



**INSULINORESISTANCE IN PATIENTS WITH FIBROCYSTIC MASTOPATHY, AND  
THE EFFECT OF METFORMIN ON IT**

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**Abstract**

Mastopathy is the most common disease in women, accounting for 90% of the flow of diseases in mammology. The etiology of fibrocystic mastopathy has not been fully elucidated, but many studied risk factors include endocrine disorders, particularly insulin resistance and thyroid disease.

**Keywords:** mastopathy, mastalgia, insulin resistance, metformin.

**Introduction.** Diffuse breast dysphoric dysplasia (mastopathy) is a common type of benign breast disease that accounts for 90% of those who consult a mammologist [3-4].

According to the American Society of Pathologists [6], atypical forms of mastopathy increase the risk of developing breast cancer by 1.5-2 times, and atypical forms by 4-5 times.

The study of the mechanisms of development also diagnostic, treatment and prevention measures of fibrocystic mastopathy is one of the necessary issues, because it is a common pathology of the breast [5].

Several endocrine and non-endocrine theories have been proposed on the etiology of



mastopathy [10].

Risk factors for the development of hyperplastic processes in the breast and neoplastic transformation include: carbohydrate metabolism disorders, hyperinsulinemia, hyperexpression of insulin receptors, insulin-like growth factor (IGF-1) and its receptors [7,8,9], increased aromatase activity in the breast [12].

Hormonal changes that can lead to the development of mastopathy in hypothyroidism include: insulin resistance and hyperinsulinemia, and therefore an increase in body weight[11]. This resistance leads to an increase in serum insulin levels and hyperinsulinemia. Insulin is a growth factor for many tissues, especially breast tissue, increases mitogenic activity, and increases the risk of breast cancer by stimulating estrogen synthesis under the influence of insulin. Numerous studies have confirmed a link between breast cancer and insulin levels [13]. However, such an association is less studied among mastopathies [14].

One of the factors of pathogenetic effect on breast tissue in fibrocystic mastopathy associated with insulin resistance is the use of biguanides, especially metformin. J. Evans et al. was one of the first to find that the use of metformin in patients with diabetes reduced the likelihood of developing malignant tumors. The intracellular target of the anti-tumor effect of metformin is adenosine - monophosphate kinase (AMPK). Its activation inhibits the mTOR- (mammalian target of rapamycin) signaling pathway. As a result, the synthesis of a number of proteins is inhibited and the cell cycle is initiated by decreasing the amount of cyclin D1 [15].

Clinical trials are currently underway to use metformin in the treatment of breast cancer [149], and it is being included in nonadjuvant therapy guidelines even in patients without impaired carbohydrate metabolism. (METTEN study, 2010). With this in mind, there is a growing interest in the use of biguanides in the secondary prevention of breast cancer and in the treatment of fibrocystic mastopathy [5].

However, the relationship between the clinical course of fibrocystic mastopathy and insulin resistance and the effect of metformin on it are poorly understood.

**Objective:** To study the incidence of insulin resistance in patients with fibrocystic mastopathy and the effect of metformin on the clinical course of mastopathy.

**Research sources and methods.** The source of the study was 71 women of childbearing age (18-49 years) who were diagnosed with fibrous cystic mastopathy on the basis of the Urgench branch of the Tashkent Medical Academy. The mean age of the patients was  $34.2 \pm 0.4$  years. In patients, the body mass index averaged  $31.4 \pm 2.54$  kg / m<sup>2</sup> and the HOMA index was  $3.2 \pm 0.25$ .

In all women, breast and thyroid ultrasound (US) was performed using a 7.5 mHz MINDRAY DC 60 (Japan) ultrasound machine.

All women underwent ultrasound examination of the mammary glands on days 5-10 of the menstrual cycle using a MINDRAY-DC 60 linear sensor with a frequency of 7.5 MHz. Diffuse or localized pain in the breast, unpleasant sensations, separation when squeezing, if necessary, mammography examination was performed in two standard projections on a Fujifilm Amulet S digital X-ray machine. All findings were evaluated according to the BIRADS system.

On ultrasound, a fine-needle aspiration biopsy (FNA) was obtained from a high-grade patient in the ACR TI-RADS and BI-RADS system.

Radioimmunological tests for serum hormones were performed using commercial test kits of the Chinese-made **MINDRAY 96A** immunoassay analyzer and the **MAGLUMI X3** chemiluminescence immunoassay analyzer (CLIA).

