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The impact of treatment exposure on diabetes biomarkers among Jordanian breast cancer women: a connection through FBG, C-peptide and HOMA-IR

Wpływ leczenia na biomarkery cukrzycy u kobiet z rakiem piersi w Jordanii: związek z glikemią na czczo, peptydem C i wskaźnikiem HOMA-IR

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Abstract

Background: Breast cancer is the most frequently occurring and life-threatening malignant tumor in women. The evidence that associates diabetes' biomarkers with breast cancer is highly controversial. **Aims:** To evaluate diabetes' biomarkers in breast cancer patients according to type of treatment exposure, breast cancer severity and menopausal status. **Material and methods:** A total of 396 breast cancer patients aged between 25 and 65 years attending breast cancer clinics were evaluated. The experimental design permitted to include 134 newly-diagnosed breast cancer patients who were not exposed to any type of interventions and 262 recently diagnosed breast cancer patients (up to three months). Recently, group members were subdivided in two subgroups to control exposure to therapy specially chemotherapy. The patients were further divided according to breast cancer stages and postmenopausal status. Diabetes biomarkers consisted of fasting blood glucose (FBG), C-peptide and HOMA-IR. **Results:** The high FBG was more prevalent in advance (24.1%) than early (10.6%) stage breast cancer. Compared with premenopausal breast cancer patients, postmenopausal breast cancer patients had higher prevalence of abnormal FBG (21.0% vs. 11.1%). The differences were also significant in the mean of FBG (103.0 ± 1.5 vs. 89.0 ± 0.0 mg/dL). In postmenopausal breast cancer patients, FBG was higher in the recently diagnosed whom expose to treatments including chemotherapy (106.5 ± 1.7 mg/dL vs. 126.2 ± 1.2 mm Hg) compared to the newly-diagnosed group whom not yet expose to any kind of treatment interventions. **Conclusion:** Diabetes was prevalent among breast cancer patients and it was higher in postmenopausal and advanced stage breast cancer women. The burden of diabetes on treatment expose breast cancer women tend to be high and warrants closer attention by health care provider to improved outcomes after diagnosis and treatment exposure.

Keywords: breast cancer stage, C-peptide, fasting blood glucose, menopausal status, treatment exposure

Streszczenie

Wstęp: Rak piersi to najczęstszy zagrażający życiu nowotwór złośliwy u kobiet. Doniesienia dotyczące związku cukrzycy z rakiem piersi są wysoce kontrowersyjne. **Cele:** Analiza biomarkerów cukrzycy u pacjentek z rakiem piersi w zależności od ekspozycji na leczenie, stopnia zaawansowania nowotworu i statusu menopauzalnego. **Materiał i metody:** Do badania włączono 396 pacjentek z rakiem piersi w wieku od 25 do 65 lat, które zgłosiły się do klinik specjalizujących się w leczeniu tej choroby. Plan badania dopuszczał włączenie 134 pacjentek z nowo rozpoznanym nowotworem, które nie otrzymały jeszcze leczenia w żadnej postaci, oraz 262 pacjentek z nowotworem rozpoznanym w ciągu ostatnich trzech miesięcy. Następnie uczestniczki podzielono na dwie podgrupy w celu kontroli ekspozycji na leczenie, szczególnie chemioterapię. Pacjentki podzielono także na podstawie stopnia zaawansowania nowotworu i statusu menopauzalnego. Oceniono następujące biomarkery cukrzycy: glikemię na czczo, peptyd C oraz wskaźnik HOMA-IR. **Wyniki:** Wysoki poziom glukozy na czczo obserwowano częściej u chorych z zaawansowanym rakiem piersi (24,1%) niż u kobiet z nowotworem we wczesnym stadium zaawansowania (10,6%). W porównaniu z pacjentkami przed menopauzą chore po menopauzie charakteryzowało częstsze występowanie nieprawidłowej glikemii na czczo (21,0% *vs* 11,1%). Różnice były także istotne dla średniej wartości glukozy

na czczo (103,0 ± 1,5 *vs* 89,0 ± 0,0 mg/dl). W przypadku kobiet po menopauzie wartości te były wyższe u chorych z rakiem piersi, które otrzymały leczenie, w tym chemioterapię (106,5 ± 1,7 mg/dl *vs* 126,2 ± 1,2 mm Hg), w porównaniu z nowo zdiagnozowanymi pacjentkami, u których nie rozpoczęto jeszcze leczenia w jakiejkolwiek postaci. **Wnioski:** W grupie badanych chorych cukrzyca była częstym problemem. Chorobę tą częściej obserwowano u kobiet po menopauzie i z zaawansowanym nowotworem. Odnotowano też istotną zależność między cukrzycą a ekspozycją na leczenie raka piersi. Na korelację tę należy zwrócić szczególną uwagę po rozpoznaniu choroby i wdrożeniu leczenia.

