

Impact of Diabetes Mellitus Type 2 on Clinical Characteristics of Breast Cancer Patients

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ABSTRACT

Objective: To study the impact of type 2 diabetes mellitus on clinical features of breast cancer.

Study Design: Cross-sectional, observational study.

Place and Duration of Study: Departments of Medicine, Bahria International Hospital and Farooq Hospital Lahore from 1st July 2017 to 1st December 2021.

Methodology: Ninety breast cancer patients with diabetes whose clinical characteristics were compared with the control group of non-diabetic breast cancer patients. After confirmation of diabetic status of the patients through evaluation of blood glucose levels, pathological findings including spread of cancerous cells, their size, lymph node involvement, oestrogen receptor (ER), progesterone receptor (PR), and Her-2 status were evaluated. Obesity was declared in patients having body mass index greater than 30.

Result: On comparison with control group, no significant difference was found in age and parity status of patients at the time of diagnosis whereas crude comorbidity score was significantly higher in diabetic patients (0.002). Average body mass index score of diabetic patients and those in control group was 30.5 than 23.7 respectively. 32 (33.5%) Diabetic breast cancer patients were declared obese than 26 (17.3%) non-diabetic patients. 82 (54%) of non-diabetic patients were diagnosed at Stage 1 of breast cancer. 93.3% of diabetic patients were found to have invasive ductal cancer (IDC). No significant difference was found in grading and hormonal status of the patients of two groups. Multivariate analyses on adjustment of body mass index found most diabetic patients to be negative for progesterone and oestrogen receptors.

Conclusion: Type 2 diabetes mellitus plays an important role in the progression and worsening of prognosis in breast cancer patients. Therefore, it should be considered as an important risk factor during the treatment of tumours including breast cancer. Controlling diabetic complications in breast cancer patients would play a pivotal role improving the clinical outcomes in breast cancer patients.

Keywords: Breast cancer, Diabetes mellitus type 2, Tumour progression, Obesity, Body mass index

INTRODUCTION

Type 2 diabetes mellitus (T2DM), accounting for 95% of diabetes cases, is characterized as increase in blood insulin levels due to its resistance in muscles and fats; however, the blood level may fall at later stages of disease due to β -cell decomposition.¹ According to global burden of disease study (2013), diabetes mellitus is the 9th most common cause of mortality around the world. In USA, 6.5% of adults and 12% of aged population are diagnosed to have T2DM and this prevalence rate is continuously on rise.² Generally, T2DM results from correlation of genetic and environmental factors. A part from that, obesity and age also serve as critical risk factors.³ Other than causing metabolic disturbances, T2DM is a potent risk factor in the onset and prognosis of various malignancies including breast cancer.⁴

Globally, breast cancer is the most prevalent form of cancer among women and second leading cause of cancer related mortality.⁴ In the last two decades, studies have found some association between the incidence of breast cancer, T2DM and obesity. Warburg effect, defined as increased reliance of cancerous cell on aerobic glycolysis, suggests the role of underlying T2DM in the growth of cancerous cells.⁵ Moreover, high circulating cholesterol and accumulation of adipose tissues around breast cells in diabetic patients create conducive environment for development of breast cancer.^{6,7} Three body mechanisms are found to exist in both T2DM and breast cancer: disturbed cycle of reproductive hormones, triggered activation of insulin like growth factor (IGF), and stimulation of insulin signalling pathways.⁸

Till date, the correlation between diabetes and breast cancer are majorly studied on animal models. Moreover, as per our knowledge no major study is conducted on the Pakistani population. We designed this study to evaluate the impact of diabetes mellitus type 2 on the prognosis of breast cancer.

