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Original Article

Relationship between Serum Prolactin Level and the Clinical Course of Fibrocystic Breast Changes: A Cross-Sectional Descriptive Study

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Abstract

Background and objectives: fibrocystic changes are the most common benign breast condition that can be seen inalmost 40% of 20-65-year-old women. This study mainly aimed to evaluate the association between the increased level of serum prolactin and fibrocystic changes. In fact, if an association could be found between the increased level of serum prolactin and fibrocystic changes, especially its atypical type, patients with fibrocystic changes and increased prolactin levels who are suspected with malignancy could undergo biopsy and be more accurately examined and followed up in terms of possible atypical cases. The study also aimed toreview the effects of thetreatments reducing the prolactin levels to control fibrocystic changes and its symptoms.

Materials and Methods: This is a cross-sectional descriptive study. The studied population includes 63 women of reproductive age (perimenopause) who had problems such as pain; feeling of heaviness, lumps and nipple discharge, in whose baseline ultrasound breast fibrocystic changes were reported. Mammography and Early MRI (if necessary) were conducted on patients and imaging and examinations were repeated every three months for one year. Patients with hyperprolactinemia were treated and breast changes in them were investigated. Data were collected by SPSS version 19 and analyzed using chi-square test, Fisher's exact test and t-test.

Results: In the Early Ultrasound, 71.4% of women with fibrocystic changes had changes in both sides, 12.7% had changes in the right side and 12.7% had changes in the left side of breast, respectively. Meanwhile, atypical changes were observed in none of the patients. The majority of patients were in normal conditions in terms of hormones of prolactin, FSH, Testosterone, TSH, DHEAS and LH, but the hormone prolactin increased in 8 patients (12.7%). After the treatment, cyst size increased in 12.5% and decreased in 37.5%, respectively. Chi-square test results showed a significant relationship between prolactin levels and cyst size (p-value <0.05).

Conclusion: The study results showed that the increased prolactin levels and fibrocystic breast changes are not associated with one another.

Key words: Fibrocystic breast, Prolactin, Breast cancer, Breast cyst

INTRODUCTION

Fibrocystic change is the most common breast lesion. This term refers to the histology image of fibrosis, cyst formation, epithelial hyperplasia, adenosis, and apocrine metaplasia (1,2). Nearly 40% of women of childbearing age have fibrocystic changes (3-4). F.C.C pathogenesis is not quite clear. In an article, it is attributed to the breast tissue's response to the monthly changes in estrogen and progesterone levels (5). Another article attributes it to the increased levels of estrogen and lower levels of progesterone (6). These lesions are often associated with benign changes in breast epithelium (1). However, 5% of fibrocystic changes have atypical hyperplasia which is associated with a five-fold increase of risk of cancer (of course, if they have a positive family history of

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breast cancer.) (3,4). In addition F.C.C is often associated with pain and breast tenderness and sometimes nipple discharge. Cyclic breast pain is the most common symptom of fibrocystic changes. Prolactin is a 198-amino acid polypeptide that is secreted by lactotroph cells in the anterior pituitary and is the main trophic factor for milk production by the breast (1). Prolactin does a lot of works in the body including the effects on Reproductive behavior and Homeostasis by regulating solar and humoral immune responses, regulating water and salt and regulating angiogenesis. Prolactin is also responsible for the growth and development of mammary glands is mamogenesis (7). There are specific prolactin receptors in breast tissue that increase during pregnancy and through estrogen therapy. In fact, estrogen has a synergistic effect with prolactin in the growth of breast tissue (8). Therefore, one of the theories is the association between the increased prolactin levels and F.C.C. Some articles would agree with this theory (9, 10 and 11). However, some other articles showed no relationship between the increased prolactin levels and F.C.C. (12, 13, and 14) which are as follows:

