



Association of Benign Breast Disorders with Hypothyroidism

Benign Meme Bozukluklarının Hipotiroidizmle İlişkisi

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Abstract/Öz

Introduction: More than half of women complaining of breast symptoms are affected by benign breast disorders (BBD). Thyroid dysfunction has been implicated as the etiology. Therefore, we conducted a study to assess the association between BBD and hypothyroidism.

Methods: In this case-control study, 226 women with BBD without a history of thyroid disorders were recruited consecutively as the case group. Controls included 206 healthy women without breast disease. Blood samples were taken, and the levels of free thyroxine, tri-iodothyronine, thyroid stimulating hormone, prolactin, and anti-thyroid peroxidase antibody were measured.

Results: Hypothyroidism was insignificantly more frequent in the case (5.8%) than in the control group (5.3%), as well as in cases of fibrocystic changes (7.9%) in comparison with mastalgia (1.4%) and nipple discharge (2.6%) in the BBD subgroups ($p=0.85$ and 0.09 , respectively). On contrary, Hashimoto's disease was slightly more frequent in controls, but the difference was not significant ($p=0.70$).

Conclusion: The present study demonstrates no significant association between hypothyroidism and BBD.

Keywords: Breast, benign, thyroid, hashimoto, autoimmunity

Amaç: Meme semptomlarından şikayet eden kadınların yarısından çoğu benign meme hastalıklarından etkilenmektedir. Tiroid fonksiyon bozukluğu etyoloji olarak ilişkilendirilmiştir; Bu nedenle benign meme hastalıklarının (BBD) hipotiroidi ile ilişkisini değerlendirmek için bir çalışma yaptık.

Yöntemler: Kesitsel tipteki bu çalışmada, tiroid bozukluğu öyküsü olmayan BBD'li 226 kadın, ardışık olarak vaka grubu olarak çalışmaya alındı. Kontroller arasında 206 sağlıklı kadın vardı. Tüm katılımcılardan kan örnekleri alındı ve her örnekte serbest tiroksin, tri-iyodotironin, tiroid uyarıcı hormon, prolaktin ve anti-tiroid peroksidaz antikorları düzeyleri ölçüldü.

Bulgular: Hipotiroidi kontrol grubunda (%5,3) de mastalji ile karşılaştırıldığında fibrokistik changes (%7,9) durumlarda olduğu gibi (%2,6) alt grupları (%1,4) ve meme deşarj daha önemli ölçüde olmayan durumda (% 5,8) daha sık sık ($p=0,85$ ve $0,09$, sırasıyla). Tersine, Hashimoto hastalığı denetimlerde biraz daha sık, ama fark önemli değildi ($p=0,70$).

Sonuç: Bu çalışmada, hipotiroidi ve benign meme hastalıkları arasında anlamlı bir ilişki bulunmadığı gösterilmiştir.

Anahtar Kelimeler: Meme, benign, tiroid, hashimoto, otoimmünite

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Introduction

Breast-related complaints comprise a significant portion of health problems in women. Studies have shown that approximately half of women attending clinics complaining of breast symptoms are affected by benign breast disorders (BBD) (1), including fibrocystic disease, nipple discharge, or mastalgia. The etiology of BBD is unknown, but various factors have been accounted for them, and endocrine disorders, including thyroid-related factors, is one of them (2-4). Although the relation between thyroid hormones and BBD is yet controversial, decreased thyroid function is considered as a probable cause of BBD, and thyroid hormone replacement therapy has positive effects on the BBD clinical outcome (2, 5-12).

The aim of this study was to investigate the association between BBD and hypothyroidism.

Methods

Participants

This case control study was conducted in the breast clinic of Arash Women's Hospital, a university hospital in Tehran, Iran, between 2013 and 2014, and 226 women diagnosed with BBD based on the eligibility criteria were consecutively selected and included in the case group. Inclusion criteria were the following: women with BBD consisted of breast pain, fibrocystic changes (FCC), or nipple discharge. Patients with a solid or large cystic mass in the breast discovered on examination or imaging or with any indication for breast surgery, breast cancer, bloody discharge, ductal or lobule hyperplasia, pregnancy, hyperprolactinemia, consumption of oral contraceptives, and recent treatment of hypo- or hyperthyroidism were excluded from the study.

