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THYROID PROFILE IN PATIENTS WITH BREAST TUMORS

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ABSTRACT

Most breast carcinoma are hormone dependent. Two-thirds of breast cancers have estrogen or progesterone receptor positivity. Conflicting results regarding the clinical correlation between breast carcinoma and thyroid diseases have been reported. The objective of this study was to determine the thyroid profile in patients with newly diagnosed benign and malignant breast tumors. Serum samples were collected from 30 female patients with newly diagnosed breast carcinoma having FNAC report as ductal cell carcinoma and 28 female patients with newly diagnosed benign breast tumors having FNAC report as fibroadenoma or fibroadenosis. Serum samples were analyzed for TSH, free T4and free T3 levels. 30 age matched normal healthy controls were also examined for the same parameters. Breast carcinoma patients had raised serum TSH levels and low freeT4 and freeT3 levels compared to controls and benign breast tumor patients. There was a significant association between thyroid hypofunction and breast carcinoma.

KEYWORDS: **Hypothyroidism, TSH, freeT4, freeT3, breast carcinoma, benign breast tumors**

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INTRODUCTION

Breast carcinoma is caused by interactions of both inherited and environment risk factors that lead to progressive accumulation of genetic and epigenetic changes in tumor suppressor genes of breast epithelial cells.[1] Breast carcinoma and thyroid disease predominantly affects females and both have a postmenopausal peak incidence resulted in a search for an association between the two diseases.[23] There was a frequent association between breast carcinoma and hypothyroidism.[4] This study was done to measure the levels of TSH, freeT4, freeT3 in patients with newly diagnosed malignant and benign breast tumors and to understand the antiproliferative role of thyroid hormones in breast tumors.

MATERIALS AND METHODS

The study was conducted after having obtained permission from the Institutional Ethics committee, Madras Medical College, Chennai, India.The study population included 30 apparently healthy female controls in the age group between 32 and 65 years attending the general OPD of Rajiv Gandhi Government General Hospital Chennai, cases comprised of 28 females with newly diagnosed benign breast tumor in the age group between 33 to 65 years and 30 females with newly diagnosed breast carcinoma in age group between 32 to 65 years. All breast tumors were proved by FNAC. Benign breast tumors comprised of fibroadenoma or fibroadenosis. Malignant breast tumor comprised of ductal cell carcinoma of breast. A detailed history of the biological parameters such as age parity, age at first child birth, duration of exposure to endogenous estrogen and family history of breast carcinoma among cases and control was taken. Newly diagnosed patients with benign and malignant breast tumors were included as cases in the study and patients with history of thyroid disorder and patients already undergoing treatment for breast tumor were excluded from the study.5 mL of venous blood was collected from all cases and controls. The sample was processed and analysed for free T3, free T4 and TSH with an open system automated ELISA analyser (Triturus analyser) and manufacturer's reagent kits.

STATISTICAL ANALYSIS

Comparison of biological parameters such as age parity,age at first child birth,duration of exposure to endogenous estrogen and family history of breast carcinoma among cases and control was determined by oneway ANOVA and chi-square .Comparison of TSH, freeT4 and free T3 among cases and controls was done using oneway ANOVA and Bonferroni t test.

RESULTS

The mean age of the controls was 48.1+/- 9.7 years, of benign breast tumor cases were 48.07 +/- 7.8 years and of malignant breast tumor cases were 51.03+/- 9.5 years.

Table 1

Shows the comparison of age, family h/o breast carcinoma, nulliparity, age at first child birth and endogenous estrogen exposure >30years among control and cases

S.No	Study group	Mean Age in years	Family H/O of breast carcinoma in %	Nulliparity in %	First childbirth >30years%	Endogenous estrogen exposure >30years%
1	Controls(n=30)	48.1±9.7	0%	6.7%	3.3%	66.7%
2	Benign (n=28)	48.07±7.8	3.6%	7.1%	0%	64.3%
3	Malignant(n=30)	51.0±9.6	3.3%	10%	3.3%	66.7%
	p-value	0.39	0.59	0.58	0.93	0.90
Level of significance		Not significant	Not significant	Not ignificant	Not significant	Not significant

The mean and S.D values of TSH among controls, patients with benign breast tumors and patients with breast carcinoma were 2.59+/-0.89mIU/L, 2.76+/-0.68mIU/L and 3.17+/- 0.62mIU/L respectively.

