

EFFECTS OF METFORMIN ON BIOCHEMICAL MARKER OF RECURRENCE AMONG POST MASTECTOMY FEMALE DIABETIC PATIENTS

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Abstract

Background: The different modalities of the treatment of diabetes such as life style modification, metformin, insulin and combination of metformin & insulin have role on breast cancer outcome. Insulin and metformin have some influence on the outcome indirectly by affecting some biochemical markers such as S. adiponectin, HOMA IR & IGF-I. Therefore this study investigates the effect of metformin and insulin in postsurgical breast cancer patients which is evaluated by S. adiponectin levels and their association with obesity.

Objectives: To evaluate effects of metformin on biochemical marker of recurrence among post mastectomy female diabetic patients.

Materials and methods: It was a retrospective cohort study done in Sir Salimullah Medical College and Mitford Hospital Dhaka, from January 2015 to December 2015. In this study purposive consecutive samples were collected at base line from 3 months to 36 months post mastectomy. After fulfill all exclusion and inclusion criteria, 82 cases were selected as sample.

Results: Mean age was found 47.2 years with ranging from 26 to 75 years. Only 9(11.0%) respondents had family history. The mean BMI was 28.4 kg/m²- and mean waist circumference was 95.2 cm. Almost half (48.8%) respondents took oral contraceptive pill and post menopausal status was found in 48(58.5%) respondents. The mean S. adiponectin level was statistically significant when compared with different type of DM treatment and different BMI group.

Conclusion: This study finally focused that the effects of metformin; the antidiabetic medication has play an important role to change the S. adiponectin level which modify the outcome among post mastectomy diabetic patients. The recurrence can't be evaluated clinically due to short period of time and need a further study for follow up.

Key words: Breast cancer, metformin, S. adiponectin, recurrence.

J Dhaka Med Coll. 2018; 27(1) : 41-46

Introduction:

Breast cancer is the second most common cancer in the world with an estimated 1.67 million new cancer cases in 2012 (25% of all cancers). Incidence rates vary nearly four-fold across the world regions, with rates ranging from 27 per 100,000 in Middle Africa and Eastern Asia to 96 in Western Europe. Breast cancer ranks as the fifth cause of death from all cancer death (522,000 deaths) and it is the most frequent cause of cancer death in women in less developed regions (324,000 deaths,

14.3% of total)¹. According to a recent report of the World Health Organization (WHO), nearly 10.50 crore women are affected around the world by cancer each year. Most of them are residing in the third world countries, including Bangladesh. The WHO report also revealed that breast cancer topped the list of the women affected with various types of cancers in Bangladesh². In Bangladesh, the rate of breast cancer occurrence is estimated to be 22.5 per 100,000 females of all ages¹. NICRH cancer registry report 2008-2010 reveals that breast

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Received: 21 July 2017

Revision: 01 September 2017

Accepted: 01 November 2017

DOI: <http://dx.doi.org/10.3329/jdmc.v27i1.38944>

cancer is the leading cancer among the women (26 per cent) and death due to breast cancer is about 10.9% of the total cancer deaths in Bangladesh³.

Treatment of early breast cancer will usually involve surgery with or without radiotherapy. Systemic therapy such as chemotherapy or hormone therapy is available. Surgery still has a central role to play in the management of breast cancer⁴. The incidence of local recurrence correlates with tumor size, presence and number of involved axillary lymphnode, the histologic type of tumor, the presence of skin oedema or skin or fascia fixation with primary tumor, hormonal receptor (ER, PR) and type of definitive surgery and local irradiation, chemotherapy and other targeted therapy. Recurrence also depends on some other associated illness such as diabetes mellitus, hypertension and obesity^{5,6,7}.

Among the associated illness, diabetes mellitus is one of the most common metabolic disease worldwide which is linked to an increased risk of developing breast cancer but an even higher risk of recurrence and dying from this disease⁸. Metformin is an oral biguanide that inhibit hepatic gluconeogenesis and sensitizes insulin action at peripheral level. It is the first line treatment of type-2 diabetes mellitus and can substantially reduce diabetic incidence in obese women with glucose intolerance with a good tolerability profile and low cost^{9,10}. Metformin may have different mechanism of tumor inhibition via insulin- dependent and insulin-independent pathways including activation of adenosine mono-phosphate-activated protein kinase (AMPK) through liver kinase B1 and ataxia teleangiectasia-mutated gene kinase, with inhibition of cancer proliferation and apoptosis induction in breast cancer cell lines^{11,12,13,14,15,16}. Other non-cancer medication may potentially have effect on breast cancer prognosis and also survival¹⁷. Alternatively insulin may promote tumorigenesis via a direct effect on epithelial tissues or indirectly by affecting other modulator

such as IGF-1, sex hormones and adipokines^{18,19}.

Another study has suggested that breast cancer is associated with insulin resistance and adipokinase level^{20,21,22,23,24,25,26,27,28}. Also obesity is commonly associated with hyperinsulinemia, insulin resistance and alterations in levels of adipokines such as S. adiponectin, all of which are associated with an increased risk of developing pre- and postmenopausal breast cancer and recurrence or death in those patients^{29,30,31,32}.