MATERIALS AND METHODS

This cross-sectional observational study was conducted at Departments of Medicine, Bahria International Hospital and Farooq Hospital Lahore from 1st July 2017 to 1st December 2021. A total of 90 diagnosed breast cancer patients were selected for the study who were compared with 150 age-matched non-diabetic breast cancer patients. The study population included newly diagnosed breast cancer female patients who were undergoing cancer treatment from last two years and had a history of type II diabetes mellitus. The diagnosis of T2DM was confirmed by evaluating the fasting blood glucose levels according to the criteria of the American Diabetic Association. All the participants were informed of study objectives and were included in the study after getting informed consent. Those who were having any other comorbidity or type I diabetes were excluded. Age matched non-diabetic breast cancer patients who had been diagnosed of breast cancer from the last two years were included in the study as control group.

For correlation of comorbidities and impact of T2DM on clinical presentation of breast cancer, patient's clinical profiles were deeply evaluated. After assessing basic parameters, the pathological findings including spread of cancerous cells, their size, lymph node involvement, oestrogen receptor (ER), progesterone receptor (PR), and Her-2 status were evaluated. Stages of cancer were defined according to the criteria of the American joint committee on Cancer staging system for breast cancer. Charlson's comorbidity score, consisting of 19 parameters, was used to determine the association between two disorders. Obesity was considered as those with body mass index (BMI) greater than 30. SPSS version 20 was used in the analysis of data. Chi square test was applied for the comparison of categorical data while quantitative data was compared through t-test. P value of less than 0.05 was considered statistically significant.

RESULTS

The mean age was between 53.2±5.6 years and no significant difference (p=0.75) was found in terms of parity between the two groups. Crude comorbidity score, measured through Charlson's co-morbidity score, was found significantly high among diabetic patients (p=0.02). As expected, mean BMI score of diabetic patients was higher, 30.5, as compared to 23.7 of non-diabetic patients. 32 (33.5%) diabetic breast cancer patients were declared obese as compared to 26 (17.3%) non-diabetic patients Table 1). Similarly, significant difference was found in term of tumour stage at the time of diagnosis between the two study groups. 82 (54%) of non-diabetic patients were diagnosed at stage 1 of the disease whereas only 15 (16.6%) of diabetic patient had stage 1 tumour while more than half of diabetic patients (54.4%) had stage 2 disease.

Table 1: Distribution of Patient's Characteristics among Two Study Groups (n=90)

Parameters	DM (N=90)	Non DM (N=150)	p-value
Age (years)	55.4±5.4	53.2±5.6	1.00
Parity			
0	7 (7.7%)	10 (6.6%)	0.75
1	15 (16.6%)	24 (16%)	
2	26 (28.8%)	56 (37.3%)	
3	32 (35.5%)	35 (23.3%)	
4+	10 (11.1%)	30 (20%)	
Comorbidity Score	1.5	0.21	0.02
BMI	30.5±5.7	23.7±4.8	0.001
Obesity	32 (35.5%)	26 (17.3%)	0.03

Table 2: Distribution of Tumour characteristics by study groups (n=90)

Parameters	DM (N=90)	Non DM (N=150)	p-value
Stage			
1	15 (16.6%)	82 (54.4%)	0.001
2	49 (54.4%)	55 (36.6%)	
3	16 (17.7%)	9 (6%)	
4	10 (11.1%)	4 (2%)	
Stage			
Early	64 (71.1%)	137 (91.3%)	0.02
Advanced	26 (28%)	13 (8.6%)	
Histology			
IDC	83 (92.2%)	95 (63.3%)	0.03
Others	7 (7.7%)	55 (33.3%)	
Grade			
1	22 (24%)	48 (32%)	0.05
2	43 (47.7%)	60 (40%)	
3	25 (27.7%)	42 (28%)	
ER- Status			
Positive	75 (83.3%)	120 (80%)	0.063
Negative	15 (16.6%)	30 (20%)	
PR- Status			
Positive	42 (46.6%)	95 (63.3%)	0.002
Negative	46 (51.1%)	55 (36.3%)	
Her2/ neu status			
Positive	12 (13.3%)	25 (16.6%)	0.05
Negative	54 (60%)	85 (56%)	

Table 3: Prediction of Major Study Variable through Odd Ratio (OR) and 95% Confidence Interval (CI) upon Adjustment of BMI (n=90)