Table 2

Shows the comparison of TSH levels among cases and controls

	Number	Mean mIU/L	Standard Deviation	SEM	Oneway ANOVA	multiple comparison using BonferroniT-test
Control	30	2.59	0.89	0.16		
Benign	28	2.76	0.68	0.13	F=4.82	Control vs carcinoma
Malignant	30	3.17	0.62	0.11	p=0.01	

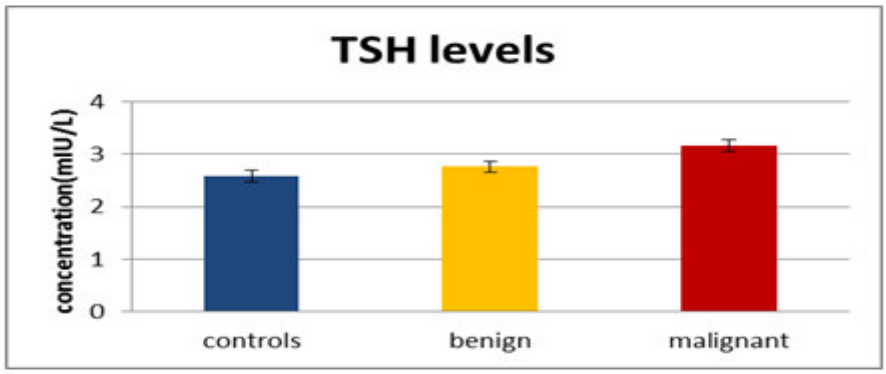

Figure 1
Comparison of TSH levels among cases and control

The TSH values was significantly high among the breast carcinoma patients when compared to the controls with a p-value=0.01. Though the mean TSH value of the benign breast tumor patients was higher than the controls it was not significant. (p-value =1.0). The mean and S.D values of free T4 among controls, patients with benign breast tumors and patients with breast carcinoma were 1.61+/-0.46 ng/dL, 1.43+/-0.33 ng/dL and 1.00+/- 0.28 ng/dL respectively.

Table 3
Shows the comparison of free T4 levels among cases and controls

	Number	Mean ng/dL	Standard deviation	SEM	oneway ANOVA and multiple comparison using Bonferroni T-test	
Control	30	1.61	0.46	0.08	p=0.19	Control vs benign
Benign	28	1.43	0.33	0.06	F=21.85	Carcinoma vs control
Malignant	30	1.00	0.28	0.05	p=0.001***	benign

p≥0.05nonsignificant;*p<0.05significant;**p<0.01 highlysignificant;p<0.001veryhighly significant***

