Influence Of Metformin Treatment On Progression Of Breast Cancer

A controlled prospective Study

Dr. Zainab Faisal Mohamed Hasan /M.B.Ch.B., FICMS/Oncology
Oncology Teaching Hospital –Medical City.
Baghdad -Iraq

Dr. Saba Mahdi Jasim /M.B.Ch.B., FICMS/ Oncology
Oncology Teaching Hospital-Medical City.
Baghdad -Iraq

Dr. Osamah Azhar Sabeeh Al-zubaidi /M.B.Ch.B./
Baghdad Teaching Hospital- Medical City.
Baghdad –Iraq

ABSTRACT

Background. It is believed that both type 2 diabetes and hyper insulinemia are risk factors for breast cancer, with evidence that metformin use might have positive impact on patients' survival and prognosis.

Aim of the study. To assess the effect of diabetes mellitus type 2 treated with metformin on the progression of invasive breast cancer in female patients.

Patients and methods. This was a prospective study involving female patients diagnosed with invasive breast cancer who attended Oncology Teaching Hospital. The patient data was collected via personal interview and clinical assessment through history , physical examination and suitable imaging modalities initially; and then were followed up for six months

Results. The total sample was 89 patients; 37 diabetics on metformin (mean age was 58.8 years) and 52 patients nondiabetics (mean age was about 52 years). Mean BMI was (32), and (29) kg/m² respectively.

Disease progression occurred in both groups with no significant difference (P- value of 0.645). All-cause mortality was recorded in 3 (8.1%) diabetic and 2 (3.8%) nondiabetics.

Post- menopausal status and more significantly metformin use predicted no progression after 6 months.

Conclusion ; In female patients with invasive breast cancer plus diabetes; menopause and more significantly the use of metformin strongly predicted no progression.

Key words. Metformin; Breast cancer; Diabetes; Outcome.

INTRODUCTION

Breast cancer is a significant health issue for women all over the world. [1,2]

Pathologically, invasive breast cancer is classified based on the morphologic appearance of tumor cells on light microscopy [3]. Invasive [infiltrative] ductal carcinoma being the most frequent type (70%-80%)[4].

Metastatic (stage IV) breast cancer occurs when the tumor disseminates hematogenously or lymphatogenously to distant anatomic sites away from the breasts and their lymphatic drainage . Bony metastasis are the most frequent sites in hormone receptor positive breast cancer patients while viscera is the most common site for hormone receptor negative and HER2 receptor positive breast cancer [5], Invasive lobular breast cancer mostly spread to serosal surfaces .[6].

Type 2 diabetes (T2DM) is considered a serious health hazard , with a global prevalence of 8.3% in 2013 [7].

There are increasing evidence that suggest DM contributes to breast cancer risk, up to 16% of breast cancer patients have T2DM, which, in turn, has been associated with a 10–20% excessive risk of BC[8]. Moreover, several evidences indicate that T2DM and impaired glucose tolerance may negatively impact breast cancer prognosis [9, 10]. To our knowledge breast cancer outcome might be affected by anti – diabetic medications. Metformin, an anti diabetic medication used for T2DM, lowers the risk for developing invasive breast cancer in comparison to insulin[8,10]. However, few studies have examined treatment of diabetes in relation to breast cancer prognosis, with inconclusive results [11, 12].

Metformin reduces levels of circulating glucose, increases insulin sensitivity, and reduces the hyperinsulinemia associated with insulin resistance [13] all of which affects breast cancer prognosis.

Activation of adenosine monophosphate activated protein kinase (AMPK) is one of the most widely studied biological pathways that play a key role in the supposed anti _tumor effect of metformin [14].

A. Patients and methods

This was a prospective cohort study that involved female patients with invasive breast cancer diagnosed

between October 1st 2015 and October 1st 2016 and attended Oncology Teaching Hospital in the Medical City for their management, patients who have one or more of the following criteria were excluded

1. Patients with in situ breast cancer without invasive component.
2. Patients on neoadjuvant therapy
3. Patients on best supportive care only.
4. Patients who had other active malignancy in addition to breast cancer.
5. Patients with type 1 diabetes mellitus.