In 2002, a study was conducted by Sieja K and Stanosz S in the Netherlands to investigate the effect of serum prolactin level and estrogen on fibrocystic changes in 81 women with FCC and 32 healthy women as control group. Hormone levels were measured in both groups and it was concluded that hyperprolactinemia and Haprastrvzhnysm are risk factors for fibrocystic breast changes (9). In 1990, Breckwoldt conducted a study in Germany on 193 women with fibrocystic changes out of whom 46% had increased prolactin levels and their response to TRH test was an increase in the prolactin level and TSH (10). Meanwhile, in 1984, Peters et al. measured serum prolactin levels in 193 patients with fibrocystic breast changes and compared it with the same number of healthy people. As a result, prolactin level was high in 45.6% of subjects and 21.2% of the control group. In fact, the greatest response of prolactin to the thyrotropin-releasing hormone (TRH) was reported in patients more than control group (11). In 2002, Wypych K et al. in the Netherlands in an article titled as "hormonal imbalance in women with breast cysts" examined 30 women with breast cysts. In 96.7% of cases, serum prolactin levels were normal and only in 8 women with recurrent cysts, prolactin levels were reported high after metoclopramide stimulation (12). In 2002, Nicol et al. in London reviewed the relationship between serum prolactin levels and benign and malignant breast diseases in 153 patients 93% of whom had normal prolactin levels. In fact, only 7% of 54 patients with benign changes had high prolactin level two of whom had fibroadenoma, one had phyllodes tumor and the other one had FCC, respectively (13). Moreover, in 1976, J-martin-comin et al. wrote an article titled "Treatment of fibrocystic breast changes with a prolactin inhibitor called 2-Br-alpha-ergocryptin. In this project, they measured serum prolactin levels in seven patients before and after taking this drug. Before the treatment, hormone levels in the patients were low. However, their symptoms were lessened during the treatment and even cyst size became smaller in one of them. Despite the satisfactory result of this drug,they failed to find a correlation between the increased prolactin levels and FCC due to the low hormone levels before the treatment, and suggested further investigations (14). However, some articles examined the relationship between the increased prolactin levels and breast cancer. In an article, PIP (prolactin-inducible protein) was considered a clinical marker to detect metastatic tumors in the breast. In this study,breast tissue samples were taken from 97 patients with primary breast tumor and PIP- Mrna was identified in most cases (15). This study aimed to evaluate the association between the increased level of serum prolactin and F.C.C. In fact, if this study could find a relationship between the increased levels of serum prolactin and FCC; especially the atypical type, it could be concluded that patients with FCC and increasedlevels of prolactinwho are suspected with malignancyshould undergo biopsy,examined in terms of possible atypical cases andfollowed carefully. The study also aimed to review the effects of the treatments reducing the prolactin levels to control F.C.C and its symptoms.

MATERAILS AND METHODS

This is a cross-sectional descriptive study. The studied population includes 63 women of reproductive age (perimenopause) who had problems such as pain; feeling of heaviness, lumps and nipple discharge, in whose baseline ultrasound breast fibrocystic changes were reported. In this study, a questionnaire was developed for patientscontaining data includingpatients' demographic recordssuch as age, weight, height, date of marriage and first pregnancy, number of pregnancies and children, historyof lactation, hormonal disorders and the treatment methodand menstruation, history of breast cancer in them or in their first degree relatives, history of surgery or trauma to the breast with a main complaint from the patient and the examination results obtained by the surgeon.

The results include hormone test results include LH, FSH, prolactin, DHEAS, Testosterone, and TSH, the results ofprimary ultrasound and mammography, the results of MRI, FNA, core needle Bx, excisional Bx, if necessary, periodic examination and ultrasound every three to four

months (one year), the results of repeatedmammography (if necessary, it willbe repeated after one year), prolactin hormone levels after the treatment (in case of any hyperprolactinemia), the results of new sampling, if necessary, repeated measurement of prolactin hormone levels in the event of a change in the disease process. Among women of reproductive age (perimenopause) who referred to clinics of Jahrom,patients with problems such as pain, feeling of heaviness, lumps and nipple discharge were selected. The patients who tookhormone medications during the study period or had a history of breast cancer or werelactatingduring the study period were excluded from the study. Then,hormone tests including LH, FSH, DHEAS, Testosterone, TSH, and prolactin were carried out on all patients. Moreover, breast ultrasound was conductedon subjects under 35 and mammography and if necessarybreast MRI were carried out on patients over 35 in addition to ultrasound. Patients with very high prolactin levels (more than 200) or symptoms such as headaches and vision changes whosebrain MRI showed pituitary macroadenoma (prolactinoma) were also excluded. Patients' demographic information was recorded in the questionnaire.Meanwhile, patients were examined by a surgeon and the results were recorded. All suspected cases in the examination and Para-clinical investigations underwent tissue sampling (FNA, core needle biopsy, and excisional biopsy) to rule out breast cancer. After hormonal examinations, imaging and tissue sampling, patients who were diagnosed with fibrocystic breast changes were included in the study and those with breast cancer were excluded. Patients were controlled for one year during whichcommon treatment of fibrocystic changes including Vita, E, weak diuretics, exercise and dietary changes as well as treatment for high levels of prolactin were conducted on them.Patients were examined and underwent ultrasoundquarterly and their prolactin level was checked after the treatment. In case ofany fibrocystic changes in the patient's breast during the study period,levels of hormonesincluding prolactin were measure again and necessary tissue sampling were conducted and all results were recorded in the questionnaire. Data were first collected by SPSS version 19 and then analyzed using chi-square test, Fisher's exact test and t-test.

