

Metabolic Syndrome and Breast Cancer Development: A Durable Friendship

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Abstract

Introduction: Breast cancer is the most common type of cancer in women; the incidence increases by 20% when associated with diabetes. Over the last decade, both the incidence and mortality through the neoplasm of the mammary gland or diabetes are constantly growing, and the links between the two are not completely clarified. Our study aimed to bring new comparative information regarding correlations between clinical, pathological, and immunohistochemical characteristics of patients diagnosed with breast cancer, and how their evolution and prognosis are influenced by the presence of diabetes.

Material and Methods: The authors proposed a 2-year case-control study of two groups of patients diagnosed with type two diabetes and breast cancer who were hospitalized at the Medical Clinic of Oncology of Craiova Clinical District Hospital (ECCHC).

Results: The incidence of breast cancer in our region was lower compared to data in Romania and around the world, but the mortality rate was significantly higher. Our study showed a more advanced clinical stage at diagnosis of breast cancer when associated with type two diabetes. Obesity and albumin levels are closely correlated with the hormone-dependent nature of postmenopausal breast cancer in patients with associated diabetes, and their level of aggressiveness is elevated. The median duration of oncological treatment and implicitly the survival rate were significantly lower in the study group, with diabetes, its presence having a high influence on the evolution and prognosis of this category of patients.

Keywords: Breast cancer; Diabetes; Hormonal receptors; Obesity; Albumin; Inflammation.

Introduction

Breast cancer is the most common location of malignant neoplasms in women, with an overall incidence of 11.7% and a significant mortality rate through this type of cancer of 6.9% [1]. Romania's incidence is 12.2%, and the death rate is 7.2% [2]. In cases where this pathology is also associated with diabetes, its incidence increases by approximately 20% [3], and the risk of it being identified in advanced stages at diagnosis is 15% higher compared to women who do not have this combination [4]. There are studies showing that, worldwide, between 2000 and 2030, the number of patients diagnosed with diabetes will increase significantly, even doubling [5].

In this context, it should be emphasized that the value of serum blood glucose is proportional to the level of IGF-1 (insulin growth factor 1), which, as it increases, influences proliferation, cell death, but also metastasis [6]. Also, given that the level of estrogen hormones has already been shown in overweight and obese patients, it is necessary to perform scheduled tests necessary for early detection of diabetes, the mechanisms of regulation of endogenous sex hormones being disturbed by its existence [7]. In this context, the risk of developing breast cancer is twice as high in postmenopausal [8]. Postmenopausal women are more likely to develop breast cancer due to the

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level, as they also have a low estrogenic level, while in obese patients, sustained production of pro-inflammatory cytokines takes place, of which especially tumor necrosis factor (TNF- ϵ) and interleukin 6 (IL-6), which accentuates the expression of aromatase in adipose tissue [9].

Increased adipose tissue aromatase activity stimulates the peripheral conversion of androstenedione and testosterone to estrogen and estradiol [10]. Acquired insulin resistance leads to secondary hyperinsulinism, which stimulates androgenic synthesis in ovarian stroma and inhibits estrogen [11]. With this combined effect, the systemic availability of estrogen is increased, having various effects on tissues, but it is proven that estrogen stimulates cell proliferation and inhibits apoptosis in the mammary gland and endometrium [12]. Ki67 protein can quantify the proliferative activity of tumor cells, often associated with the appearance, development, and prognosis of certain types of tumors [13,14]. Metabolic imbalances, and especially diabetes, have a significant impact on the treatment and evolution of the cancer patient, requiring in-depth study of both diseases [15,16]. Our study aimed to bring new comparative information regarding the pathologic and immunohistochemical characteristics of patients diagnosed with breast cancer, and how their evolution and prognosis are influenced by the presence of diabetes.

Material and methods

A case-control study was proposed, between 2016 and 2017, on two groups of patients diagnosed with type two diabetes and breast cancer who were hospitalized at the Medical Clinic of Oncology of the Craiova Clinical District Hospital. Patients with a performance status of a maximum of two, eligible for cancer therapy were selected. The study aimed to highlight the immunohistochemical characteristics of breast cancer, in correlation with the clinical and biological data of these patients, given the pre-existence of type two diabetes. Included in the diabetic patient group are those patients who had a glycosylated hemoglobin value greater than 6.5% at the time of breast cancer diagnosis. The study group included 106 patients, divided into 53 with type two diabetes, and 53 without diabetes.

