

Original Research Article

Magnitude of Hypothyroidism in Benign Breast Disorders and Effect of Thyroxin Replacement on Clinical Outcome of Benign Breast Disorders with Hypothyroidism as Comorbidity

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ABSTRACT

Background: This study was done with aim to determine magnitude of hypothyroidism in Benign Breast disorders and effect of thyroxin replacement therapy on clinical outcome of benign breast disorders with hypothyroidism as co morbidity.

Methods: This prospective study included 340 patients of benign breast disease having no history of hypothyroidism and who fulfill all eligibility criteria. After thorough clinical and radiological examination, they were divided into two groups- i) BBD with euthyroidism ii) BBD with hypothyroidism, on the basis of baseline T4 and TSH level. Euthyroid group was given standard conservative treatment and hypothyroid group was given thyroxin replacement therapy. Response to both therapies was assessed at 6 weeks and 3 months interval and data obtained from both groups was compared.

Results: Mean age of patients was 33±8 years. Prevalence of hypothyroidism was 30% and out of these 74.5% cases were having subclinical hypothyroidism. The association of hypothyroidism was greater with higher age group and nipple discharge than mastalgia or breast nodularity. Hypothyroid patients presenting with nipple discharge and mastalgia responded better to thyroxine replacement therapy than those with breast nodularity. Overall thyroxine replacement therapy was proven effective for patients of benign breast disease with hypothyroidism.

Conclusion: As indicated by our results, hypothyroidism may be associated with development of benign breast disease as a risk factor. So hypothyroidism should be considered as underlying cause of BBD and adequate screening should be done in patients of BBD as thyroid replacement therapy might be the only definitive treatment required in most of these cases.

Key words: Benign breast disease (BBD), Hypothyroidism, Breast.

INTRODUCTION

Benign breast disorders are commonly encountered in Indian clinical practice. Cultural inhibitions prevent many Indian women for articulating a breast related problem. This deep seated taboo and illiteracy exert a pernicious effect by making the average Indian woman unaware of the breast changes that usually occur and

these changes may be normal or abnormal. Cancer phobia drives a small number of the urban women to directly seek the services of medical and surgical oncologist even for benign problems.

Breast is embryologically a modified sweat gland. Immature breast consists mainly of fibrous stroma and scattered ducts

while mature breast is composed of fat, stroma, lactiferous ducts and lobular units.

Maturation of breast is hormone dependent. This process of growth and cell division and breast maturation is under control of estrogen, progesterone, adrenal hormones, pituitary hormones and trophic effect of insulin and thyroid hormone. Beside these local growth factor networks also play important role in breast development and maturation.

In women between adolescence and mid 20s, the lobule and stroma may respond to the hormonal stimuli in an exaggerated manner with development of single and multiple fibroadenomas. In the 3rd and 4th decade of life, the degree of diffuse palpable nodularity may increase. The stroma may undergo hypertrophy, resulting in palpable areas or ill defined fullness frequently in upper outer quadrant or axillary tail areas.

In the past breast lump was considered the most common presenting complain of BBD and a lump in breast of young female is either fibroadenoma or a fibroadenosis. About ninety percent breast problems are benign in origin.

In 1982 Hughes proposed the theory of "Aberrations in the Normal Development and Involution of the breast (ANDI)".^[1] According to this theory, benign breast disorders occur due to minor aberrations of the normal processes of development and involution of breast and aberration in cyclical hormonal response.

Activity of sodium iodide symporter (NIS) in breast tissue had been demonstrated and many studies had concluded that at certain stages of life breast epithelium should actively be involved in iodine uptake and concentration.

The increased prevalence of thyroid disorders in women with BBD and various thyroid disorders such as autoimmunity, goiter and hypothyroidism have been linked with BBD and its outcome.

Moreover, iodine replacement had been shown to result in improved clinical outcome in BBD patients. However, the association between thyroid dysfunction and

BBD has not been well established and there is no consensus regarding monitoring of thyroid function in patients. Most of the published work has focused on the relation of breast cancer with the thyroid despite the fact that BBD is far more prevalent than breast cancer.

Though being a significant cause of concern in almost half of the female population, association of BBD with thyroid dysfunction is not well established. Therefore, there are no guidelines regarding monitoring of thyroid function during the workup of BBD cases.