RESULTS

In this study, the average age of patients was 38.84 years, the average age of marriage was 17.45 years, the average age of first childbirth was 18.47 years and each woman had an average of 2.57 children. Table 1-4 shows the demographic characteristics. 31.3% of women of childbearing age had fibrocystic changes and overweight (BMI level of 25 to 29.9) and 22.2% of them were obese (BMI of greater than 30). Out of these patients,25.4% had a family history of breast cancer, 14.3% had a history of breast surgery and 7.9%had a history of hormonal disorders. Out of patients, 74.6%had fibrocystic breast changes and regular menstrual status,19.0% had irregular menstrual status and the others had hysterectomy and menopause status. Out of patients, 88.9% had fibrocystic changes along with breast pain. Moreover,55.6% had a feeling of heaviness in their breast of, 34.9% felt a lump in their breast, 12.7% had nipple discharge and lump was palpable in the examination of 47.6% of patients. In the Early Ultrasound, 71.4% of patients had fibrocystic breast changes in both sides, 12.7% had changes in the right side and 12.7% had changes in the left side of breast, respectively.Meanwhile, atypical changes were observed in none of the patients. Early mammographywas not performed on 39.7% of patients, but performed on 60.3%the result of which was reported to be benign. MRI was performed onlyonone patient (1.6%) the result of which was reported to be benign.27% of women underwent fine needle aspiration (FNA)andtook samples from their breast lumps the result of which was reported to be benign. Breast fine needle aspiration was performed on 18 patients. Moreover,core needle aspiration biopsy (CNAB) of breast and breast biopsy and excision was performed onlyon one patient (1.6%) the result of which was reported to be benign.Most women with fibrocystic changes were in normal conditions in terms of hormones of prolactin, FSH, Testosterone, TSH, DHEAS and LH, but hormone prolactin level was increased in 8 patients (12.7%) of women with fibrocystic changes. FSH levels were increased in 5 patients (7.9%) of women and testosterone levels were decreased in 2 patients (3.2%) of patients. TSH level was increased in 3 patients (4.8%) of women with fibrocystic changes and decreased in 1 patient (1.6%). DHEAS levelwas also decreased in 1 patient (3.2%) with fibrocystic breast changes.

In patients who underwent periodic ultrasoundevery three months, cyst size did not change in 60.3%; it increasedin 27%and decreased in 4.8%. Moreover,cyst size changed in 4.8% of women and new cysts have been developed in the opposite breast as well.Chi-square test results showeda significant relationship betweenprolactin levels and cyst size with conducting periodic ultrasoundevery three months (P-value <0.05). In patientswith increased levels of prolactin,cyst size was increased in 12.5% and decreased in 37.5%.However, in patients with normal prolactin levels,cyst size was increased in 29.5% and new cysts have been developed in the opposite breast as well in 9.1%.This resultshowed that the prolactin increasing treatment is effective in reducing cyst size.

Table 1: Hormone levels in patients with fibrocystic breast changes:

Variable	Decreased		Increased		Normal	
	Percentage	Number	Percentage	Number	Percentage	Number
Hormone Prolactin	87.3	55	12.7	8	0.0	0
Hormone FSH	92.1	58	7.9	5	0.0	0
Hormone Testosterone	96.8	60	0	0	3.2	2
Hormone TSH	93.7	59	4.8	3	1.6	1
Hormone DHEAS	98.4	62	0.0	0	1.6	1
HormoneLH	93.7	59	6.3	4	0.0	0

Table 2: A comparison between prolactin levels and clinical course of breast fibrocystic changes in patients

Clinical course	Normal		Increased		P-value
	Percentage	Number	Percentage	Number	
Periodic checkup every three months					
Periodic checkup every three months	92.7	51	87.5	7	0.505
Periodic ultrasound every three month	7.3	4	12.5	1	
Periodic ultrasound every three months					
It has not changed	61.8	34	50.0	4	0.505
It has changed and cyst size is increased	29.1	16	12.5	1	
It has changed and cyst size is decreased	0	0	37.5	3	
It has changed and new cysts have been developed in the opposite breast	9.1	5	0	0	

Independent T test results showedno significant relationship between prolactin levels and the demographic variables of age, weight and height (p-value>0.05).

Chi-square test results showed no significant relationship between prolactin levels and BMI (p-value>0.05). Although more women with overweight and obese had increased prolactin levels (62.5%) compared to the control group (52.7%), this difference was not statistically significant. Chi-square test results showed a significant relationship between prolactin levels and marital status (p-value <0.05). Out of subjects,37.5% of married women had increased levels of prolactin, while 90.9% of the control group had increased levels of prolactin. Chi-square test results showed a significant relationship between prolactin levels and a history of lactation (p-value <0.05).