Histopathological and immunohistochemical characteristics were obtained on surgical pieces or biopsies in very advanced cases, analyzing Estrogen (ER), Progesterone Receptors (PR), Ki67 values, and Human Epidermal growth factor 2 (HER2) statuses. We also focused on the histological and immunohistochemical characteristics of the described group in comparison to the group without the corresponding type 2 diabetes diagnosis. In addition, we looked at the epidemiological distribution of the patients by age, sex, ethnicity, and number of stage-4 diagnosed patients with type two diabetes.

To conclude the progression of patients with breast cancer linked with type 2 diabetes, the biological inflammatory panel at the time of each patient's diagnosis and the survival rate for each group of patients were also assessed. Laboratory analyses were performed using the following equipment: COULTER DXH for complete hemograms, MINDRAY BS 800 For Alkaline Phosphatase (FAL) and Lactic Dehydrogenase (LDH) measurements, ARCHITECT C8000 for serum albumin measurements, and COBAS E411-2 for glycosylated hemoglobin measurements.

Microsoft Excel (Microsoft Corp., Redmond, WA, USA), the XLSTAT package for MS Excel (Addinsoft SARL, Paris, France), and IBM SPSS Statistics 20.0 (IBM Corporation, Armonk, NY,

USA) were used, for statistics. Student T-Test was used, with a statistical significance of ' $p < 0.05$ ', and ' r ', correlation index. The study's data collection was stored in Excel files (from the Microsoft Office 2010 suite).

Ethical approval: The protocol of the study received the approval of the Ethics Committee of the University of Medicine and Pharmacy of Craiova, approval number 39/20.01.2023.

Results

During the analyzed period, 2016-2017, in Dolj County, the incidence rate was 10.95%, and the mortality rate was 7.37%.

Of the group of oncological patients with diabetes, 53 patients were selected, of which 50 were women, 3 were men, 28 were in rural areas, and 25 were in urban areas.

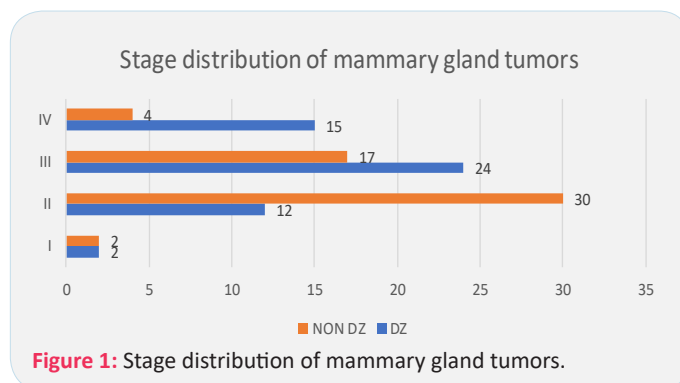


Figure 1: Stage distribution of mammary gland tumors.

By stage at diagnosis, 15 patients were diagnosed in stage IV (28.3%); 24 in stage III (45.28%), 12 in stage II (22.64%), and 2 in stage I (3.77%). By comparison, in the control group, without associated diabetes, 4 patients in stage IV (7.54%), 17 in stage III (32.75%), 30 in stage II (56.6%), 2 in stage I (3.77%) Figure 1.

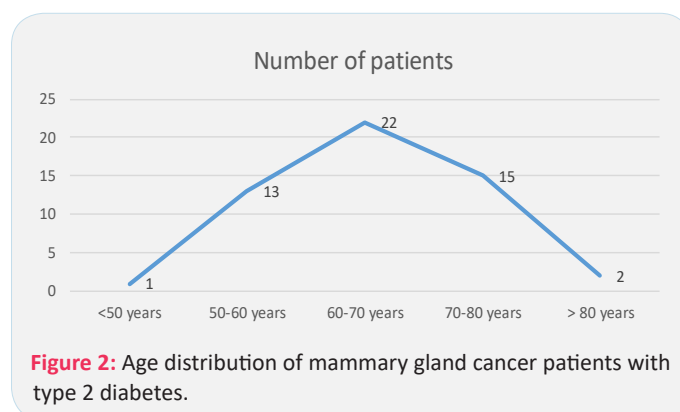


Figure 2: Age distribution of mammary gland cancer patients with type 2 diabetes.

Depending on age, the maximum incidence of mammary gland neoplasm was between 60 and 70 years, 22 patients, 41.5%. 1 patient was under 50 years old, 13 patients were between 50 and 60 years old, 22 were between 60 and 70 years old, 15 patients aged between 70 and 80 years, and 2 patients were over 80 years old (Figure 2).

32 of the patients with associated diabetes could be operated on radically, and in 21 cases surgery was not possible. In the group of patients without diabetes, radical surgery was performed in 43 cases (81.13%), while in 10 cases (18.86%), this could not be done, the stage of the disease at diagnosis being a very advanced one.

