

Evaluation of Estradiol Levels, Lipid Profile, Estrogen Receptor Status and its Correlation with Histological Variants in Benign Breast Diseases

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Background: Benign breast diseases encompass a heterogeneous group of lesions which are thought to have an endocrine basis. They occur at a younger age in comparison to breast cancer and their etiopathogenesis has not been studied in as much detail as breast cancer.

Aim: To estimate the serum estradiol levels, serum lipid profile and tissue estrogen receptor status in patients of benign breast disease.

Material & Methods: Serum estradiol and lipid levels were measured biochemically while tissue estrogen receptors were assessed by immunohistochemistry in 60 patients of benign breast disease and 20 normal age matched controls.

Results: Serum estradiol and triglyceride levels were significantly higher in benign breast disease patients compared to controls (149 pg/ml vs 115 pg/ml and 164 mg/dL vs 105 mg/dL). The highest estrogen receptor status positivity was observed in fibroadenoma and lesser in fibroadenosis and fibrocystic disease.

Discussion: Higher levels of serum triglycerides and estradiol observed in benign breast disease compared to control suggest their possible etiopathological role. It is possible that higher lipid level leads to increased peripheral production of estrogen. Estrogen receptor positivity was higher in fibroadenomas compared to fibroadenosis and fibrocystic breast disease. Endocrine treatment of these conditions needs to be considered in light of findings of our study.

Introduction

The mammary gland is one of the most complex endocrine organs. Its growth, secretory differentiation, lactogenesis and galactopoiesis are the interplay of ovarian and adrenal steroids, pituitary, thyroid and pancreatic hormones. Both

mesenchymal and epithelial growth activities are responsible for morphological and functional changes in the mammary gland and are influenced by hormonal actions.

The term 'Benign Breast Disorders' encompasses a heterogeneous group of lesions. Its incidence begins to rise in the second decade of life and peaks in the 4th to 5th decades, as opposed to malignant diseases, which continues to increase in incidence after menopause. The increased risk of heterogeneous benign breast disease in women of younger age may reflect a

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Table 1: Comparison of serum estradiol and lipid profile among benign breast disease patients and controls

	Benign Breast Disease (n=60)	Controls (n=20)	p-value
Estradiol (pg/ml)	149 ± 4.5	115 ± 4.8	<0.001
TG (mg/dL)	165 ± 5.7	105 ± 4.5	<0.001
LDL (mg/dL)	138 ± 6.2	120 ± 3.4	0.112
Cholesterol (mg/dL)	207 ± 4.4	188 ± 6.2	0.029

time period where breast has reached its maximal cyclical proliferative capacity, in contrast to the women with postmenopausal status where the breast is subjected to less hormone cycling and reduction in proliferative cell amount and hence less symptoms.

The aim of this study was to estimate the estrogen receptor status, estradiol levels, total lipids, triglycerides and cholesterol levels in patients of benign breast disease and correlate them with various histological variants of benign breast disease.

Material and Methods

Prospectively 60 patients of benign breast disease and 20 normal age matched control subjects were enrolled between July 2009 to June 2011. Patients with complaints suggestive of benign breast disease such as breast pain, cyclical mastalgia, nodularity in breast and nipple discharge were included. Patients with histologically proven breast cancer, pregnancy, patients on oral contraceptive pills for last 3 months, patients receiving hormone replacement therapy (HRT), patients with hepatic or lipid disorder, and patients with cyclical mastalgia without palpable nodularity were excluded.

All patients underwent Trucut™ needle biopsy from suspicious area to exclude carcinoma of breast and confirm diagnosis of benign breast

disease. The tissue obtained from needle biopsy was used for histological study as well as estrogen receptor status. Estrogen receptor (ER) status was assessed by immunohistochemistry (IHC). The control subjects did not undergo needle biopsy. Serum sample (10 ml) was obtained from the 60 patients as well as 20 controls for estimation of estradiol, triglycerides, (TG), low density lipoprotein (LDL), and cholesterol.

Results

The mean age of patients was 31 years (range 17–42) and of controls 33 years (range 21–41). The common symptoms and signs were breast lump (n=28), tender nodularity in breast with or without breast lump (n=36), breast nodularity with mastalgia (n=24) and nipple discharge (n=2). The histopathological diagnosis made on the trucut needle biopsy specimen was fibro adenoma (n=28), fibroadenosis (n=22), and fibrocystic disease (n=10).

The serum levels of estradiol were found to be significantly higher among benign breast disease patients compared to controls (149 pg/ml vs. 115 pg/ml, $p < 0.001$). Similarly the triglyceride levels were higher among patients compared to controls (164 mg/dL vs 105 mg/dL, $p < 0.001$). However Low Density Lipoprotein (LDL) and serum cholesterol levels were found to be similar among patients and controls (Table 1). Among the benign disease patients, estradiol levels were highest in fibroadenoma (157 pg/ml) and similar among fibroadenosis (129 pg/ml) and fibrocystic disease (124 pg/ml) patients (Table 2). The lipid profile of the 3 groups was almost similar.