Variable	OR	95%CI
Stage		
2 vs 1	2.59	1.12-7.30*
3 vs 1	2.62	0.30- 19.89
4 vs 1	4.23	0.59-30.92
3+1 vs 1+2	1.7	0.47-6.4
2-4 vs 1	2.88	1.20-7.32*
Histology		
IDC vs Non-IDC	1.61	0.45-5.37
Grade		
3 vs 1+2+9	1.0	0.31-2.75
ER status		
Positive vs negative	0.40	0.13-0.94*

Almost all the diabetic breast cancer patients (93.3%) were found to have invasive ductal cancer (IDC) as opposed to 63.3% of non-diabetic cancerous patients. No significant difference was in tumour grading, oestrogen status (ER-status), Her2/ neu status whereas progesterone status was positive in more non-diabetic patient (63.3%) than diabetic patients (46.6%). Multivariate adjustment of study variables was made on the basis of BMI and odd ratios were calculated on comparison of diabetic and non-diabetic breast cancer patients. A significant association (p<0.05) stages difference and oestrogen status with diabetic status of the disease whereas mostly diabetic women had negative progesterone status (Tables 2-3).

DISCUSSION

The study showed that at the time of presentation, diabetic patients presented with more tumour progression than non-diabetic patients as reflected by tumour stages. This was further validated by the adjustment of tumour stage for BMI of both groups. Moreover, majority of diabetic patients were found negative for hormonal receptors status.

Literature has explained two mechanisms, namely direct and indirect, through which diabetes can affect the outcome of breast cancer. Among these, biological mechanisms, including defective sex hormonal cycles and stimulation of insulin signalling pathway, are found to have direct impact on the prognosis of breast cancer.^{9,10} Our study revealed that a significant number of patients were obese (p=0.03) and obesity has been linked with worsening of breast cancer through increased production of estradiol from adipocytes and decline in sex hormone binding globular proteins leading to a higher blood oestradiol level which is considered as a risk factor in the development of breast cancer.¹¹ Moreover, the involvement of insulin and insulin growth factor (IGF) signalling pathways have been validated by the low expression of oestrogen and progesterone receptors among diabetic patients. These results are consistent with the findings of previous studies.

Muoio et al¹² found S100A7, a novel protein, as a target of IGF-1 in the spread of cancerous tissues among diabetic breast cancer patients. Similarly, previous studies have found increase in insulin receptors in breast cancer patients which confirm the role of insulin in the growth of breast cancer.⁸ This is in accordance with the findings of our study. Besides breast cancer, insulin has also been found as an important risk factor in the progression of other types of tumours. Li et al¹³ found an increase in the amount of insulin growth factor as osteosarcoma progresses in their patients. Further he noticed that increase in insulin level was directly proportional to the metastasis of cancerous tissues.

Furthermore, in our study, histological examination of breast tissue revealed majority of diabetic patients as having diabetic invasion than non-diabetic patients. Similar results were observed by Schrauder et al¹⁴ who found tumours of larger size and more ductal involvement in diabetic patients. In another study conducted on breast cancer patients, Gillespie et al., observed significant relation between obesity and angiolymphatic invasion of the cancer. He also found high incidence of Er-negative status among obese breast cancer patients, as in our study.¹⁵ Therefore, it is safe to predict the association of obesity, diabetes and incidence of breast cancer.

Our study was based on the evaluation of characteristics of breast cancer patients with type 2 diabetes. We didn't assess the difference of conventional treatment strategies on these patients in contrast to non-diabetic patients. Therefore, it is recommended to conduct further studies in therapeutic dimension so that treatment strategies could be evaluated.

CONCLUSION

Type 2 diabetes play an important role in the progression and worsening of prognosis in breast cancer patients. Therefore, it must be considered as a critical risk factor during the treatment of breast cancer. Controlling diabetic complication in breast cancer

patients can play an important role in improving the clinical outcome in these patients.

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