The mean body mass index in diabetic patients was similar to the mean value recorded in the control group (29.48 versus 29.79)

Analyzing histopathological types, 39 cases with ductal carcinoma (73.58%), and 14 lobular carcinomas (26.41%) were diagnosed. In the control group, 23 cases of ductal carcinoma (43.39%), and 30 cases of lobular carcinoma (56.6%) were identified.

From an immunohistochemical point of view, in patients in the study group, 50 patients who had ER values >10% and/or PR >10% were identified, 2 patients with triple-negative characteristics, and 9 patients with HER2 positive genetic test (3+). Regarding the Ki67 values, the determined value was between 5 and 70%, with an average value of 30.33%. Analyzing the same parameters in the control group, 35 patients were identified, with ER and/or PR values >10%, 3 HER2 positive patients.

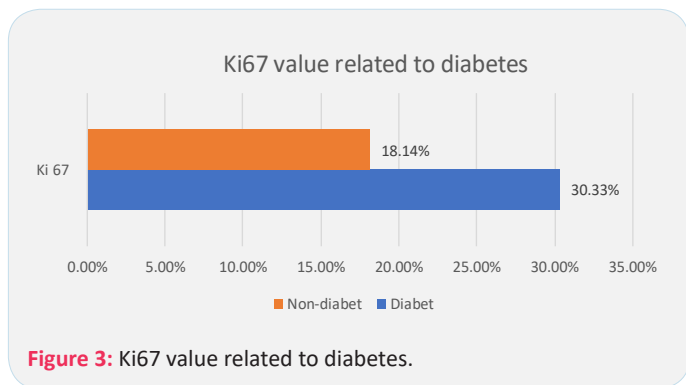


Figure 3: Ki67 value related to diabetes.

The mean value of ki67 is 18.14%, significantly lower compared to the value of the group with associated diabetes, 30.33% (Figure 3, p=0.003)

Analyzing the biological and immunohistochemical data collected, but also the links between them, in patients with associated diabetes a significant positive linear correlation was identified between both LDH and Ki67 values (Figure 4, r=0.96) as well as between alkaline phosphatase and Ki67 index (Figure 5, r=0.9).

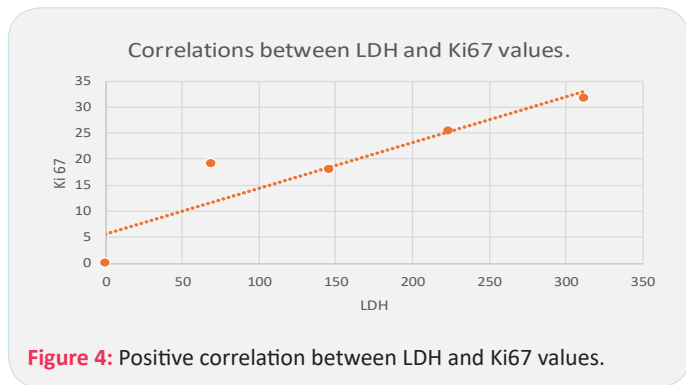


Figure 4: Positive correlation between LDH and Ki67 values.

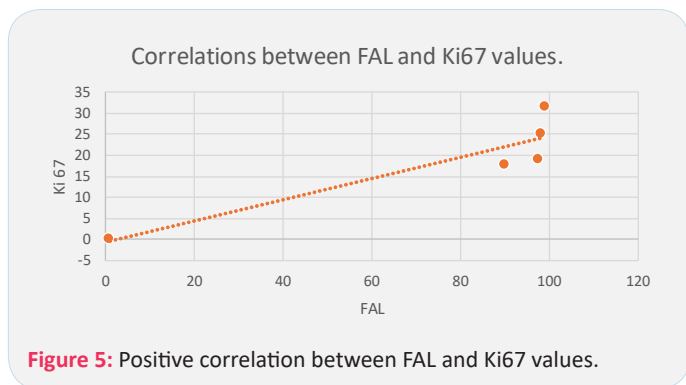


Figure 5: Positive correlation between FAL and Ki67 values.