MATERIALS AND METHODS

A hospital based comparative interventional study was done in upgraded department of general surgery, SMS hospital Jaipur from May 2014 to April 2015 or till 3 months follow up of all selected cases. 340 eligible cases of benign breast disorder were included as study population. The patients were required to give written informed consents and clearance was taken as per the institute's ethical committee guidelines.

Inclusion criteria

- All the cases of benign breast disorder coming to SMS OPD.
- Those who have given written informed consent.

Exclusion criteria

- Pregnant or patients taking oral contraceptive
- Cases of fibroadenoma indicated for surgery
- Blood stained nipple discharge
- Pt. with significantly raised Prolactin level (>10 ng/ml)
- Pt. with suspicious finding during clinical examination or on FNAC or during radiological examination
- Patients refusal to give informed consent

All of the patients were evaluated by thorough history and clinical examination of breast and thyroid. Mastalgia was graded in three category- absent, mild (tolerable), severe (disturbance in daily activity). Breast

nodularity was classified with an ordinal scale in four grades- 1) none 2) rice grain sized 3) coarse pea sized 4) coarse bean sized. Patients were also asked about subtle sign of hypothyroidism like weight gain, muscle cramps, mood changes, and menorrhagia. Screening breast ultrasonography or mammography (>35 year age group) were done in all cases. FNAC were done on all palpable breast lump or suspicious lesion detected by USG or mammography. Thyroid profile- T4, TSH and prolactin were measured in all cases and compared with standard lab values. The normal reference range for serum TSH and T4 from our laboratory was 0.4-4.0 mIU/L and 0.89-1.76 ng/dl, respectively.

- Hypothyroid: T4 <0.89 ng/dl and TSH >4mIU/L
- Subclinical hypothyroidism: Normal serum T4 and TSH >4mIU/L

Cases of BBD with euthyroid status were given conventional t/t like vitamin-E & Evening primrose oil. Diagnosed cases of hypothyroidism with BBD were given thyroxine supplement and were kept in follow up for 3 months and reevaluated. Both groups were compared in terms of changes in breast nodularity, amount of nipple discharge, and mastalgia. Mastalgia treatment response was grade with the Cardiff breast pain score.

CBS I- excellent response with no residual pain;

CBS II- significant response with bearable residual pain;

CBS III- poor response with significant residual pain

CBS IV- no response

Nodularity treatment response was graded with an ordinal scale as described previously. Follow-up of patients with nipple discharge was recorded as persistent, decreased (>50%), and disappeared (none >1 month). On follow up at 6 weeks and 3 months thorough clinical examination was done on each patient and findings were recorded in a preformed performa and data was compared. Patients who were on thyroxine replacement had repeat serum T4

and TSH estimations done. For analysis, patients were divided in two groups: group a) euthyroid patients without thyroxin replacement; group b) hypothyroid patients given thyroxin replacement therapy, and clinical outcomes of these groups were compared.

Observations

The mean age of 340 patients was 33 ± 8 years. Peak incidence of BBD was found in age group of 25-34 years in euthyroid and in 35-44 yr age group in hypothyroid. Frequency of the disease decreases after 4th decade of life. Prevalence of hypothyroidism in this study was 30%. Out of these 24.5% cases were overt hypothyroid while 75.5% cases were subclinical hypothyroid. Association of hypothyroidism with BBD was greater in higher age group.

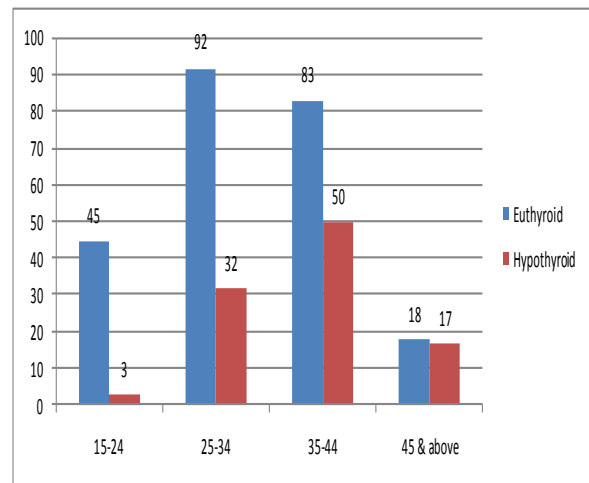


Figure 1: Age Distribution of Benign breast disease

Overall prevalence of BBD was higher in patients belonging to middle class of society. Association of hypothyroidism with BBD was slightly higher in upper class of society but was not significant. Majority of cases were having symptoms for more than 6 months. The mean duration of symptoms was 8.67 months (1-30 months). In all, 95.59% of the women were premenopausal, and 3.24% were postmenopausal. The remaining 1.17% of women had undergone a hysterectomy, and their exact menopausal status was not known.