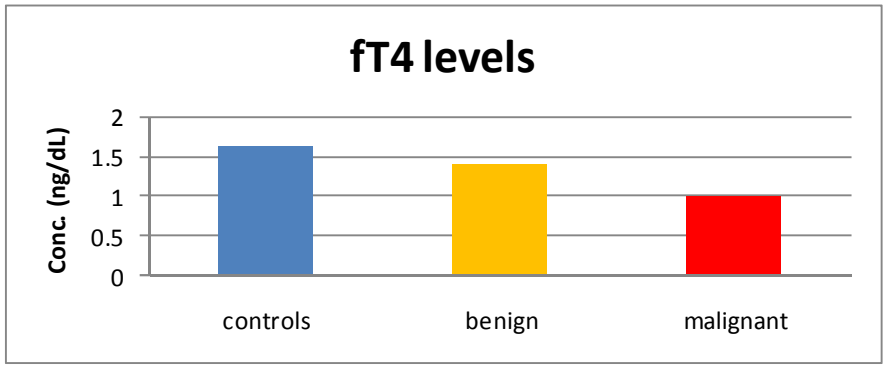

Figure 2
Comparison of free T4 levels among cases and controls

The free T4 values was significantly low among the breast carcinoma patients when compared to the controls and benign breast tumor patients with a p-value=0.001.Thoughthe mean free T4 value of the benign breast tumor patients was lower thanthe controls it was not significant. (p-value=0.19). The mean and S.D values offree T3 among controls,patients with benign breast tumors and patients with breastcarcinoma were 2.89+/-0.85pg/mL,2.66+/- 0.70pg/mL and 2.05+/-0.73 pg/mL respectively.

Table-4
Shows the comparison of free T3 levels among cases and controls

	Number	Mean pg/mL	Standard deviation	SEM	Oneway ANOVA and multiple comparison using Bonferroni T-test	
Control	30	2.89	0.85	0.16	p=0.756	Control vs benign
Benign	28	2.66	0.70	0.13	F=9.82	Carcinoma vs control,
Malignant	30	2.05	0.73	0.13	p=0.001***	benign

p≥0.05nonsignificant;*p<0.05significant;**p<0.01 highlysignificant;p<0.001veryhighly significant***

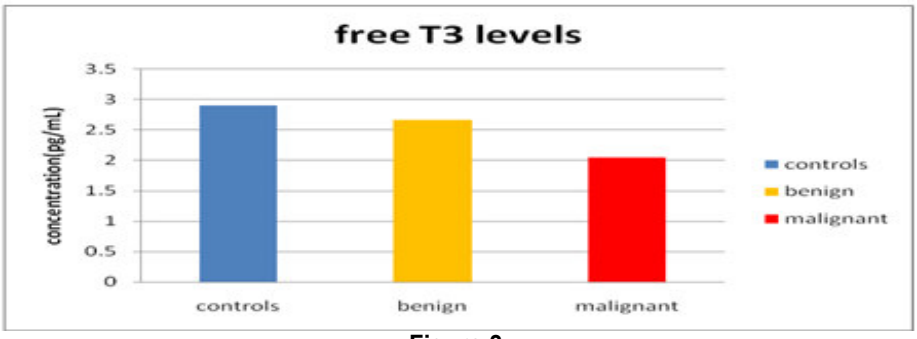

Figure 3

Comparison of free T3 levels among cases and controls

The free T3 values was significantly low among the breast carcinoma patients when compared to the controls and patients with benign breast tumors with a p-value=0.001. Though the mean free T3 value of the benign breast tumor patients was lower than the controls it was not significant. (p-value=0.756).