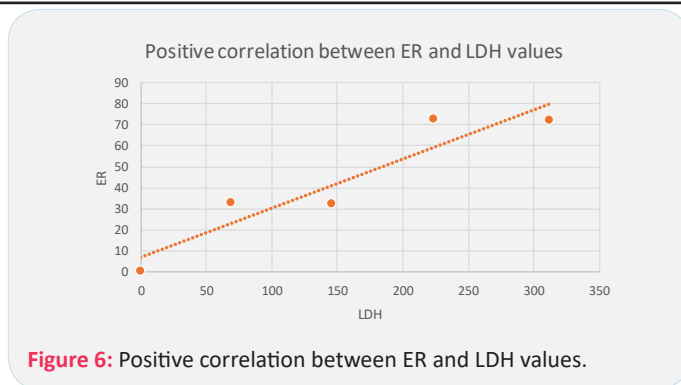


Figure 6: Positive correlation between ER and LDH values.

LDH has also been positively correlated with estrogen receptors (Figure 6, r=0.95)

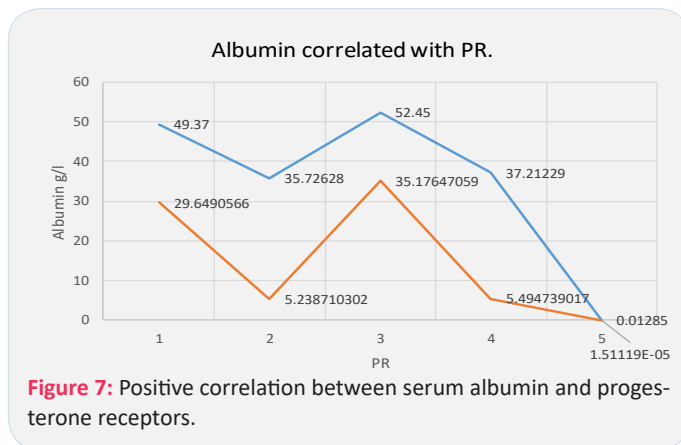


Figure 7: Positive correlation between serum albumin and progesterone receptors.

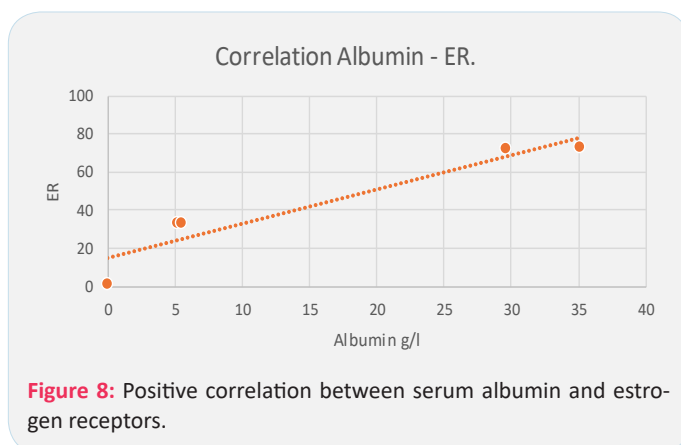


Figure 8: Positive correlation between serum albumin and estrogen receptors.

For albumin levels, it was found that those are closely correlated with progesterone receptors (Figure 7, r=0.79) with estrogen receptors (Figure 8, r=0.94), but also with Ki67 (r=0.79).

The evolution under oncologic treatment of patients with breast cancer and diabetes is different from that of those without associated diabetes. Thus, 40 of the patients in the diabetic group (75.47%) and 51 of the patients in the control group (96.22%) received oncological treatment for more than 3 months, including surgery, external irradiation, and chemotherapy based on platinum salts.

The hemoglobin value at diagnosis is positively correlated with the duration of oncological treatment performed (p=0.001, r=0.8).

The mean duration of treatment was significantly shorter in diabetic patients with mammary gland neoplasm - 8.71 months, compared to the control group, where the average treatment lasted 21.41 months (p=0.00011).

The median duration of treatment was 6 months for the associated diabetes group and 14 months for the non-diabetic group.

Antidiabetic medication followed was for 23 of the patients oral antidiabetic therapy (43.39%), 13 under treatment with insulin (24.52%), and 4 patients followed an adequate nutritional regimen (7.54%). The mean value of glycosylated hemoglobin in the analyzed group was 8.33%. The average body mass index was 29.79.

The median survival of the mammary gland neoplasm group and associated diabetes is 12 months, while the median survival of the control group was 22 months (Figure 9).

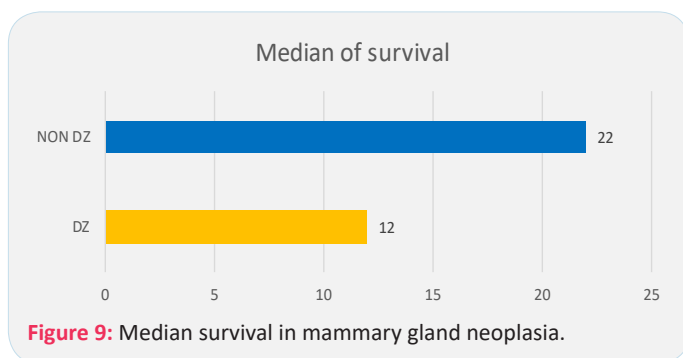


Figure 9: Median survival in mammary gland neoplasia.