Chi-square test results showednosignificant relationship between prolactin levels and menstrual status (p-value>0.05). Chi-square test results showednosignificant relationship between prolactin levels and levels of hormones LH, FSH, Testosterone, DHEAS and TSH (P-value>0.05).

Table 3: A comparison between prolactin levels and demographic variables

Variable	Prolactin level				P-value
	Normal		Increased		
	Standard deviation	Mean	Standard deviation	Mean	
Age	7.75	39.42	10.70	34.88	0.145
Weight	10.34	64.33	4.03	60.75	0.085
Height	6.51	155.64	7.41	153.00	0.297

DISCUSSION

Breast cancer is the most common cancer in women (except from skin neoplasia) and the second leading cause of death resulting from cancer after lung cancer [2, 12]. In recent years, incidence of breast cancer has increased [12].

Women with a history of benign breast disease will include a small group of patients with breast cancer in the presence of atypia in their histological study (almost 5%) (Table 1) [9]. Therefore, the clinical diagnosis of fibrocystic changes can cause severe anxiety in patients, while if malignancy is ruled out by history, physical examination and imaging techniques will have little clinical importance [1]. That is because fibrocystic disease is attributed to a group of histopathologicalchanges that arediagnosable and treatable [12]; whereas, one of the tasks of prolactin in the body is to grow mammary gland (mamogenesis) [7] (Table 2). There are specific prolactin receptors in breast tissue which areincreased during pregnancy and through estrogen therapy. In fact, estrogen and prolactin have a synergistic effect on breast tissue growth [8]. On the other hand, pathogenesis of fibrocystic changes is not quite known [11]. Given the role of prolactin in breast tissue, another theory is the association between the increased level of prolactin and

Table 4: A comparison between prolactin levels and a history of breast disorders in patients with fibrocystic breast changes

Variable	Prolactin level				P-value
	Normal		Increased		
	Mean	Standard deviation	Mean	Standard deviation	
History oflactation					
Yes	9	16.4	6	75.0	<0.05
No	46	83.6	2	25.0	
Personal history of breast cancer					
Yes	55	100.0	8	100.0	-
Nio	0	0	0	0	
Family history of breast cancer					
Yes	40	72.7	7	87.5	0.370
No	15	27.3	1	12.5	
History oftrauma to the breast					
Yes	55	100.0	8	100.0	-
No	0	0	0	0	
History of breast surgery					
Yes	48	87.3	6	75.0	0.354
No	7	12.7	2	25.0	
History ofhormonal disorders					
Yes	52	94.5	6	75.0	*0.117
No	3	5.5	2	25.0	

Table 5: A comparison between prolactin levels and other hormones in women with fibrocystic breast changes

Variable	Prolactin level				P-value
	Normal		Increased		
	Mean	Standard deviation	Mean	Standard deviation	
Hormone FSH					
Normal	51	92.7	7	87.5	0.505
Increased	4	7.3	1	12.5	
Decreased	0	0	0	0	
Hormone TES					
Normal	52	96.3	8	100	0.580
Increased	0	0	0	0	
Decreased	2	3.7	0	0	
Hormone TSH					
Normal	52	94.5	7	87.5	0.513
Increased	2	3.6	1	12.5	
Decreased	1	1.8	0	0	
Hormone DHEAS					
Normal	54	98.2	8	100	0.701
Increased	0	0	0	0	
Decreased	1	1.8	0	0	
Hormone LH					
Normal	52	94.5	7	87.5	0.427
Increased	3	5.5	1	12.5	
Decreased	0	0	0	0	

breast fibrocystic changes.Some articles proposed this theory including the study of Sieja K StanoszS conducted in 2002 in the Netherlands to investigate the effect of serum prolactin level and estrogen on fibrocystic breast changes on 81 women with fibrocystic changes and 32 healthy women as control group. Hormone levels were measured in both groups and it was concluded that hyperprolactinemia and Hyprastrvzhnysm fibrocystic are risk factors of breast changes [15].Breckwoldt conducted a study in 1990 in Germany on 193 women with fibrocystic changes 46% of whom had increased levels of prolactin and responded to TRH test by increased levels of prolactin and TSH [16].Moreover, Peters et al. in 1984 measured serum prolactin level in 193 patients with fibrocystic breast changes, and compared the results with the same number of healthy individuals and concluded that prolactin levels were increased in 45.6% of subjects and 21.2% of the control group. In fact, most prolactin response to thyrotropin-releasing hormone (TRH) was reported in patients compared to the control group [17].