The most common clinical presentation of BBD was pain full lumpiness/breast nodularity in 62.35% followed by mastalgia/breast pain and nipple discharge in 37.64% and 14.7% of women respectively. Association of hypothyroidism with BBD was slightly higher in women presenting with nipple discharge than mastalgia and breast nodularity. Serous nipple discharge and

mild-cyclical mastalgia were common in both hypothyroid and euthyroid condition. In both hypothyroid and euthyroid condition, grade II nodularity i.e. rice grain size was commonly present. & there was no statistical difference between the two groups.

The clinical profile of all the BBD cases is summarized in following table:

Table 1: Clinical profile of the benign breast disease

S. No.	Clinical Presentation	Total no.	Euthyroid	Hypothyroid
1.	Mastalgia, total cases	339		
	Mastalgia alone	128	94	34
	Mastalgia + Nipple discharge	49	27	22
	Mastalgia + Breast nodularity	212	144	68
	Nature of mastalgia			
	Cyclical	246	175	71
	Noncyclical	93	63	30
	Character of mastalgia			
	Mild	285	199	86
	Severe	54	39	15
2.	Nipple Discharge, total cases	50		
	Only Nipple discharge	1	-	1
	Nature of nipple discharge			
	Milky	4	3	1
	Serous	46	25	22
3.	Breast nodularity grade			
	I	128	94	34
	II	138	93	45
	III	61	43	18
	IV	13	8	5

Regarding symptoms of hypothyroidism, 66.67% cases of hypothyroidism did not show any symptoms while 11.76% cases presented with weight gain and 8.82% cases complained about associated menorrhagia.

It was observed that most of patients who did not show any sign of hypothyroidism were having normal T4 level with TSH being less than 10mIU/L while patients showing the symptoms were overt hypothyroid with TSH > 10mIU/L in majority of cases. One case was having goiter which was later on diagnosed with papillary carcinoma of thyroid and underwent total thyroidectomy with modified radical neck dissection. In this study there was no significant difference in mean T4 & TSH level for different clinical presentation BBD with Hypothyroidism.

Initially 100% Euthyroid patients were given Evening Primrose oil and Vitamin-E for 6 weeks. 13.03% (31) cases needed Danazol in follow up who did not respond to previous treatment, mainly for Mastalgia. Out of these, 67.74% (21) cases needed Danazol 50 mg, 24.24% (8) cases needed Danazol 100 mg and remaining 8.02% cases required Danazol 200 mg bd.

The daily doses of thyroxine needed to achieve euthyroidism were 25, 50, 75, 100 and 125ug in 38, 18, 26, 10, and 8% patients, respectively. By the end of 3 months all of the patients had achieved euthyroidism. 12% of cases who did not respond to thyroid completely were subsequently given evening primrose oil.

On follow up at 6 weeks and 3 months, findings were recorded in a preformed performa and data was compared.