Information about age, menopausal state, body mass index (BMI), status of breast cancer, diabetes mellitus and anti- diabetic medications were all

gathered. Patients were followed up for six months after initial assessment.

For patients with non- metastatic early breast cancer; assessment included history and physical examination and annual mammogram when indicated. On the other hand, metastatic patients were assessed by history, physical examination, thorough investigation and imaging studies, which included computed tomography (CT) of chest, abdomen and pelvis and magnetic resonance imaging for the musculoskeletal system whenever indicated.

Statistical analysis of data was carried out using statistical package of SPSS-24. The significance of difference of qualitative data was tested using Pearson Chi-square test (χ2-test) with application of Yate's correction or Fisher Exact test whenever applicable. P value was considered significant when ≤ 0.05. Binary logistic regression analysis used to calculate the odd ratio (OR) and their 95% confidence intervals.

Results

The total number of patients initially was 126**,** but 37 of them were lost through the course of follow up and were dropped from the study, leaving 89 female patients. Fifty-two patients (58.4%) were non diabetics and 37patients (41.6%) were diabetics on metformin ± other treatments.

Both groups were age matched. the mean age of the diabetics group was (58.8± 8.5) years with a range of (38-72) and for the non- diabetics group was (52 .1±7.75) years with a range of (35-68) with a P- value of (0.056) (tab. 1)

The two groups were also weight matched with a p value of (0.278) (tab. 2)

On the other hand postmenopausal patient (defined as age ≥ 60 y. or with amenorrhea for 12 months or more in the absence of chemotherapy and hormonal therapy) were more predominant in diabetic patients compared to non-diabetic ones (tab. 3)

progression within 6months of follow up was found in 4 (7.7 %) of non- diabetic group versus 2 (5.4%) of diabetic patients with a nonsignificant P- value of (0.645) (tab. 4), and death was recorded in 3 diabetics (8.1%) compared to 2 (3.8%) in the non- diabetics with a non significant P- value of (0.389) (tab. 5).

Table 1. Age distribution among studied groups

Age (years)	Diabetics on Metformin		Non-diabetics		P-value
	No	%	No	%	
<40	1	2.7	2	3.8	0.056
40-49	9	24.4	15	28.8	
50-59	11	29.7	26	50.0	
≥60	16	43.2	9	17.4	
Total	37	100	52	100	
Mean± SD (Range)	58.8± 8.5 (38-72)		52.1±7.7 (35-68)		

Table 2. Body mass index evaluation in the studied groups

BMI (Kg/m²)	Diabetics on Metformin		Non-diabetics		P-value
	No.	%	No.	%	
Underweight (<18.5)	0	0	0	0	0.278
Normal (18.5-24.9)	5	13.5	11	21.2	
Overweight (25-29.9)	11	29.7	19	36.5	
Obese (30-34.9)	9	24.4	14	26.9	
Morbid obesity (≥35)	12	32.4	8	15.4	
Total.	37	100	52	100	
Mean± SD (Range)	32.1± 6.1(23-48)		29.5± 6.2(20-49)		

Tab. 3 Menaposal status in the studied groups

Post-menopausal	Diabetics on metformin		Non-diabetics		P- value
	No.	%	No.	%	
Yes	26	70.3	14	26.9	0.0001
No	11	29.7	38	73.1	
Total	37	100	52	100	

Tab. 4.: Progression within 6 months of follow up in the studied groups

Progression within 6 months	Diabetics on Metformin		Non-diabetics		P-value
	No.	%	No.	%	
Yes	2	5.4	4	7.7	0.645
No	32	86.5	46	88.5	
Dead	3	8.1	2	3.8	
Total	37	100	52	100	