Immunohistochemical studies for ER in the tissue sample revealed the highest and most intense positivity among fibroadenoma patients as compared to fibroadneosis and fibrocystic disease. Among fibroadenoma patients 3+ ER

Table 2: Comparison of serum estradiol levels in various types of benign breast diseases

Types of BBD	S. estradiol level (pg/ml)	p value
Fibroadenoma	157 ± 6.0	
Fibroadenosis	129 ± 8.2	0.006
Fibrocystic disease	124 ± 9.0	

Table 3: Comparison of Estrogen Receptor (ER) status among different types of BBD

ER Status	Types of BBD		
	Fibroadenoma (n=28)	Fibroadenosis (n=22)	Fibrocystic disease (n=10)
1+	0	7 (32%)	4 (40%)
2+	6 (21%)	4 (18%)	3 (30%)
3+	22 (79%)	11 (50%)	3 (30%)

status was seen in 22 (79%), among fibroadenosis in 11 (50%) and among fibrocystic disease in 3 (30%) patients (Table 3). On analysis, stronger ER positivity in tissues correlated with greater serum estradiol levels ($p < 0.01$) (Table 4).

Discussion

The causative link between serum estradiol levels, estrogen receptor status (ER) and breast cancer is well established. Serum lipid levels and obesity are a major source of estrogen especially in the post menopausal women and are associated with higher incidence of breast cancer [1]. However the role of estradiol levels and lipid profile in the causation of benign breast disease is not well established.

It has been postulated that both benign and malignant breast tumors have a hormonal origin. Because of its profound stimulatory influence on breast ductal epithelium, it was thought that estradiol must play a central role. It has been suggested that some benign breast diseases and breast cancer have common etiological factors or even represent different stages of one process [2]. Yue *et al.*, reported that E-2 stimulates growth of breast tumor cells in both pre and post menopausal women [3]. Following menopause, plasma levels of E₂ are 10-50 times lower than in pre menopausal women. In the present prospective study we have focused on serum E₂ concentration in benign breast disease and found

them to be significantly higher than in normal controls ($p < 0.001$). We found that E₂ levels varied among different histopathological variants being highest in fibroadenoma and lesser in fibroadenosis and fibrocystic disease patients.

There is substantial evidence to support the hypothesis that estrogen receptors (ER) play an important role in the pathogenesis of benign breast disease. Khanna *et al.*, found that patients with ER positive breast disease responded better to Danazol as compared to patients with ER negative breast disease [4]. Mady considered that the ER status reflected the intrinsic property of tumor tissue in terms of its therapeutic response [5]. They observed significantly higher ER positivity in breast cancer compared to benign breast disease. Sapino *et al.*, observed that the highest percentage of ER positivity among benign breast disease was seen in fibroadenomas with cellular stroma [6]. This is in concordance with our study which shows that ER positivity is more in fibroadenomas compared to fibroadenosis or fibrocystic disease. They also found that ER positivity diminishes with age which was found in our study as well.

One of the aims of our study was to examine the association of serum lipid profile in benign breast disease. We found that triglyceride and cholesterol levels were significantly higher in diseased compared to control subjects although the LDL levels were similar. Previous studies have reported a significantly higher level of serum lipid moieties among breast cancer patients [7]. Other studies have proposed an abnormality of prostaglandin synthesis secondary to deficient essential fatty acid (EFA) intake in diet. Measurement of plasma fatty acids have confirmed abnormal lipid profiles in patients with mastalgia and reduced levels of the metabolites of linolenic acid [8]. Elevation of High Density Lipoprotein – C (HDL) has been reported in

Table 4: Correlation between tissue ER status and S. estradiol levels in BBD

ER Status	Estradiol concentration (pg/ml)	p value
1+	110 ± 9.0	<0.001
2+	106 ± 7.7	
3+	163 ± 3.6	

patients with cyclical mastalgia but not in those with non-cyclical pain. We feel that higher levels of serum lipid leads to higher peripheral conversion of androstenedione into estrogen. Thus there is a direct link between higher serum lipid levels, higher serum estradiol levels and benign breast disease.

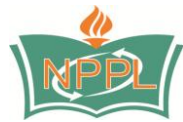
In a study Mishra SK *et al.*, found that low fat diet improves the symptoms as well as the lipid profile in patients with benign breast disease [9]. After 6 months of a low fat diet there was improvement in mastalgia, nodularity and discharge. In another prospective study the serum lipid profile was measured on day 1, 15 and 25 of menstrual cycle. It was concluded that cyclical mastalgia may be a result of cyclical aberration in lipid metabolism [10].

Conclusions

The results of the present study suggests a causal interlinked role between serum estradiol levels, estrogen receptors and lipid profile in the etiopathogenesis of symptoms and signs of benign breast diseases.

Authors' contribution

SK conceived and designed the study, analyzed the results and prepared the draft manuscript.
SS Collected and analyzed the data and conducted the literature search
HDK Supervised biochemical studies
MK Analyzed pathological data
SKG Edited the manuscript for intellectual contents



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Conflict of Interests

The authors declare that there are no conflicts of interests.

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Ethical considerations

The study was approved by the Institute Ethics Committee

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