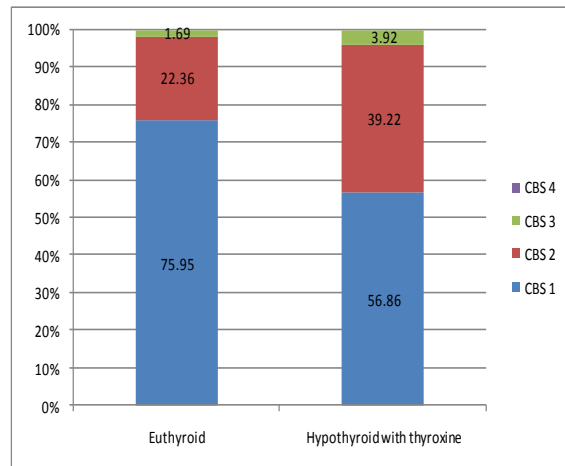
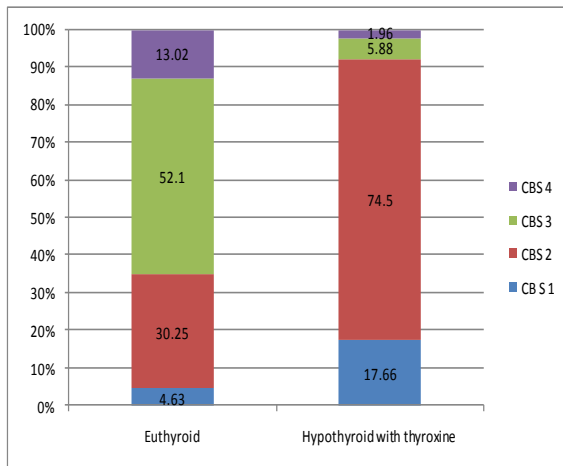


Figure 2: Response to treatment (Mastalgia)

P value= 0.000, after 6 weeks of follow up

P value = 0.002, after 3 months of follow up,

*CBS= Cardiff breast pain score,

*At 3 month of follow up, no patient was in CBS IV category.

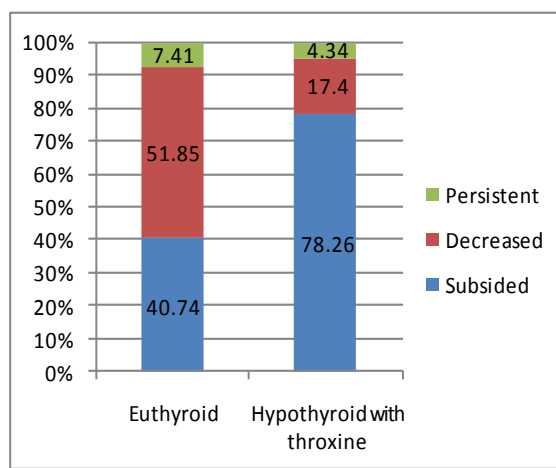
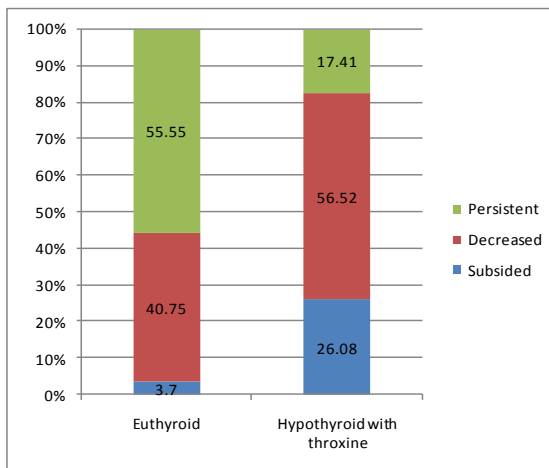


Figure 3: Response to treatment (Nipple discharge)

P value = 0.007, after 6 weeks of follow up

P value= 0.026, after 3 months of follow up

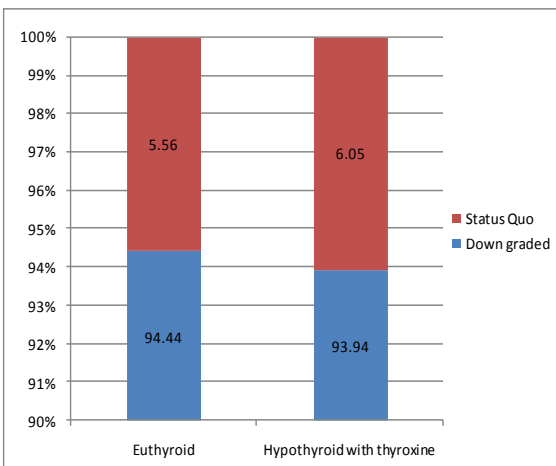
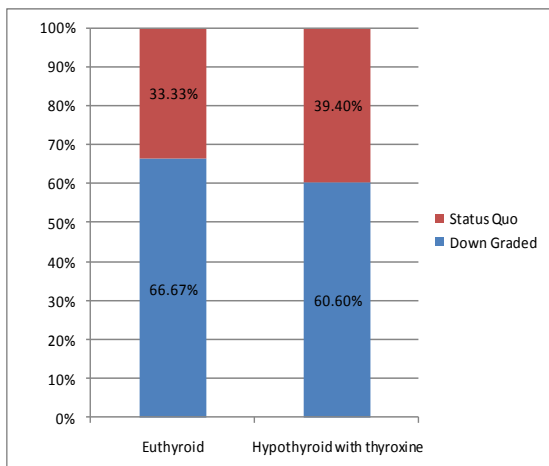