Słowa kluczowe: stopień zaawansowania raka piersi, peptyd C, glikemia na czczo, status menopauzalny, ekspozycja na leczenie

INTRODUCTION

Diabetes mellitus type 2 (DM II) is a common metabolic disorder affecting people in the whole world, which is caused by insulin secretary defect and resistance[1]. It is a chronic disorder associated with serious comorbidities that require continuous follow-up and monitoring[2]. Impaired fasting glucose indicates an increased risk for the future development of diabetes[1]. Diabetes affects almost 7% of the adult population[3]. In Jordan, the prevalence of diabetes and impaired fasting blood glucose (FBG) has been found to be high – 17.1% and 7.8%, respectively[4]. According to Khader et al.[5] almost 25% of Jordanian had high FBG. The high FBG has been also observed in more than 40% of women[6]. The DM II and cancer, like breast cancer (BC), could be linked through metabolic mechanisms related biomarker such as insulin and its growth factor[7]. Insulin acts as a growth factor influencing cell proliferation and cell death, also it is a powerful mutagenic agent in tissue and cells[8,9]. BC is the most frequently occurring and life-threatening malignant tumor in women and the leading cause of cancer-related deaths among women worldwide[10]. Women are at highest risk for BC when insulin levels are high[11]. In pre- and postmenopausal women, insulin acts as a growth factor with mutagenic effects on breast tissue; it has direct and indirect effect on tumors growth[12]. In Jordan, BC ranked first among cancers in females, accounting for about 37% of all female cancers[13], a figure that agrees with that obtained from different countries in the region[13]. The combined evidence supports presence of association between DM II and BC risk, particularly BC incidence[14,15]. Both DM II and BC frequently coexist as diabetes increases the risk of BC up to 20%, and 18% of patients with BC have DM II[7]. Although DM II has been related to BC[16], a significant debate is recently addressed[17,18]. C-peptide is another biomarker molecule produced from cleavage of proinsulin into equimolar amounts of insulin and C-peptide. Previous studies have shown conflicting results about the association of C-peptide and insulin level with BC[19–21]. Homeostasis model assessment estimated insulin resistance (HOMA)-IR is a reliable indicator of insulin resistance[22]. It is associated with reduced BC survival[23].

Knowing that both BC and DM II are products of the interaction between genetic and environmental risk factors and share many comorbidities[15,24]. Understanding the biomarkers of DM II and its contribution to BC, may have implications in helping predict BC incidence and prognosis in terms of recurrence, pathogenesis, distal metastasis, and overall treatment outcome and patient's quality of life. Considering that DM II is a modifiable risk factor[25], thus primary and secondary preventive measures such as lifestyle and dietary modifications, can be suggested to reduce BC risks and improve its incidence or outcome[24]. Thus, the objectives of the present study were to:

1. Investigate the impact of treatment exposure on diabetes biomarker like FBG, C-peptide and HOMA in Jordanian women with BC.
2. Evaluate the FBG in a group of BC Jordanian women with accordance to BC stage severity, menopausal status and treatment exposure.

MATERIAL AND METHODS

Study sample and design

In this study, 396 Jordanian BC patients aged between 25–65 years attending BC clinics at the Jordanian Royal Medical Services in Amman, Jordan for management and follow-up of their conditions during the period from January 2013 to February 2014 were evaluated for the presence of diabetes and its related biomarkers. The experimental design permitted to include 134 newly-diagnosed BC patients who were not exposed to any type of treatment interventions and 262 recently diagnosed BC patients (up to three months) whom exposed to any type of treatment interventions. Recently, group members were subdivided in two subgroups to control exposure to chemotherapy. The experimental design also permitted to include pre- and postmenopausal BC patients for hormonal balance control. The patients were further divided according to BC stages into early stage and advanced stage as a measurement of BC severity[26,27]. The sample size (396) was statistically sound and accounts for about 50% of the BC cases in the year 2011[28]. The median age of BC females in Jordan is 51 years, and about 80% of the diagnosed cases were between the ages 35 and 65 years[28].