DISCUSSION

Thyroid hormones are important regulators of growth, development and metabolism in higher animals and humans.[5] Thyroid hormones act as major physiological regulator of mammalian development through specific effect on the rate of cell differentiation and gene expression.[6] Thyroid hormones and cognate nuclear receptors are involved in cell growth and differentiation of many cell types.[7]Thyroid hormones play an important role in the normal development of breast by stimulating ductal branching and alveolar budding.[8] Growing and developing breasts require the coordinated action of several hormones such as estrogen (E2), progesterone, thyroid hormones, adrenal steroids, insulin, and prolactin.[9]The possible interactions between thyroid gland and breast tissue are based on the common property of the mammary and thyroid epithelial cell to concentrate iodine by a membrane active transport mechanism as well as on the presence of TSH receptors in mammary gland.[10]The biological activity of thyroid hormones and estradiol are only manifested in cells expressing thyroid hormone and estrogen receptors respectively. These receptors belong to the nuclear receptor superfamily.They share a common mechanism of action whereby hormone-receptor complexes bind to cis acting DNA elements and enhance or repress transcription of target genes[11].Estrogen is considered to be a potent mitogen for the normal mammary gland, whereas thyroid hormones appear to stimulate lobular development, contributing to the differentiation of normal breast tissue.[12] Consistent with the proposal that thyroid hormones act on the breast, thyroid receptors have been described in breast carcinoma.[13] There are reports on interference between estradiol and thyroid hormones. Studies suggested a cross talk between estrogen receptors and thyroid receptors in neuroendocrine tissues leading to inhibition of estrogenic effects by thyroid hormone.[14]Excess proliferation of breast epithelial cells is caused by unopposed action of estrogen and various mitogenic growth factors like EGF and IGF, by stimulating the growth factor signaling pathway leading to the development and progression of breast carcinoma. Thyroid hormone, by causing differentiation of breast epithelial cells antagonizes the proliferative effect of estrogen and mitotic growth factors. Thyroid receptors can also alter expression of genes that do not contain a hormone response element through positive or negative interference of other transcription factors and signaling pathways Increasing evidence shows that loss of expression and or function of the thyroid hormone receptors could result in a selective advantage for tumor development, as transformed or immortalized cells in general express very low levels of thyroid receptors. Hypothyroidism affects tumor growth and invasiveness differentially.[15]The anti-tumor role T3 in liver carcinomas is also supported by the observation that hypothyroidism is a possible risk factor for hepatocellular carcinoma in patients with no known underlying cause of liver disease.[16]We evaluated the association between thyroid dysfunction and breast tumors in this study.The TSH values were significantly high among the breast carcinoma patients when compared to the controls proving the association of thyroid hypofunction and resultant increase in TSH in breast carcinoma patients.The levels of free T4 and free T3 were significantly low among the breast carcinoma patients when compared to the controls and the benign breast tumor patients. The low free T4 and free T3 further substantiates that there is association between hypothyroidism and breast carcinoma. Similar association has been shown by Goldman et al who found that hypothyroidism was the most frequently observed finding when thyroid disease and breast carcinoma coexisted.[3] The nonsignificant p-value of TSH, free T4 and freeT3 between benign breast tumor patients and controls suggest a possibility that the pathogenesis of benign breast neoplasia involves other unidentified mechanism not involving thyroid hormones.The observed association between hypothyroidism and breast carcinoma may be due to the biological effect of T3 at the cellular level through either a direct interaction with the thyroid receptor or a modulation of the TSH receptor .[17]Another intriguing possible role in breast carcinogenesis may be ascribed to iodide, based on its protective antioxidant mechanism. This theory has been postulated based on the capacity of breast tissue to transport and concentrate iodide similar to thyroid. Both organs require a method of oxidizing iodide to iodine in order to produce iodoproteins and iodolipids.[18] Iodolipids like 6-iodolactones which act via peroxisomal proliferator activator receptors – gamma (PPAR-y) and prevent proliferation of mammary epithelial cells. Cross talk between PPARs and thyroid receptors may also be mediated indirectly by modulating the gene of

deiodinase-2 enzyme involved in T3 metabolism.[19]Hypothyroidism is a common disorder with an incidence of approximately 3-4% of symptomatic disease in general population that increases to up to 13-14% among individuals aged more than 65 years. Hence hypothyroidism may be an independent risk factor for development of breast carcinoma.[17] Early detection in the form of a biomarker can be used to predict onset of, identify the presence of a tumor, and determine its stage, subtype, and ability to respond to therapy.[20]

CONCLUSION

The association between thyroid dysfunction and breast tumors was evaluated in this study.TSH values were significantly elevated and freeT4 and free T3 values were lowered in breast carcinoma patients compared to controls depicting the possible risk of breast carcinoma in hypothyroid individuals. However these data must be confirmed in large patient cohorts and long duration follow-up.

SCOPE FOR FUTURE STUDY

Thyroid receptor status of breast cancer tissue can be studied and a possible association between thyroid receptor and estrogen receptor status can be investigated.

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CONFLICT OF INTEREST

conflict of interest declared none.

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