Moreover, some studies have examined the effects of prolactin-lowering drugs in reducing the size of benign breast cysts.Moreover, in 2013, a study was conducted by Castillo-Huerta E et al.inDr. Silva Hospital in Mallya(Spain) on 171 patients with fibrocystic breast changes.In this study, patients were divided into two groups of 81 and 90 subjects. The first groupreceived Dihydroergocryptin (DHEC) and the second group received cabergoline (Table 3). Patients' symptoms decreased in both groups during the first month of drug use. However, this effect was greater in patients treated with Dihydroergocryptin(DHEC) [18]. In an article conducted on 77 patients with fibrocystic breast changes in 2006, Castillo-Huerta E et al. showed the effect of the treatment of patients with Dihydroergocryptin (DHEC) in relieving the disease symptoms, including the improvement ofgalactorrhea andmastalgia and disappearance of breast nodules (23.1%) compared to placebo [19].The decrease of the size of breast cysts with prolactin-lowering drugs, mentioned in this article, could indicate the role of prolactin in the emergence of breast fibrocystic changes (Table 4). Some articles have also addressed the relationship between the increase of prolactin and breast cancer. In this study,breast tissue samples were taken from 97 patients with primary breast tumor and PIP-mRNA was detected in most patients (Table 5) [20].In this study, from among the patients with breast problems who referred to the clinics over a year,those with malignancy were excluded and 63 patients with fibrocystic changes were included in the study. In this study, it was tried to exclude the patients who were taking any hormone medicinesduring the study period, or had a history of breast cancer or werelactating during the study period. Meanwhile, patients with very high prolactin levels (more than 200) or symptoms such as headaches

and vision changes that their MRI showed brain pituitary macroadenoma (prolactinoma) were also excluded. In the Early Ultrasound, 71.4% of patients had changes in both sides, 12.7% had changes in the right side and 12.7% had changes in the left side of breast, respectively. Meanwhile, atypical fibrocystic breast changes were observed in none of the patients. In the meantime, the greatest complain of patients was from breast pain (88.9%) and lumps were palpable in the examination of 47.6% of patients. Out of the patients selected for the study, only 8 ones had high prolactin level, which was not statistically significant. However,Chi-square test results showed a significant relationship between prolactin levels and cyst size through periodic ultrasoundevery three months (p-value<0.05). In fact, after treatment with prolactin-lowering drugs, breast cyst size remained unchanged in 50% of women, increased in 12.5% and decreased in 37.5%. It indicates the role of serum prolactin lowering treatmentsin reducing in the size of the cysts. Meanwhile, after treatment by hyperprolactinemia,the examination results of only one patient changed and in furtherexaminations, breast lump was touched while no breast lump was touched in periodic examinations in seven other patients. Despite the use of common treatments for fibrocystic changes such as vitA, E, weak diuretics, exercise and diet changes in patients with normal prolactin levels,cyst size did not change in none of the subjects after the periodic ultrasound and new cysts were developed in the opposite breast in9.1% of subjects. Considering the absence of atypical fibrocystic breast changes in the selected patients, the study failed to review the effects of the increased prolactin level on atypical changes as well as the effect of prolactin lowering treatments in changing the clinical course of atypia; which seems to be due to the low number of subjects.

CONCLUSION

The study results showed no relationship between the increased level of prolactin and fibrocystic breast changes. However,hyperprolactinemia treatment with prolactin-lowering drugs reduces the size of breast cysts.

Limitations of the study

Short period of study and the small number of subjects, lack of cooperation of some patients with researcher in completing the questionnaires, the lack of further reference of some individuals for which some tests was requested or lack of cooperation of some patients for running tests and follow-up, possible errors of laboratory in the measurement of prolactin, lack of cooperation of patients in taking medication, lack of cooperation of patients in conducting periodic mammography, ultrasound and examinations,

Recommendations for future research

- For better investigation of the relationship between the increased level of prolactin and fibrocystic breast changes,further studies should be conducted in other areas withlarger study population.
- Longitudinal studiesshould be conducted in which women with increased level of prolactin will be examined for the presence fibrocystic breast changes.
- Further studies should be conducted on prolactin performance in human body.
- Further studies should be conducted to examine the relationship between high serum prolactin level and possible increase of breast cancer cases
- The relationship between demographic variables, marital status, BMI, history of previous breast problems, menstrual status, hormone levels of LH, FSH, DHEAS, Testosterone and TSH with serum prolactin levels and the incidence of fibrocystic breast changes should be examined.

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