Women aged between 25 and 65 years, with newly and recently diagnosed BC by the physician consultant were included in the study. The patient was excluded if she had any clinical or laboratory evidence of congestive heart failure, coronary disease, chronic renal failure, polycystic ovary syndrome hyper- or hypothyroidism, pregnancy or lactation. Any subject who did not fit the inclusion criteria was excluded. Subjects below 25 or above 65 years of age, type I diabetes mellitus, epilepsy and those taking medical herbs were also excluded. Five times a week, with an average of 15 patients/week were recruited to take part in the study, so that at the end of the 12-month study period, the number of screened patients was 396. This study was conducted according to the Declaration of Helsinki (2008, including 2013 amendments) and written informed consent was obtained from all participants at the start of the study. The Royal Medical Services Ethical Committee approved this study (reference number 1/2013).

Data collection

A questionnaire which included personal information, health, anthropometric and biochemical measurements was used for data collection. The medical specialist filled basic medical information about BC.

Anthropometric measurements

Anthropometric indicators including height, weight, waist circumference (WC) and hip circumference (HC) were measured in duplicates with subjects lightly clothed and without shoes. These indicators were performed by the investigator following the methodological protocol described by Lee and Nieman[29]. Height were measured to the nearest 1.0 mm using a wall-mounted stadiometer and weight to the nearest 0.1 kg using an electronic scale. The body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. The BMI ≥30 was considered obese[30]. The WHpR was calculated as WC divided by HC while the WHtR was calculated as WC divided by height.

Biochemical analysis

The fasting blood samples were collected then the plasma had been harvested and stored at −80°C for analysis. Biochemical analysis were carried out in Princess Eman Center for Laboratory Research and Science. The following laboratory measurements were performed in duplicates for each subject and the mean values were taken in subsequent calculations for biomarkers such as FBG, FBI and C-peptide. Plasma glucose was determined by the glucose dehydrogenase method. The color intensity of the resulting red dye was directly proportional to glucose concentration and was measured photometrically by the analyzer at 512 nm wavelength (Wako Pure Chemical Industries, Ltd., Osaka, Japan) on LABOSPECT 008 Hitachi Automatic Analyzer (Hitachi, Ltd., Tokyo, Japan). C-peptide was measured by a solid-phase, two-site chemiluminescent immunoassay (IMMULITE 2000 C-peptide assay, Siemens AG, Erlangen, Germany). The fasting blood insulin levels were quantitatively determined by chemiluminescent microparticle immunoassay (CMIA) technology (ARCHITECT Insulin assay, Abbott Laboratories, IL, USA). The insulin sensitivity was then calculated using HOMA according to the following formula:

$$\text{Log (HOMA)} = \log [\text{FBG (mmol/L)} \times \text{FBI (}\mu\text{U/ml)}/22.5]$$[31].

Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS), version 10.0 (SPSS Inc., Chicago, USA). Differences were significant at $p < 0.05$. Results were expressed according to the study needs as either frequency distribution with their percentages (%) or means ± standard error of the mean (*SEM*). Frequency distribution and percentages or means ± *SEM* were performed for the health characteristics, prevalence of DM II and compare early and advanced BC stage or menopausal status according to study groups. The independent sample *t*-test or the chi-squared test were used between DM II biomarkers risk and menopausal status and various BC status.

RESULTS

Biochemical characteristics of the study sample according to treatment exposure are given in Tab. 1. In the whole sample the prevalence of previously diagnosed diabetic BC patient was more than 20% and it was 32.1% of high FBG. C-peptide was 15.4% and it was 42.2% for HOMA. The prevalence was not significantly different ($p \geq 0.05$) among study groups. Anthropometric measurements were not significantly different ($p \geq 0.05$) among treatment exposure groups. The prevalence of high BMI was 53.0% (Tab. 1).

The frequency of the obesity and biomarker risk factors in the study sample according to treatment exposure are given in Tab. 2. None of biochemical characteristics showed significant differences ($p \geq 0.05$) among study groups. Fasting blood glucose (FBG), fasting blood insulin (FBI), C-peptide and HOMA for whole sample were 95.0 ± 0.9 mg/dL, 14.5 ± 0.8 MU/mL, 130.8 ± 3.4 mg/dL, 1.4 ± 0.1 ng/mL and 3.6 ± 0.2, respectively (Tab. 2).