The Numeric Rating Scale for Pain (NRS) was used to describe mastalgia. This scale is a numerical form of the Visual Analog Scale for pain (VAS) used to represent pain. The numerical rating scale of pain is an easy assessment method for the patient and the observer, taking into account only the intensity and duration of pain [230].



It consists of a horizontal line of numbers from 1 to 10. In this case, 0 - "no pain", 1-3 - "weak pain", 4-6 - "pain of moderate intensity" and 7-10 - "strong intense pain".

In this case, the pain expressed by the patient during the day is expressed in numbers in 1 minute. Expression of pain can be done verbally, even over the phone. Pain was re-evaluated during dynamic follow-up to evaluate treatment efficacy.

### **Results.**

The study examined 3 levels of mastalgia in patients with mastopathy initially diagnosed with insulin resistance (Table 1).

Table 1.

#### **The relationship between the course of mastopathy in patients and insulin resistance**

|                     | Weak pain     | Moderate pain | Severe pain   | in general |
|---------------------|---------------|---------------|---------------|------------|
| Hyperinsulinism abs | M±m%          | abs           | M±m%          | abs        |
|                     | 29 40,85±1,83 | 25 35,21±1,67 | 17 23,94±1,06 | 71         |

When examining the relationship between the occurrence of hyperinsulinism in patients and the clinical course of mastopathy, it was found that in 29 of the 71 patients diagnosed with hyperinsulinism (40.85 ± 1.83%) mastopathy with mild pain syndrome, 25 (35.21 ± 1.67%) with moderate pain in 17, (23.94 ± 1.06%) with severe, intense pain.

$p \geq 0,05$

Table 2.

#### **Correlation between decreased insulin resistance and clinical signs of mastopathy.**

| a6<br>c | Insulin             |                    | p      | index of HOMA       |                    | p      | Chest<br>pain<br>before<br>treatment | Chest<br>pain<br>after<br>treatment | p      | BIRAD<br>S RATE<br>before<br>treatment | BIRAD<br>S RATE<br>after<br>treatment | p     |
|---------|---------------------|--------------------|--------|---------------------|--------------------|--------|--------------------------------------|-------------------------------------|--------|----------------------------------------|---------------------------------------|-------|
|         | before<br>treatment | after<br>treatment |        | before<br>treatment | after<br>treatment |        |                                      |                                     |        |                                        |                                       |       |
| A50     | 19,73±0,14          | 10,38±0,19         | ≤0,001 | 4,38±0,32           | 2,31±0,49          | ≤0,001 | 5,51±0,27                            | 4,23±0,34                           | ≤0,001 | 3,48±0,12                              | 2,83±0,13                             | ≤0,05 |
| B21     | 17,43±0,31          | 16,98±0,30         | ≥0,05  | 3,87±0,13           | 3,73±0,33          | ≥0,05  | 5,35±0,18                            | 5,12±0,46                           | ≥0,05  | 3,43±0,13                              | 3,13±0,83                             | ≥0,05 |

A -  $p \leq 0,05$ , B -  $p \leq 0,001$ , C -  $p \geq 0,05$

A. received regular treatment B. Regular untreated

Most studies have studied the effects of insulin resistance and hyperinsulinism in patients with mastopathy, but since this has not been studied in women with mastopathy in our region, we have focused part of our study on hyperinsulinism and its effects on mastopathy. To do this, we divided patients with hyperinsulinism in the study into two groups: patients who received regular treatment (A) and complied with the recommendations for the elimination of insulin resistance (diet, physical activity and metformin 1000 mg / day) and patients who did not fully comply with irregular treatment (B). Both the dynamics of serum insulin levels and the level of BIRADS in the mammary glands UTT conclusion, as well as the clinical course of mastopathy were monitored.

A. In patients receiving regular treatment following the recommendations, postoperative serum insulin levels were found to decrease from 19.73 ± 0.14 mEd / ml to 10.38 ± 0.19 mEd / ml ( $r \leq 0.001$ ), while the HOMA index was decreased from 4.38. ± 0.32 to 2.31 ± 0.49 ( $r \leq 0.001$ ), the numerical scale of pain was found to decrease from 5.51 ± 0.27 to 4.23 ± 0.34 ( $r \leq 0.001$ ). In the same group of patients, the BIRADS category in the UTT of the mammary gland was found to decrease on average from 3.48 ± 0.12 to 2.83 ± 0.13 ( $r \leq 0.05$ ).