So this study will investigate whether the metformin and insulin have really any effective modulation in diabetic breast cancer patients in post surgical trial which can significantly change S. adiponectin level. The patients, who will have changed the level of S. adiponectin, need further investigation to see any type of recurrence by ultrasonogram, CT scan and Bone scan.

Materials and methods:

This was a retrospective cohort study done from January 2015 to December 2015. Study was conducted in selected Government and Private Hospitals, Dhaka. All post mastectomy female patients having type 2 diabetes mellitus who were treated by different modalities of treatment such as life style modification, metformin, insulin and combined insulin and metformin.

Inclusion criteria:

All mastectomy female patients having type 2 diabetes mellitus irrespective of age included in the study -

- up to stage IIIa of TNM classification
- who have tumor clearance margin
- at least 3 months of post mastectomy
- who are willing to participate

Exclusion criteria: Diabetic breast cancer patients -

- with distant metastasis
- treated with other than surgery
- with pregnancy

- with other metabolic and hormonal diseases
- with chronic kidney disease

Data was collected by using a standardized questionnaire. Height and waist circumference (WC) were measured by measuring tape and weight by weighing machine and the values were recorded in the checklist. Generalized obesity was determined by BMI and central obesity by WC. WC was measured by a tape placing horizontally midway between the two points of lowest rib margin and the top of the iliac crest. And the central obesity was defined as WC e" 90th percentile for age and gender (established based on the BCAM study) and categorized as per WHO Guideline for Asian populations.

After fulfilling of all the criteria, diabetic post mastectomy patients bought under plan for measurement of following biochemical markers such as fasting blood glucose and S. adiponectin,. After 8 to 10 hour overnight fast, a fasting blood sample was collected with expert technician in aseptic precaution and sent to the laboratory for biochemical test. Plasma glucose level was measured by the glucose oxidase method, and S. adiponectin by ELISA (Enzyme Linked Immunosorbent Assay). Serum biochemical markers were monitored after getting of insulin and metformin following simple mastectomy with completion of Adjuvant Therapy (chemo/radiotherapy).

All data was expressed as the frequency, percentage and mean±SD as appropriate. Statistical analyses were carried out by using the Statistical Package for Social Sciences version 17.0 for Windows (SPSS Inc., Chicago, Illinois, USA). The quantitative observations were indicated by frequencies and percentages. The mean values were calculated for continuous variables. Unpaired t-test and ANOVA test was used for statistical analysis.

Observation and Results:

Table I

Socio-demographic distribution of the respondents (n=82)

| Age Groups (years) | Number of respondents | Percentage (%) |
|--------------------|-----------------------|----------------|
| 25-34 | 8 | 9.8 |
| 35-44 | 21 | 25.6 |
| 45-54 | 35 | 42.7 |
| 55-64 | 15 | 18.3 |
| >65 | 3 | 3.7 |

Family history

| | | |
|---------|----|------|
| Present | 9 | 11.0 |
| Absent | 73 | 89.0 |

Table showed that majority (42.7%) respondents belonged to age 45-54 years, and mean age was 47.2 years with ranging from 26 to 75 years. Only 9(11%) respondents had positive family history.

Table II

Anthropometric distribution of the respondents (n=82)

| BMI (kg/m ²) | Number of respondents | Percentage (%) |
|--------------------------|-----------------------|----------------|
| <18.5 | 1 | 1.2 |
| 18.5-24.9 | 19 | 23.2 |
| 25.0-29.9 | 42 | 51.2 |
| ≥30.0 | 20 | 24.4 |

Waist Circumference (cm)

| | | |
|-----------------|----|------|
| Normal (<90 cm) | 5 | 6.1 |
| Obese (>90 cm) | 77 | 93.9 |

Table II shows that more than half (51.2%) of the respondents were overweight (25.0-30.0 kg/m²), mean BMI was found 28.4±7.7 kg/m²- with ranging from 16.7 to 78.2 kg/m². Normal (<90 cm) waist circumference was found in 5(6.1%) respondents; mean waist circumference was found 95.2±15.7 cm with ranging from 66 to 191 cm.

Table III

Values of the biochemical marker according to the age group of the respondents (n=82)

| Biochemical Marker | Age Groups (years) | | | | | P value |
|------------------------|--------------------|-----------------|-----------------|-----------------|--------------|---------|
| | 25-34 (n=8) | 35-44 (n=21) | 45-54 (n=35) | 55-64 (n=15) | >65 (n=3) | |
| | Mean±SD | Mean±SD | Mean±SD | Mean±SD | Mean±SD | |
| S. adiponectin (µg/ml) | 9.3±0.6 | 9.1±0.5 | 9.1±0.7 | 9.1±0.6 | 9.5±0.3 | 0.899 |

P value reached from ANOVA test

It was observed that mean S. adiponectin level was not significant when compared in different age groups.

