below normal and high TSH as overt hypothyroidism. In patients found to be hypothyroid ultrasound of neck and thyroid antibodies were also done. All patients with altered hormone levels were sent for endocrine consultation. Thyroxin replacement given according to consultation and patients were assessed after 6 weeks. These patients were followed up along with endocrine department by estimation of TSH level to achieve optimum dose level and to make them euthyroid. The patients were reassessed for breast symptoms after receiving Thyroxin replacement. If still symptomatic, they were given conservative management as the other patients with normal hormone levels. Patients were given analgesics (NSAID) for pain, Primrose oil and/or Vitamin E and if there was no improvement of symptoms Danazole (100) was given. Patients with hyperprolactinaemia with or without nipple discharge were also evaluated with endocrine consultation. All patients were followed up initially, monthly and then 3 monthly.

Statistical analysis: All data were entered into Office Microsoft Excel 2016. Data analysis was performed by Statistical Package for the Social Science (SPSS) version.[21] To explore the crude correlation of age, TSH, FT4 and Prolactin, pair scatter plot was done. We performed Pearson correlation test to explore the significance of the correlation. We categorized the age of the positive cases into two groups upto 40 years of age and another above 40 years. We executed independent sample t test to examine the relationship between TSH, FT4, Prolactin and age category.

Results

The total number of patients attending the outpatient department with breast disease in the mentioned time duration were 336 females. 66 malignant and 39 benign breast lumps, 10 patients with breast abscess demanding surgical management. 5 patients presented with blood stained nipple discharge +/- lump, suspicious lesion on mammography or cytology requiring core or open biopsy. 8 patients were already on Thyroxine replacement so they were excluded from the study. The study was carried out on 208 female patients with benign breast disease.

Number of patients-208

Age range 21-52 years

Patient's menstrual status- Premenopausal: 198 (95 %)
Postmenopausal: 6 (3%)
Surgical menopause: 4 (2%)

Clinical Presentation

1. Mastalgia- total 140 (67.30%), 10 hypothyroid
   Cyclical- 43
   Non cyclical-97
2. Mastalgia + nipple discharge- 46 (22.11%); 13 hypothyroid
3. Nipple discharge- 13 (6.25%); 8 hypothyroid
4. Lumpiness +/- mastalgia- 9 (4.32%)

Thyroid Status

Hypothyroidism- 31 (14.9%)

Of the 31 cases with hypothyroidism

0vert- 12 (38.7%)

Subclinical -19 (61.3%)

Serum prolactin level

Serum Prolactin level raised in 10 females (4.8%)

Hyperprolactinemia with overt hypothyroidism - 5 (50%)

Hyperprolactinemia without hypothyroidism -5 (50%)

Treatment

Thyroxine given according to endocrine consultation to 16 patients (12 with overt hypothyroidism 2 subclinical with thyroid antibodies positive and 2 with history of weight gain, menstrual abnormality and infertility).

14 patients (87.5%) were completely symptom free with Thyroxine replacement only.

2 (12.5%) patients needed Evening Primrose oil and Paracetamol with Thyroxin

Bromocriptin was given to 4 patient out of 5 patients with raised Prolactin level without associated Hypothyroidism and Serum Prolactin level monitored according to endocrine consultation. None of the patients with both Hyperprolactinemia and Hypothyroidism were given Bromocriptin. They were given Thyroxine only and Serum Prolactin measured.

Descriptive Analysis

The mean age of the total population was 36.36 (Standard Deviation (SD): 8.18). The mean level of TSH, FT4 and Prolactin were 4.02 SD:3.15 , 9.88 SD:2.13 and 352.62 SD 251.63 respectively. (Table-1)

Table-1: Descriptive analysis for all patients

Variables name	Mean±SD	Minimum	Maximum
Age	36.36±8.18	22	52
TSH	4.02±3.15	1.11	18.32
FT4	9.88±2.13	2.06	21.06
Prolactin	352.62±251.63	62	2253

Considering the positive cases (n=31), the mean age is 38.29 (SD: 9.00). The mean of TSH, FT4 and Prolactin was 10.76 (SD: 3.28), 7.80 (SD: 2.76) and 609.45 (SD: 538.40) respectively. Prolactin had very high range (minimum 72 and maximum 2253) (Table 2).