Figure 4: Response to treatment (Breast Nodularity/lumpiness)

P value = 0.485, after 6 weeks of follow up

P value = 0.770, after 3 months of follow up

DISCUSSION

Benign breast disease has a high prevalence and noticeable impact on women life. It has been estimated that one out of

two women develops some form of BBD in her life. Multiple risk factors have been described to be associated with BBD.

Age

First in 1980 a study named “Thyroid function in patients with benign and malignant breast disease” by Macfarlane et al was done. It included 60 patients of BBD and 162 patients of breast cancer. Mean age of BBD was 40 yrs with most common age group was 30- 40 yrs. [2]

Goehring C et al in “Epidemiology of Benign Breast Disease” analyzed multiple studies and concluded that the incidence rate per 100,000 woman-years of fibrocystic breast disease increases progressively from 137 at ages 25-29 years to 411 at ages 40-44 years and to 387 at ages 45-49 years, and then decreases regularly. [3]

Nanveet Kaur et al 2012 studied clinic-pathological profile of BBD in Indian women in 199 patients and concluded that BBD most commonly affect 15-35 yrs age patients with mean age 28 yrs. [4]

In the study of Bhargav P R et al 2009 mean age group were 34±8 yrs which are almost equal to our study. [5]

In our study, mean age group was 33±8 yrs. 40.88% and 36.17% cases were in age group of 25-34 yrs and 35-44 yrs respectively. Association of hypothyroidism with BBD was greater in higher age group.

All these studies show that BBD mostly affect patients in reproductive period of life and must be associated with hormonal changes that occur in this age group.

Social Status

According to Goehring C et al “Epidemiology of Benign Breast Disease”, studies that compared groups using higher socioeconomic status as a risk factor, found it to be positively associated with fibrocystic breast disease. [3]

In our study highest group of BBD belongs to middle class of society. Association of hypothyroidism with BBD was slightly higher in upper class of society.

According to National Council of Applied Economic Research (NCAER), India's Premier economic research institution, India's middle class population would be 267 million in 2016 and if current trends continue, Indian per capita purchasing power parity will significantly increase from 4.7 to 6.1 percent of the world share and dietary habits and life style will improve to higher class society level. Changed food habits make the middle class group prone to BBD, being largest part of population.

Menstrual History

According to Goehring, age at menarche is not associated with either fibrocystic breast disease or fibroadenoma but age at menopause may possibly be related to fibrocystic breast disease but not to fibroadenoma. Nulliparous women may be at increased risk of fibrocystic breast disease and higher parity may be protective against fibrocystic breast disease but not against fibroadenoma. Findings relating late age at first live birth to fibrocystic breast disease are inconsistent. [3]

In the study by Bhargav P R et al, 88% of the women were premenopausal, and 6.5% were postmenopausal. The remaining 5.5% of women had undergone a hysterectomy, and their exact menopausal status was not known. [5]

In our study 95.59% of the women were premenopausal, and 3.24% were postmenopausal. The remaining 1.17% of women had undergone hysterectomy.

Evidence suggests that prolonged exposure to estrogen increases the risk of fibrocystic breast disease. An approximate twofold increased risk of fibrocystic breast disease has been noted with use of estrogen replacement therapy in multiple cohort studies and in hospital-based case-control studies.

Table 2: Presenting complain

Symptoms	Bhargav et al. 2009	Navneet kaur et al 2012	Mima B. Maychet Sangma et al 2013	Present study 2015
Only Mastalgia	74.5%	16%	9%	37.64%
Mastalgia + Nipple Discharge	25.5%	5.7%	3%	14.70%
Mastalgia + Breast Nodularity	72.2%	23%	20%	62.35%

The most common clinical presentation of BBD was pain full lumpiness/breast nodularity in 62.35% followed by mastalgia/breast pain and nipple discharge in 37.64% and 14.7% of women respectively. 37.64% cases presented with mastalgia only. Only 1(0.29%) patient presented with complains of nipple discharge only.