B. In patients who did not follow the recommendations, the level of insulin in the serum after treatment was reduced from  $17.43 \pm 0.31$  mEd / ml to  $16.98 \pm 0.30$  mEd / ml ( $r \geq 0.05$ ), the HOMA index was decreased from  $3.87 \pm 0.13$  to  $3.73 \pm 0.33$  ( $r \leq 0.001$ ), the result of the numerical scale of pain was found to be reduced from  $5.35 \pm 0.18$  to  $5.12 \pm 0.46$  ( $r \geq 0.05$ ), and in this group of patients, the BIRADS category in the Sonography of the mammary gland was found to decrease on average from  $3.43 \pm 0.13$  to  $3.13 \pm 0.83$  ( $r \geq 0.05$ ).

#### **Discussion of the results:**

Numerous studies have confirmed the link between breast cancer and insulin levels. However, such an association is less studied among mastopathies [14].

One of the factors of pathogenetic effect on breast tissue in fibrocystic mastopathy associated with insulin resistance is the use of biguanides, especially metformin. J. Evans et al. was the first to find that the use of metformin in patients with diabetes reduced the likelihood of developing malignant tumors [17].

Clinical trials are currently underway to use metformin in the treatment of SBS [16], even in patients without impaired carbohydrate metabolism, and it is included in nonadjuvant therapy recommendations. (METTEN study, 2010).

The main purpose of the use of metformin in fibrocystic mastopathy is the effect of reducing its antiproliferative and estrogen receptor activity. Even in patients with no insulin resistance, metformin has been shown to reduce aging and cell immortality [19].

It is recommended to add metformin to the treatment of pathological conditions associated with hormonal disorders, characterized by excessive proliferation [18].

Many studies [9,18,19] have studied the effect of insulin resistance and hyperinsulinism factor on the course of mastopathy in patients. In particular, E.V. Musina, I.Yu. Kogan [5] found significant positive dynamic changes in the clinical course of mastopathy using metformin in women with fibrous cystic mastopathy, as well as exogenous mammary gland parenchyma in sonography. They studied mastalgia using a visual analog scale (Visual Analog Scale for pain, VAS) used to express pain, and observed patients for 3–6 months, after 6 months of treatment, no patients with severe pain remained and moderate-intensity pain was significantly reduced. However, in this study, the event control method (control group) was not used to assess the effectiveness of treatment in patients.

Sadaf Alipour and Hadith Rastad [1]. In a study of 154 patients who received metformin (main group) and those who did not (control group), metformin intake did not affect the size of the cysts, although it significantly reduced mastalgia.

However, there are also studies showing that metformin has an effect on the reduction of fibroadenomas in size [2].

There are no studies in our region to study insulin resistance in women with mastopathy and the effects of metformin on it. That is why we have focused part of our research on hyperinsulinism and its effects on the course of mastopathy. It was found that 71 (38.58%) of women of childbearing age with 184 fibrous cystic mastopathy detected in examinations over 2 years had insulin resistance. Patients were divided into two groups: those who received regular treatment in full compliance with the recommendations for insulin resistance (A) and those who did not fully comply (B), in which the relationship between insulin levels, HOMA index, BIRADS category level, and clinical course of mastopathy was studied. In contrast, we noted that under the influence of metformin, changes in the mammary gland in the sonography according to the BIRADS system also change from a relatively high to a smaller category. In patients receiving regular treatment following the recommendations, the BIRADS category was found to decrease on average from  $3.48 \pm 0.12$  to  $2.83 \pm 0.13$  after treatment ( $r \leq 0.05$ ). Changes in the clinical signs of mastopathy confirmed the results obtained before us. In particular, the conclusion of the digital scale of pain was found to decrease from  $5.51 \pm 0.27$  to  $4.23 \pm 0.34$  ( $r \leq 0.001$ ).



**Conclusion.** There is a strong correlation between decreased insulin resistance and the clinical course of mastopathy. ( $r \leq 0,001$ )

There is a reliable correlation between metformin intake and UTT conclusion BIRADS category reduction in women with insulin-resistant mastopathy. ( $r \leq 0.05$ )

**PRACTICAL RECOMMENDATIONS:**

1) Patients with mastopathy should be included in the examination plan for structural and functional status of the thyroid gland and serum insulin levels and NOMA index and endocrinologist examination;

2) Patients with mastopathy should include in the treatment plan a rational diet and physical activity, if necessary, metformin;

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