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For documenting of breast pain, cases of mild, moderate, or severe mastalgia, described respectively as tolerable or disabling pain by the patients, were included. Nipple discharge was defined as spontaneous or nonspontaneous nonbloody, nonwatery, and non-serous uni- or bilateral discharge from one or more ducts, which was recognized by the patient as bothersome. FCC was diagnosed according to either breast clinical features, identified as cyclic bilateral breast nodularity and tenderness without true mass, or the ultrasonographic or histological detection of FCC.

The control group consisting of 206 healthy women was selected among women who had attended the clinic for breast cancer screening without any breast symptoms, who were not receiving treatment for thyroid disease, and who had normal breast clinical exam and breast ultrasonography as well as normal mammography if above 39 years of age. Exclusion criteria consisted of detection of a solid or large cystic mass on the breast exam or imaging or any indication for breast surgery, breast cancer, pregnancy, hyperprolactinemia, consumption of oral contraceptives, and recent treatment of hypo- or hyperthyroidism.

The study was approved by the Institutional Review Board of Tehran University of Medical Sciences by the number of 18090-39-04-91 in Feb 2013, and written informed consent was obtained from all participants.

In all participants, breast and thyroid exam were performed by two surgeons experienced in breast disease. Demographic characteristics of all participants and any nonspecific symptoms related to hyper- or hypothyroidism were recorded. Blood samples were

collected from all participants, and sera were stored at -40 °C until assay. Thyroid laboratory blood tests including free thyroxin (FT4), tri-iodothyronine, thyroid stimulating hormone (TSH), prolactin (PRL), and thyroid peroxidase antibody (TPO Ab) were performed by the electrochemiluminescence immunoassay (ECLIA) method, using Roche diagnostics kits and a Roche/Hitachi Cobas e-411 analyzer (GmbH, Mannheim, Germany).

The diagnosis of thyroid disease was performed according to hormonal parameters. The TSH level ≥ 5 micro-international unit per milliliters ($\mu\text{IU/mL}$) as well as TPO Ab levels above 40 international units per milliliters (IU/mL) were considered abnormal. Normal ranges of TSH and T4 (total thyroxine) in adults are 0.2-4.2 IU/mL and 4.8-14.1 $\mu\text{g/dL}$, respectively. The patients with $\text{TSH} \geq 5$ and a normal T4 concentration were considered to have subclinical hypothyroidism, and those with a T4 concentration below the normal range were categorized as having overt hypothyroidism. Detection of serum TPO Ab was diagnosed as autoimmune or Hashimoto's thyroiditis.

Statistical Analysis

Statistical analysis was performed with the Statistical Package for Social Sciences software version 16.00 for Windows (SPSS Inc.; Chicago, IL, USA). Descriptive statistics are presented as mean \pm SD or numbers and percentages. An analysis by χ^2 test or Fisher's exact test was performed to evaluate qualitative variables. For continuous variables, Student's t-test was used. A logistic regression model was used to adjust the association between BBD and thyroid function tests for confounding factors including age, body mass index (BMI), and family history of BBD, and to estimate the strength of this association.

A $p < 0.05$ was considered to be statistically significant. In addition to TSH, other variables including age, BMI, and a family history of BBD were separately entered into the model of multinomial logistic regression (univariable model), and the crude odds ratio (OR) of each was obtained. The variables with $p < 0.02$ were entered into the model. The p -value < 0.05 was considered to be statistically significant. In addition, another multinomial logistic regression model was used for association between the TPO Ab level and BBD, and the same confounding variables were considered.

Results

Overall, a total of 432 women including 226 women with BBD and 206 healthy controls without BBD were included in the study. The mean age of patients and controls was 40 ± 8.8 years (20 to 63 years) and 46 ± 9.8 years (23 to 71 years), respectively.

In the patients group, mastalgia with 62% (cumulative rate) was the most common benign breast disorder, followed by FCC (52.65%) and nipple discharge (16.80%). The frequency of various types of BBD is shown in Table 1.

When comparing the case and control groups, no significant difference was found in the hypothyroidism and thyroid autoimmunity rate between the two groups ($p = 0.85$ and 0.70 , respectively) (Table 2).