In the study by Bhargav P R et al, mastalgia (72%) was the commonest clinical complaint, followed by nipple discharge and lump and/or lumpiness in 29.4 and 17% women, respectively. [5]

In another study, A Clinicopathological Study on Benign Breast Diseases by Mima B. Maychet Sangma et al, the most common presentation was breast lumps which comprised 87 (87%) cases, out of which 27 (27%) had associated complaints like breast pain and nipple discharge. More than one symptom was present for the same patient. Among 33 (33%) patients with breast pain, 9 (9%) patients complained of breast pain (mastalgia) only. [6]

The incidence of breast pain in our series was 37.64%, which was nearly equal to the breast pain series, which ranged from 12.8%- 30.3%.

Leis HP et al. reported that the incidence of nipple discharge was only 9% of all the breast complaints in his study, [7] while it was 14.70% in our study.

Table 3: Prevalence of Hypothyroidism

Studies	Prevalence of hypothyroidism (%)
Macfarlane et al.	8.33%
Bhargav et al	23.2%
Epidemiological study	9.3%
Present study	30%

Epidemiologically prevalence of hypothyroidism in Rajasthan is 9.3%.

The prevalence of hypothyroidism in the study by Bhargav et al was 23.2%. Out of these 74% cases were overt hypothyroid while 26% cases were subclinical hypothyroid. [5]

Prevalence of hypothyroidism our study was 30%. The serum T4 concentration was below the reference range in twenty five cases (24.5%), indicating overt

hypothyroidism. Altogether, 33.33% women in the hypothyroid group had subtle clinical features suggestive of hypothyroidism. Thus, if these symptoms are taken into account, 33.33% patients might be considered as having overt hypothyroidism.

Table 4: Association of Hypothyroidism with BBD

Symptoms	Bhargav et al. 2009	Present study
Only Mastalgia	14.8%	26.57%
Mastalgia + Nipple Discharge	45.9%	44.89%
Only Nipple discharge	36.8%	2%
Mastalgia + Breast Nodularity	17.4%	32.07%

In our study hypothyroidism was associated with 26.57% cases of only mastalgia compared to the 14.8% cases in study by Bhargav et al. 2009. [5] In both studies mastalgia was most predominant component of BBD.

Above table shows that association of hypothyroidism with nipple discharge + mastalgia was near equal to study by Bhargav et al. 2009.

Table 5: Relationship of TSH with BBD

Studies	Mean TSH level (uU/ml)
Ademopolous et al 1985	3.9 ± 1.9
E Giustarini et al 2006	1.19 ± 0.85
Present study	8.2 ± 3.69

The study by Ademopolous et al 1985 demonstrated that a higher incidence of thyroid enlargement and a greater frequency of thyroid function disturbances occurred in patients with breast cancer. These differences were not confined only to patients with breast malignancy, hut were also seen in women with fibrocystic disease of the breast. [8]

In another study by E Giustarini et al 2006, FT4 and TSH concentration showed no differences between breast cancer patients, BBD patients and controls. The prevalence of TPOAb and TgAb in BC patients was significantly higher than in BBD patients and in controls. Generally, 66.7% of BC and 36% of BBD ($P = 0.02$) had signs of thyroid autoimmunity and 5.55% of BC and 4% of BBD patients had autoimmune hypothyroidism and no hypothyroidism was found in controls. [9]

From these findings it can be assumed that the relation of thyroid

disturbances to breast disease seems to be nonspecific in character but there is no doubt that thyroid hormone imbalance do affect breast disease.

Table 6: Relationship of TSH with clinical profile of BBD

Clinical presentation	Mean TSH level (mIU/L)	
	Bhargav et al. 2009	Present study
Mastalgia	6.3	8.06
Nipple Discharge	10.8	8.83
Breast Nodularity	6.7	8.38

In the study by Bhargav et al. 2009, the rate of hypothyroidism and the mean

TSH concentration were significantly higher in patients presenting with nipple discharge than in those presenting with mastalgia or breast lump/lumpiness. However, these values did not differ significantly between the mastalgia and breast lump patients. [5]

In our study, rate of hypothyroidism was significantly higher in patients presenting with nipple discharge but mean TSH concentration values did not differ significantly between the mastalgia, nipple discharge and breast lump patients.