Discussion

Over the last decade, both the incidence and mortality caused by breast gland neoplasm or diabetes are constantly increasing, while possible links between the two are not fully clarified. The incidence rate of breast cancer in Dolj County (10.95%) was lower than global Globocan data (11.7%) and in Romania (12.2%), but the mortality rate was higher than in both groups described (7.3% vs. 6.9% and 7.2% respectively). Diabetes can be considered a risk factor for the development of breast cancer [17], and one of the risk factors involved in the pathogenesis of both diseases is obesity [18]. The data in the literature support this statement, the average values of the body mass index not being significantly differentiated between the groups with breast cancer and those that also have associated diabetes [14]. There are no significant differences in our study either. In fact, some studies support an increased frequency in overweight and obese patients to develop a breast gland neoplasm in the postmenopausal period [19], which also results from the data we analyze, most patients with a metabolic syndrome being hormone dependent. The maximum incidence of breast cancer in diabetic patients was around 60 years of age (22 patients, 41.5%). The explanation is that the existence of obesity increases the level of adipocytokines, alters the biological functions of leptin and estrogen, developing insulin resistance and thus unbalancing the levels of pro-inflammatory cytokines [20].

There are also studies that have highlighted the impact that obesity has on the development of breast cancer in pre-menopausal women, who are especially prone to the negative triple subtype [21]. Given the mean value of the body mass index in the analyzed group (IMC=29.48), a close link was found between the serum albumin level and the expressiveness of the estrogen and progesterone receptors, strengthening the idea of hormone dependence in overweight and obese patients.

While recent studies highlight the detection of new cases of breast gland neoplasms in stages II and III (74.5%), with a less favorable prognosis [14,22], in our study, the percentage of initial detection was one with an unfavorable prognosis, with

45.28% in stages III and 28.3% stage IV in patients with the association of the two diseases, while in those without diabetes, 56.6% patients were in stage II and 32.75% in stage III. Peairs et al. conclude that the survival rate of patients with breast cancer and pre-existing diabetes is significantly lower compared to patients without diabetes, and the duration of treatment is also influenced, mainly due to higher toxicity [22].

Analyzing the duration of treatment, directly influenced by the course of the disease and its side effects as well as therapy-despite dose reduction, the duration of oncological treatment in patients with associated diabetes was shortened by 12 months. Thus, in the control group, complex therapy lasted, on average, for 21.4 months, while the presence of diabetes in cancer patients shortened the possibility of treatment to 8.7 months. The median duration of survival was also significantly influenced, being 12 months in patients with diabetes, compared with 22 months in patients in the control group. Previous data show a direct correlation of Ki67 with tumor proliferation rate [23], with the degree of differentiation, G' but also with the initial clinical stage of the disease [24]. In our study, in patients with diabetes, the Ki67 value was significantly higher than in the control group (30.33% for diabetic patients vs 18.14% in the control group). It was directly correlated with inflammatory biomarkers LDH and FAL in diabetic patients, explaining the increase in the aggressiveness of mammary gland tumors and implicitly reducing their prognosis, thus suggesting the direct involvement of the inflammatory process.

Conclusion

The incidence rate of breast cancer in Dolj County (10.95%) was lower compared to the incidence rate recorded in Romania (12.2%), but also to the global one – Globocan (11.7%). Instead, the mortality rate is higher than both in the world and Romania (7.3% vs. 6.9% and 7.2% respectively).

The clinical stage at diagnosis of breast cancer in combination with diabetes was more advanced compared to the diabetes-free group.

Obesity and albumin levels are closely correlated with the hormone-dependent nature of postmenopausal breast cancer in patients with associated diabetes.

The aggressiveness of breast cancer in diabetic patients is significantly increased, the Ki67 value being higher in the group of diabetic patients, and is directly correlated with the biomarkers of inflammation, negatively influencing the prognosis.

The duration of oncological treatment in the neoplasm of the mammary gland is strongly influenced by the presence of diabetes, being 8.7 months vs. 21.4 months, and is closely related to hemoglobin at diagnosis.

The median survival of patients with breast cancer and associated diabetes was significantly shorter than 12 months compared to 22 months in the control group.

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