The rate of hypothyroidism and high TPO Ab between the BBD subgroups (FCC, mastalgia, and nipple discharge) were not significantly different ($p = 0.09$ and 0.8 , respectively). The frequency of

Table 1. Frequency of BBD subtypes

Type of BBD	Number (%)
FCC	53 (23.5%)
Mastalgia	74 (32.7%)
ND	30 (13.3%)
FCC+Mastalgia	61 (27%)
FCC+ND	3 (1.3%)
Mastalgia+ND	3 (1.3%)
Mastalgia+FCC+ND	2 (0.9%)
Total	226 (100%)

BBD: benign breast disorders; FCC: fibrocystic change; ND: nipple discharge

Table 2. Comparison of serum TSH and TPO Ab between the two groups

	Cases n (%)	Controls n (%)	Crude OR* (95% CI)	p
Serum TSH level ($\mu\text{IU/mL}$)				
$< 5^{**}$	213 (94.2)	195 (94.7)	1.08 (0.47-2.4)	0.85
≥ 5	13 (5.8)	11 (5.3)		
TPO Ab level				
$\leq 40^{**}$	176 (77.9)	158 (76.6)	0.9 (0.59-1.48)	0.70
> 40	50 (22.1)	48 (23.3)		

* OR: odds ratio; ** reference category

Table 3. TSH and TPO Ab in BBD subgroups

Type of disorder	TSH Level (μ IU/mL)		p	TPO Antibody		p
	n (%)			n (%)		
	<5	\geq 5		\leq 40	>40	
FCC	105 (92.1)	9 (7.9)	0.09	87 (76.3)	27 (23.7)	0.84
Mastalgia	73 (98.6)	1 (1.4)		59 (79.7)	15 (20.3)	
ND	37 (97.4)	1 (2.6)		30 (78.9)	8 (21.1)	

BBBD: benign breast disorder; FCC: fibrocystic change; ND: nipple discharge; TSH: thyroid stimulating hormone; TPO: thyroid peroxidase

Table 4. TSH and TPO Ab in patients with different levels of pain

Breast Pain Intensity	Serum TSH (μ IU/mL)		p	TPO Antibody		p
	n (%)			n (%)		
	<5	\geq 5		\leq 40	>40	
No	28 (90.3)	3 (9.7)	0.15	23 (74.2)	8 (25.8)	0.39
Mild	56 (98.2)	1 (1.8)		51 (89.4)	6 (10.5)	
Moderate	60 (93.8)	4 (6.2)		50 (78.1)	14 (21.9)	
Severe	9 (81.8)	2 (18.2)		9 (81.80)	2 (18.2)	

TSH: thyroid stimulating hormone; TPO: thyroid peroxidase

these thyroid abnormalities in different BBD subgroups is shown in Table 3 in detail. In the same group, an abnormal TPO antibody level was detected in 27 (23.7%) women with FCC, 15 (20.3%) with mastalgia, and 8 (21.1%) with nipple discharge.

The frequencies of hypothyroidism and thyroid autoimmunity at different levels of breast pain are demonstrated in Table 4.

In the unadjusted analysis, serum TSH (OR: 0.98, 95% confidence interval [CI]: 0.9-1.02) and TPO Ab levels (OR: 0.9, 95% CI: 0.99-1) had no impact on BBD.

These results did not change after an adjustment for age, BMI, and a family history of benign breast disorders, and the association between BBD and serum TSH (OR: 0.98, 95% CI: 0.9-1.04) and TPO Ab levels (OR: 1, 95% CI: 0.99-1) was not shown.

Discussion

Benign breast disorders are a heterogeneous group of disorders that, although not dangerous, can affect the quality of life and have multiple adverse effects. Concerns of patients about breast symptoms, disability, and sometimes disturbed partnership due to severe breast pain or discharge are some common examples. BBD is very widespread among women, especially in women of young and reproductive age.

In our study, hypothyroidism was insignificantly more common in women with BBD in comparison with the control group. Thyroid autoimmunity was slightly more frequent in the case group, but the difference was not significant. In the BBD subtypes, the abnormal levels of TSH (\geq 5 μ IU/mL) were detected more frequently in the FCC group. Nevertheless, these higher levels were not statistically significant in the final analysis. In addition, among women in the mastalgia subgroup, hypothyroidism was more common in patients with moderate breast pain than in the severe and mild cases, but this also was not statistically significant.