Analysis of response to thyroxine in Hypothyroidism

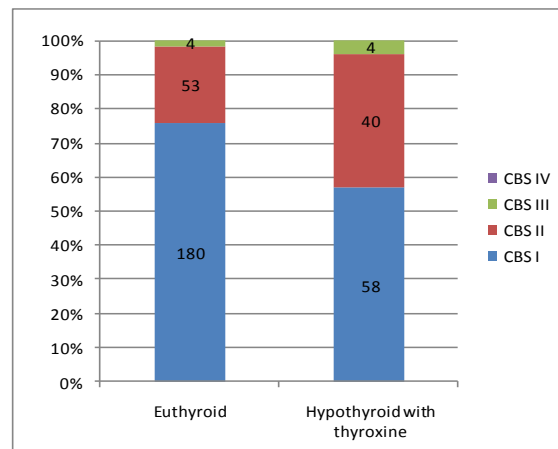
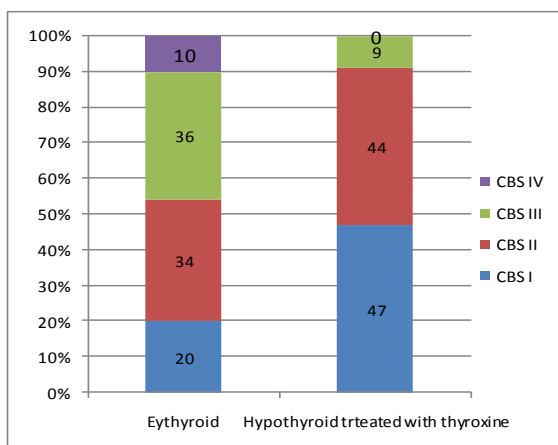


Figure 5: Response to mastalgia (After 3 months of follow up)

Bhargav et al. 2009, n = 201, Hypothyroid = 47, P = 0.001

Present study, n = 340, Hypothyroid = 102, P = 0.002

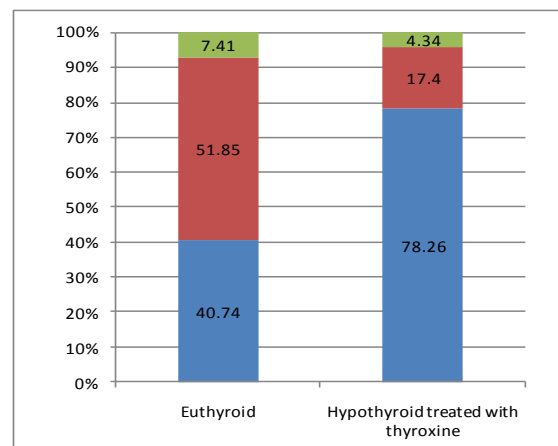
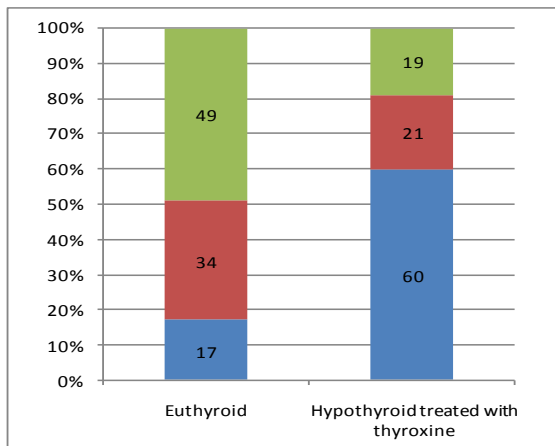


Figure 6: Response to nipple discharge (After 3 months of follow up)

Bhargav et al. 2009, n = 201, Hypothyroid = 47, P = 0.028

Present study n = 340, Hypothyroid = 102, P = 0.02

Above graph shows that thyroxine replacement has shown total improvement in mastalgia in 47% and 56.86% cases of hypothyroidism in Bhargav et al and our study respectively. [5]

On analyzing both study, we found that a significant percentage of hypothyroid

patients has responded to thyroxine replacement only. Evening primrose oil (EPO) and/or vitamin E or danazol may be better to be used in early in euthyroid patient or hypothyroid patient not responding to thyroxine replacement.