Table-2: Descriptive analysis (Hypothyroid patients n=31)

Variables name	Mean±SD	Minimum	Maximum
Age	38.29±9.00	22	52
TSH	10.76±3.28	5.85	18.32
FT4	7.80±2.76	2.06	10.69
Prolactin	609.45±538.40	72	2253

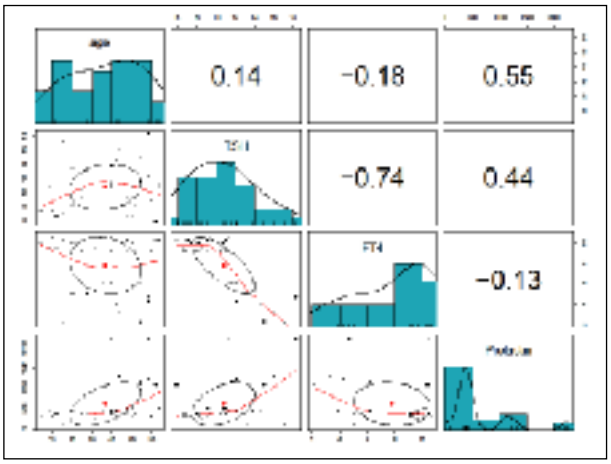

Figure 1:

Pair scatter plot between age, TSH, FT4 and Prolactin

Figure 1 illustrates the crude correlation between THS, FT4 and Prolactin.

Table-3: Pearson Correlation test

Correlations					
		age	**TSH**	**FT4**	**Prolactin**
age	Pearson Correlation	1	.157	-.141	.465**
	Sig. (2-tailed)		.398	.449	.008
	N	31	31	31	31
TSH	Pearson Correlation	.157	1	-.847**	.393*
	Sig. (2-tailed)	.398		.000	.029
	N	31	31	31	31
FT4	Pearson Correlation	-.141	-.847**	1	-.211
	Sig. (2-tailed)	.449	.000		.254
	N	31	31	31	31
Prolactin	Pearson Correlation	.465**	.393*	-.211	1
	Sig. (2-tailed)	.008	.029	.254	
	N	31	31	31	31

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

Table 3 describes the results of Pearson correlation test. The correlation between age and TSH was positive but not statistically significant ($r=0.157$, $p>0.05$). On the other hand, the correlation between age and FT4 is negative and non-significant ($r=-0.141$, $p>0.05$). However, the correlation between age and Prolactin is positive and statistically significant ($r=0.465$, $p<0.05$).

We also compared the mean of TSH, FT4 and Prolactin according to age category (describe it into methods before 40 and after 40 years of age) by Independent sample T test. TSH ($t=-0.878$, $p>0.05$) and FT4 ($t=0.601$, $p>0.05$) are not significant whereas Prolactin ($t=-3.14$, $p<0.05$) (Table 4). The result suggests that age has significant role in Prolactin hormone secretion.

Table 4: Result of Independent sample t test

Independent Samples Test									
		Levene's Test for Equality of Variances	t-test for Equality of Means						
		Sig.	**t**	**df**	**Sig. (2-tailed)**	**Mean Difference**	**Std. Error Difference**	**95% Confidence Interval of the Difference**	
								Lower	Upper
TSH	Equal variances assumed	.660	-.878	29	.387	-1.04462	1.18946	-3.47733	1.38809
	Equal variances not assumed		-.891	28.925	.380	-1.04462	1.17186	-3.44162	1.35237
FT4	Equal variances assumed	.538	.601	29	.553	.60685	1.00989	-1.45860	2.67230
	Equal variances not assumed		.605	28.437	.550	.60685	1.00379	-1.44791	2.66161
Prolactin	Equal variances assumed	.000	-3.140	29	.004	-536.15966	170.72489	-885.33126	-186.98807
	Equal variances not assumed		-3.449	17.283	.003	-536.15966	155.46227	-863.74745	-208.57188