The association of breast diseases with thyroid disorders have been widely studied (2-5, 13-16). Bhargav et al. (5) evaluated data on 201 patients with BBD to determine the prevalence of hypothyroidism in these patients in 2009. They assessed the serum levels of T_4 , TSH, and PRL in cases of BBD (plus TPO Ab when hypothyroidism or goiter was detected). The overall prevalence of hypothyroidism was 23.2% (nipple discharge 37%, mastalgia 23%, lump/lumpiness 17.4%). In this study, the highest rate of hypothyroidism was seen in the nipple discharge group, while in the present study, the FCC group had the highest rate of hypothyroidism, which was not statistically significant (5).

In a study by Anil et al. (2) including patients with nodular thyroid disease and Hashimoto's thyroiditis, a significant association was found between BBD and thyroid disorders. The rate of hypothyroidism in the BBD group was higher than in the control group (31.4% vs. 21.1%), although insignificantly. Also, the prevalence of BBD in patients with nodular thyroid disease was significantly higher than in other groups. In addition, the TSH level in the BBD group was higher than in the control group, but the difference was not significant (2). Such association was also confirmed by Hardefeldt et al.'s (3) study.

Ditsch et al. (7) evaluated the thyroid status in 143 women with different benign and malignant breast disorders and identified a significant association between the thyroid hormones level and BBD. They showed higher levels of FT3 and FT4 in patients with BBD than in the control group. Also, their study found a higher rate of hypothyroidism in patients with BBD compared to controls (18.5% vs. 7.9%), without significant difference (7).

Giustarini et al. (4) evaluated thyroid function of 61 women with nodular breast disease who were selected for breast surgery and compared them with 100 healthy age-matched women. They showed the strong association between breast cancer and thyroid autoimmunity. The mean TSH concentration was not different be-

tween breast cancer, BBD, and control groups. In this study, the prevalence of TPO Ab was significantly higher in patients with BBD than in the control group, whereas this difference was not demonstrated in our study.

Mardaleishvili et al. (16) screened a group of 90 women for thyroid and breast disease and showed an indirect association between the thyroid function and FCC.

In addition, in 2011, Muller et al. (8) showed a higher prevalence of breast cancer in women affected by benign thyroid diseases, and Hajtmanova et al. (9) demonstrated a positive association between these disorders and Grade I breast carcinoma in 2012. The studies by Hardefeldt et al. (10) and Tosovic et al. (11) in 2012 also confirmed a probable association between breast cancer and autoimmune thyroid disease. Schonfeld et al. (17) in their study showed another association and found a significant association between BBD and thyroid cancer, while others did not find such association (18).

In addition to BBD, the association between breast cancer and thyroid disease has been studied as well (7, 13, 14, 19, 20). Brandt et al. (19) in their study on 766 patients with breast cancer found a significant positive association between increased FT4 levels and reduced breast cancer mortality and increased survival. However, Chan et al. (20) did not find any association between thyroid hormones and breast cancer. In a study by Angelousi et al. (13), a proliferative effect of thyroid hormones on breast cells was identified. In that study, the TSH level was not significantly different between the study groups, but the FT4 level was significantly higher in the BBD and breast cancer group compared to the control group, and the prevalence of goiter in the BBD group was higher than in the breast cancer and control group as well. Also, thyroid autoimmunity in the BBD group was higher than in the breast cancer and control groups. In that study, an improved prognosis of breast cancer in patients with hypothyroidism was confirmed with a lower incidence of lymph node metastasis (13). In another study by Brandt et al. (21), a significant association between FT4 and TPO Ab with breast cancer risk was detected. They found a higher risk of breast cancer associated with increased FT4 and reduced TPO Ab and identified protective role of TPO Ab against breast cancer risk, while others reported opposite results (22).

In comparison with previous studies (2-6, 13-17), the present one has a case-control design, compares the study group with normal controls, and includes an adequate sample size, while the rate of hypothyroidism in the control group is as expected for the general population. According to these results, it appears that there is no association between the thyroid function and breast pain, fibrocystic disease of the breast, and nonbloody/nonserous nipple discharge.

Conclusion

In reviews of previous studies and in our study, an important question arises: Is screening for thyroid dysfunction among patients with BBD justified? According to our results, there is no association between hypothyroidism and BBD. However, to answer this question, we suggest double-blind RCT in women with BBD and subclinical hypothyroidism with levothyroxin treatment for evaluating long-term outcomes.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Tehran University of Medical Sciences (Approval Date: Feb 2013; Approval No.: 18090-39-04-91)

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