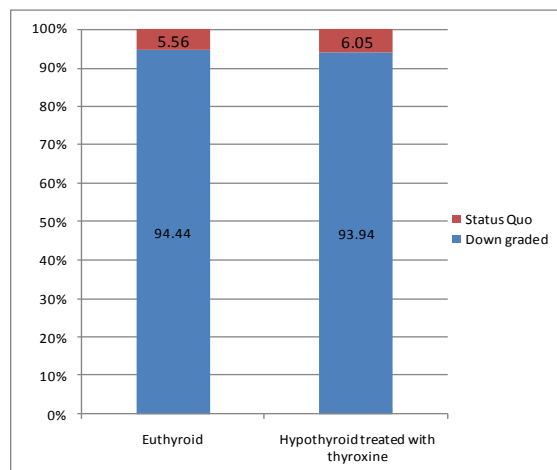
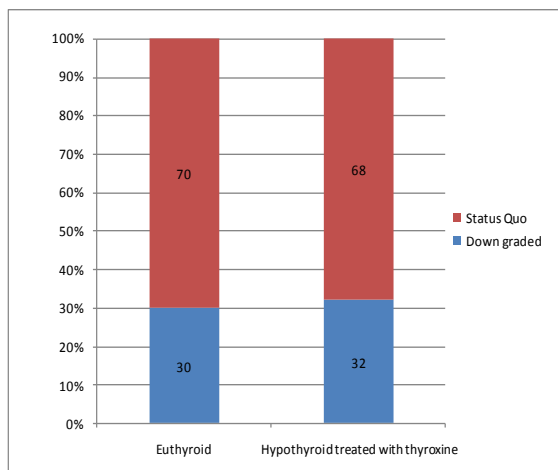


Figure 7: Response to breast nodularity (After 3 months of follow up)

Bhargav et al. 2009, n = 201, Hypothyroid = 47, P = 0.144

Present study, n = 340, Hypothyroid = 102, P = 0.0770

In the study by Bhargav et al 2009, 60% of hypothyroid patient had nipple discharge subsided on thyroxine replacement only, while 21% showed decreased nipple discharge. 19% showed persistent discharge. [5]

The findings of our study were almost the same. Our study shows that 78.26% hypothyroid pt. treated with thyroxine, responded with complete subsidence of nipple discharge.

In the study by Bhargav et al. 2009, 32% of hypothyroid patients have breast lumpiness subsided on thyroxin replacement only, 68% pt remain unresponsive. Quite similar findings were observed for euthyroid patients. [5]

The findings of our study were quite different. Our study shows that 93.94% hypothyroid patient treated with thyroxine, responded with down grading of breast nodularity, as was for euthyroid patients.

Both studies show that there was no statistically significant difference in response to breast nodularity in both euthyroid and hypothyroid treated with thyroxin.

Summary

Benign breast disease is a common problem in women. It starts in adolescence and reaches its peak in age group of 25-34yrs. Incidence of BBD decreases after 4th decade of life. Association of hypothyroidism increases with age. Earlier it used to be more common in high

socioeconomic groups but now it tends to affect middle socioeconomic groups more. The most common presentation of BBD is pain full lumpiness/breast nodularity followed by mastalgia/breast pain and nipple discharge. Mastalgia is usually mild in character and cyclical in nature. Hypothyroidism does not alter the presentation of mastalgia. In both euthyroid and hypothyroid patients, nipple discharge was serous in nature. Association of hypothyroidism with BBD was slightly higher in women presenting with nipple discharge than mastalgia and breast nodularity. In hypo and euthyroid condition, grade II nodularity i.e. rice grain size was commonly present. There was no statistical difference between the two groups in form of breast nodularity i.e. hypothyroidism does not alter nodularity of breast. Prevalence of hypothyroidism in this study was 30% which is higher than epidemiologically reported hypothyroidism in Rajasthan. Response to thyroxine for nipple discharge was significantly better than mastalgia and breast nodularity.

CONCLUSION

As indicated by our results, hypothyroidism may be associated with development of benign breast disease as a risk factor. So hypothyroidism should be considered as underlying cause of BBD and adequate screening should be done in patients of BBD as thyroid replacement

therapy might be the only definitive treatment required in most of these cases.

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