Discussion

Thyroid dysfunction has been established as a cause of infertility or repeated abortions in female[2] but whether it has a roll in breast pathology is under evaluation. Breast development and maturation is under the master control of hormones such as estrogen, progesterone, growth hormone, pituitary hormones, insulin and thyroid hormones. Benign breast disease (ANDI) is considered as aberration in normal development and involution of breasts, therefore any abnormality in these hormone levels can lead to this aberration. Keeping this in mind we proceeded with our study. Among the different hormones taking part in the development of normal breast tissue thyroid hormones stimulate lobular development, contributing to the differentiation of normal breast tissue.[3] FT3 plays an important role in the normal development of the ductal system and alveolar budding.[4] Since thyroid hormones have an important role in normal development of breast tissue abnormalities in normal levels of this hormone may be a causal factor for the benign breast disease (BBD). It may also play an important role in maintaining breast health as we have seen in our study that hypothyroidism developing in patients in later age group (after 40 years) also presents with fibrocystic disease. It has also been established that thyroid hormones by causing differentiation of epithelial cells antagonizes the proliferative effect of estrogen and mitotic growth factors in the development of breast carcinoma.[5,6] Malignant

breast disease have also been linked with autoimmune thyroid disease and thyroid cancer.[7,8]

In our study 14.9% of cases had Hypothyroidism 12 overt and 19 subclinical although it is difficult to comment with such a small sample size but this may serve as a pilot for future evaluation. In our patients with hypothyroidism and benign breast disease Thyroxine replacement was the only treatment required in 14(87.5%) patients and they were symptom free so this finding may also be taken into consideration that patients with hypothyroidism and benign breast disease may only require treatment for hypothyroidism to treat breast symptoms.

Anil C, Guney T and Gursoy A, confirmed the co-occurrence of benign breast disease and thyroid pathology from a different perspective by studying prevalence of benign breast disease in patients with nodular goiter and Hashimoto's thyroiditis.[9] Sidoni A, Fama F *et al.* found in their study the 6.7% of women referred for thyroid ultrasound had also undergone mammary ultrasound had breast lesions detected which were cystic in 2/3 patients and solid in 1/3 patients.[10] However the exact biological connection between breast disease and thyroid disease is still unclear. The pathogenicity of BBD has also been accepted to be associated with increased estrogenicity due to decreased luteal P secretion and thyroid hormones antagonizes effect of estrogen.[11] In our study prolactin level was also seen in patients with or without nipple discharge. Prolactin level was raised in 10 patients of 208 subjects. 50% of the whom had associated hypothyroidism. Hyperprolactinaemia is not seen in all patients with hypothyroidism but has been reported to occur. Thyroid releasing hormone (TRH) in addition to increasing TSH causes a rise in Prolactin level and studies have shown the TRH induced PRL responses in BBD.[12] However, our sample size was very small to comment with statistical significance but we wish to pursue the study in future.

A study by Hekimsoy Z, Kafesciler S *et al.* found statistically significant elevation of PRL in patients with overt hypothyroidism and subclinical hypothyroidism.[13] The levels of PRL descended to normal after thyroid function normalized with treatment with L-thyroxin. Our patients with hypothyroidism and hyperprolactinemia also had normal levels of serum Prolactin on follow up after treatment of hypothyroidism. Several mechanisms have been proposed. Elevated levels of Prolactin can be attributed to increased PRL secretion under influence of TRH which stimulates TSH as well.[13,14,15,16,17] Second Prolactin clearance may be decreased in hypothyroid patients.[14,18] Thyroid hormone itself may play a role in causing hyperprolactinemia.[19] Davis et al concluded in their study that decreased circulating thyroid hormone result in increase prolactin synthesis by demonstrating that 3,5,3 triodiothyroxin decrease prolactin messenger RNA levels in rodent pituitary cells.

It is expected that with increasing age the prevalence of subclinical or overt hypothyroidism will be increased.[20] However, in our study the changes in hormone level with age for TSH and Prolactin are difficult to comment in level of significance considering study population.

Limitations

Sample was small and done over a short period of time. Other confounding factors such as BMI, Estogen levels, diabetes mellitus etc were not taken into consideration.

Conclusion

This study has provided a platform to address a number of factors relating to benign breast disease. Evaluating the thyroid status of patients with BBD can at times provide early diagnosis and treatment of symptoms. Hypothyroidism and hyperprolactinaemia may be responsible aetiological factors in some cases of benign breast disease, however not all.