Table IV

Values of biochemical marker according to BMI in respondents (n=82)

| Biochemical marker | BMI (kg/m ²) | | | P value |
|------------------------|--------------------------|-----------|-----------|---------|
| | 18.5-24.9 | 25-29.9 | ≥30.0 | |
| | (n=19) | (n=42) | (n=20) | |
| | Mean±SD | Mean±SD | Mean±SD | |
| S. adiponectin (µg/ml) | 9.62±0.19 | 9.25±0.44 | 8.36±0.42 | 0.001 |

P value reached from ANOVA test

Table showed that mean S. adiponectin was significantly lower in BMI ≥ 30 kg/m².

Table V

Values of biochemical marker according to waist circumference in respondents (n=82)

| Biochemical marker | Waist Circumference (cm) | | P value |
|------------------------|--------------------------|----------------|---------|
| | Normal (<90 cm) | Obese (>90 cm) | |
| | (n=5) | (n=77) | |
| | Mean ±SD | Mean±SD | |
| S. adiponectin (µg/ml) | 9.8±0.1 | 9.1±0.6 | 0.011 |

P value reached from unpaired t-test

Table V observed that mean S. adiponectin level was statistically significant between normal and obese person.

Table VI

Values of the biochemical marker according to the treatment modalities of DM in respondents (n=82)

| Biochemical parameter | Treatment of DM | | | | P value |
|------------------------|--------------------------------|------------------|----------------|----------------------------|---------|
| | Life Style modification (n=22) | Metformin (n=20) | Insulin (n=20) | Metformin + insulin (n=20) | |
| | Mean±SD | Mean±SD | Mean±SD | Mean±SD | |
| S. adiponectin (µg/ml) | 9.6±0.21 | 9.1±0.57 | 8.7±0.71 | 9.2±0.21 | 0.001 |

P value reached from ANOVA test

This table showed that level of S. adiponectin were significantly lower in only insulin treated group than other groups.

Table VII

Values of the biochemical marker among only Metformin treated respondents according to BMI

| Biochemical parameter | BMI(Kg/m ²) | | | P value |
|------------------------|-------------------------|---------|---------|---------|
| | 18.5-24.9 | 25-29.9 | ≥30.0 | |
| | (n=5) | (n=6) | (n=9) | |
| | Mean±SD | Mean±SD | Mean±SD | |
| S. adiponectin (µg/ml) | 9.5±0.3 | 9.3±0.4 | 8.5±0.3 | 0.001 |

P value reached from ANOVA test

It was observed that mean S. adiponectin was significantly high in normal weight patients when compared with obese subjects.

Discussion

This retrospective cohort study was carried out with 82 post mastectomy female diabetic patients to evaluate the effects of metformin on S. adiponectin level.

In this present study it was observed that majority (42.7%) respondents belonged to age 45-54 years, mean age was found 47.2 years. Similarly, Plengpanich et al. and Muti et al. had found that the mean age was 43.11 years and 44.8 years respectively^{33,30}. On the other hand the mean age was 56 years ranged from 18–103 years, which was higher than current study³⁴. Similarly another study Yu et al. found the mean age was 60 years³⁵. In this current study it was observed that 11.0% respondents had known positive family history.

In this study it was observed that 51.2% respondents were overweight and mean BMI was 28.4 kg/m²- which was closely resembled with the study of Duggan et al³⁶. However, Plengpanich et al. study reported the mean BMI was 23.6 kg/m²³³. Mean waist circumference was found 95.2 cm.

S. adiponectin levels did not differ significantly in different age groups. This observation was consistent with the study carried out by Plengpanich et al³³. But S. adiponectin level differed significantly when compared with different BMI groups. Low levels of S. adiponectin with increasing BMI were evident in this study. Similar observation was reported in Duggan et al³⁶. High level of S. adiponectin was associated with improved breast cancer survival with controlled blood glucose (<126mg/dl) level and with a BMI <25 kg/m². They concluded that low level of S. adiponectin were associated with obesity and increased breast cancer mortality.

It was evident from this study that S. adiponectin level were low in WC > 90 cm when compared with normal waist circumference. Tian YF et al. study resulted that increasing WC was significantly associated with higher risk in breast cancer patient when adjusted the plasma level of S. adiponectin²⁶.

It was observed that mean S. adiponectin was statistically significant when compared with different modalities of DM treatment. Level of S. adiponectin were significantly lower in only insulin treated patient than other groups. It was also evident that metformin treated patients were significantly associated with higher S. adiponectin level.

In only metformin treated patients, S. adiponectin level differed significantly in various BMI categories. The study also showed significant negative correlation between S. adiponectin and BMI. Duggan et al. suggested that BMI was inversely correlated with S. adiponectin levels in overweight or obese patients³⁶.

Conclusion

It was evident from the study that S. adiponectin was high in metformin treated post mastectomy female diabetic patients then treatment by insulin alone. Through this actions on biochemical marker metformin play an important role for prevention of recurrence in post mastectomy female patients.

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