Tab. 5 occurrence of death in studied groups within 6 months of follow up

Death recorded	Diabetic on metformin		Non-diabetic		P value
	No.	%	No.	%	
yes	3	8.1	2	3.8	0.389
no	34	91.9	50	96.2	
total	37	100	52	100	

Both post-menopausal status and diabetic patients using metformin predict no progression after 6 months (both reduce risk of progression). For postmenopausal status OR- 0.491, 95% CI (0.090 – 2.689) p value 0f (0.413), and for Diabetic status OR -0.575, 95% , CI (0.105 – 3.150) and P- value of (0.524).(tab. 6)

In diabetic patients, use of metformin strongly and significantly predict no progression P value (0.002), while post- menopausal status associated weakly with no progression OR= 0.391, 95% CI (0.022 – 6.949) and P- value was 0.391.(tab. 7)

Tab. 6 Binary logistic regression showing relationship between different variables and progression in all patients; OR: odd ratio, CI: confidence interval.

	OR	95% CI	P- value
Age	0.952	0.885 – 1.025	0.191
Body mass index	0.983	0.873 – 1.106	0.771
Post- Menopausal status	0.491	0.090 – 2.689	0.413
Diabetic status	0.575	0.105 – 3.150	0.524

Table 7. Binary logistic regression showing relationship between different variables and progression in DM patients; OR: odd ratio, CI: confidence interval.

	OR	95% CI	P- value
Age	0.957	0.811 – 1.128	0.599
body mass index	0.812	0.551 – 1.197	0.292
Post- Menopausal status	0.391	0.022 – 6.949	0.391
Metformin use	9.6E-9	3.5E-9 – 2.0E-8	0.002

DISCUSSION

In the view of our results, and after 6 months of follow up 3 patients died and other two patients showed disease progression among the diabetic group, compared to two patients died and other four patients progressed among non-diabetic group.

Increased mortality in patients with type 2 diabetes in our study is consistent with results of meta-analysis on DM and breast cancer outcomes done by Peairs KS et al [13],which concluded that ; compared to non diabetic ; patients with breast cancer and pre-existing diabetes have a greater risk of mortality and tend to present at later stages and receive adjusted and different treatment regimens .

1. Our study showed that there is a significant decrease in the progression of invasive breast cancer in patients who had diabetes treated with metformin with P- value (0.002). The effect of metformin therapy in invasive breast cancer patients in our study matches the currently conducted studies in that it is associated with favorable outcome and trend toward better survival with metformin use for example ;

2. A Meta- analysis of 11 studies that involved 5,464 breast cancer patients with diabetes, of those : 2,760 were treated by metformin. The meta-analysis found that overall survival and cancer specific survival were better with the use of metformin **[14].**

However, in terms of overall survival assessment, there is a serious need for larger studies with more extended timeline for meticulous results.

In this study 70.3% of the diabetic patients were postmenopausal, while 26.9 % among the non-diabetic were postmenopausal, post- menopausal status showed weak association with decreasing the risk of progression of invasive breast cancer , OR= 1.958, 95% CI (0.311-12.344) with P- value [0.474].

Most studies that assessed the effect of menopause in breast cancer, found that comorbidity in older age women {post menopausal} was one of the obstacles to obtain sufficient prognostic information. For example a retrospective analysis of medical records of 6 cancer institution in the United States and Canada to assess the effect of age and comorbidity in

postmenopausal breast cancer patients aged 55 years and more [15] , concluded that there is an increase in the risk of death in this population of patients from causes other than breast cancer which in turn differs from our results which showed a decreased risk of progression in post menopause although not to the extent of statistical significance.

Obesity and body mass index in our study did not influence the progression or mortality.

Conclusion

Invasive breast cancer disease showed a trend towards reduce risk of disease progression in postmenopausal diabetic patients, and the use of metformin in diabetic patients strongly, predict no progression in a 6 months period of follow up.

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REFERENCES

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