Conflict of interest: We have no conflict of interest.

Reference

1. Lemaire M, Baugnet-Mahieu L. Nuclear thyroid hormone receptors in human cancer tissues. Anticancer Res. 1986; **6:** 695-700.

2. Pushpagiri N, Gracelyn LJ, Nagalingam S. Prevalence of subclinical and overt hypothyroidism in infertile women. Int J Reprod Contracept Obstet Gynaecol. 2015 Dec; **4(6):** 1733-1738.

3. Neville MC, Mc Fadden TB, Forsyth I. Hormonal regulation of mammary differentiation and milk secretion. Journal of Mammary Glad Biology and Neoplasia. 2002; **1:** 49-66.

4. Ming-Li H, Horng-Heng J. Cell Growth Effects of triodothyromome and Expression of Thyroid Harmone Receptor in Prostate Carcinoma Cells Journal of Andrology. 2005; **26(3)**.

5. Morgan A, Dellovade TL, Plaff W. Effect of thyroid hormones and Behavior. 2000; **37:** 15-22.

6. Martinez-Iglesias O, Garcia-Silva S, Regadera J, *et al*. Hypothyroidism enhances tumor invasiveness and metastasis development. PLoS One. 2009; **4:** e6428.

7. Adamopoulos DA, VassilarrosS, Kapolla N *et el*. Thyroid diseases with benign and malignant mastopathy. Cancer 1986; **57:** 125-128

8. Giustarini E,PincheraA, Fierabracci P *et el*. Thyroid autoimmunity in patients with malignant and benign breast disease before surgery. Eur J Endocrinol 2006; **154:** 645-649

9. Anil C, Guney T, Gursoy A. The prevalence of benign breast disease in patients with nodular goiter and Hashimoto,s thyroiditis. J Endocrinol Invest 2015 Sep; **38(9):** 971-5.

10. Sidoni A, Fama F, Rosano A, Scisca C. Thyroid nodule coexisting with either cystic or solid breast nodules: a new clue for this association between nodules coming from ultrasonography. Gland Surg 2017; **6(6):** 630-637.

11. Sitruk-Ware LR, Sterkers M, Mowszowicz L *et al.* Inadequate corpus luteal function in women with benign breast diseases. J Clin Endocrinol Metab 1977; **44:** 771-774.

12. Peters F, Pickardt CR, Breckwoldt M. Thyroid hormones in benign breast disease. Normalization of exaggerated prolactin responsiveness to thyrotropin releasing hormone. Cancer.1985 Sep 1; **56(5):** 1082-5

13. Hekimsoy Z, Kafesciler S, Guclu F, *et al*. The prevalence of hyperprolactinaemia in overt and subclinical hypothyroidism. Endocrine Journal 2010, **57(12):** 1011-1015.

14. Asa SL, Ezzat S. The pathogenesis of pituitary tumours. Nat Rev Cancer 2002; **2:** 836-849.

15. Seri O, Chik CL, Ur E, Ezzat S. Diagnosis and management of hyperprolactinemia. CMAJ 2003; **169(16):** 575-581.

16. Honbo KS, van Herle AJ, Kellett KA. Serum prolactin levels in untreated primary hypothyroidism. Am J Med 1978; **64:** 782-787.

17. Kroese JM, Grootendorst AF, Schelfhout LJ. Postpartum amenorrhoea-galactorrhoea associated with hyperprolactinaemia and pituitary enlargement in primary hypothyroidism. Neth J Med 2004; **62(1):** 28-30.

18. Cave WT Jr, Paul MA. Effects of altered thyroid function on plasma prolactin clearance. Endocrinology 1980; **107:** 85-91.

19. Davis JR, Lynam TC, Franklyn JA, Docherty K, Sheppard MC. Tri-iodothyronine and phenythoin reduce prolactin messenger RNA levels in cultured rat pituitary cells. J Endocrinol 1986; **109:** 359-364.

20. Ceresini, G, Lauretani, F, Maggio, M, *et al.* "Thyroid function anbormalities and cognitive impairment in elderly people: results of the Invecchiare in Chianti Study". *J Am Geriatr Soc*. vol. 57. 2009. pp. 89-93.