Prevalence of high FBG in the study sample according to BC stage and treatment exposure are shown in Tab. 3. According to the early and advanced stage BC respectively, the prevalence of high FBG (10.6% vs. 24.1%) were significantly different ($p \geq 0.05$). Most of the recently diagnosed patients had advanced stage BC ($N = 187$) while most of newly-diagnose patients had early stage BC ($N = 114$). The prevalence of high FBG were significantly different ($p < 0.05$) between early and advanced stage BC

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Risk factor	Cut-off point	Newly-diagnosed (*N* = 134)		Recently diagnosed (*N* = 262)						Whole sample (*N* = 396)	
				Non-chemo (*N* = 86)		Chemo (*N* = 176)		Total (*N* = 262)			
		n	%	*n*	%	*n*	%	*n*	%	*n*	%
Previously diagnosed as diabetic		26	19.4	16	18.6	40	22.7	56	21.4	82	20.7
FBG (mg/dL)	>100 (IDF, 2015)[2]	38	28.4	30	34.9	59	33.5	89	34.0	127	32.1
C-peptide (ng/dL)	>2 (Autier et al., 2013)[33]	22	16.4	7	8.1	32	18.2	39	14.9	61	15.4
HOMA	>2.5 (Autier et al., 2013)[33]	56	41.8	45	52.3	66	37.5	111	42.2	167	42.2
BMI (kg/m^2)	≥30 (WHO, 2000)[30]	68	50.7	45	52.3	97	55.1	142	54.2	210	53.0

Values are given as mean ± *SEM*.
Cross differences between treatments exposure groups were not significant ($p \geq 0.05$).
SEM – standard error of the mean; **newly-diagnosed** – breast cancer patients who are not exposed to any type of interventions; **recently diagnosed** – breast cancer patients within 3 months of diagnosis who are either exposed (**chemo**) or not exposed (**non-chemo**) to chemical therapy; **FBG** – fasting blood glucose; **HOMA** – homeostasis model assessment according to the following formulas: Log (HOMA) as log [FBG (mmol/L) × FBI (μU/mL)/22.5] (Matthews et al., 1985)[31]; **BMI** – body mass index.

Tab. 1. Biochemical characteristics of the study sample according to treatment exposure[1–3]

Character	Newly-diagnosed (*N* = 134)		Recently diagnosed (*n* = 262)						Whole sample (*N* = 396)	
			Non-chemo (*N* = 86)		Chemo (*N* = 176)		Total (*N* = 262)			
	Mean	*SEM*	Mean	*SEM*	Mean	*SEM*	Mean	*SEM*	Mean	*SEM*
FBG (mg/dL)	92.3	1.5	96.3	2.1	96.4	1.5	96.3	1.2	95.0	0.9
FBI (MU/mL)	15.0	1.4	15.7	1.6	13.6	1.3	14.3	1.0	14.5	0.8
C-Peptide (ng/mL)	1.6	0.2	1.2	0.1	1.3	0.1	1.3	0.1	1.4	0.1
HOMA	3.7	0.4	3.9	0.5	3.4	0.3	3.6	0.3	3.6	0.2

Documented international cut-off points: Autier et al., 2013[33]; IDF, 2015[2]; WHO, 2000[30].
Cross differences between treatments exposure groups were not significant ($p \geq 0.05$).
Newly-diagnosed – breast cancer patients who are not exposed to any type of interventions; **recently diagnosed** – breast cancer patients within 3 months of diagnosis who are either exposed (**chemo**) or not exposed (**non-chemo**) to chemical therapy; **FBG** – fasting blood glucose; **FBI** – fasting blood insulin; **HOMA** – homeostasis model assessment according to the following formulas: Log (HOMA) as log [FBG (mmol/L) × FBI (μU/ml)/22.5] (Matthews et al., 1985)[31].

Tab. 2. The frequency of the obesity and biomarker risk factors in the study sample according to treatment exposure[1–5]

Variables	Newly-diagnosed (*N* = 134)				Recently diagnosed (*N* = 262)				Whole sample (*N* = 396)			
	Early stage (*N* = 114)		Advanced stage (*N* = 20)		Early stage (*N* = 75)		Advanced stage (*N* = 187)		Early stage (*N* = 189)		Advanced stage (*N* = 207)	
FBG >100 (mg/dL)*	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
	12	10.5	5	20.0	8	10.6	45	24.0	20	10.6	50	24.1

Values are given as number of patients (*n*) and their percentages out of *N*.
* Significant differences ($p < 0.05$) between early and advanced stage breast cancer for treatment exposure groups.
Newly-diagnosed – breast cancer patients who are not exposed to any type of interventions; **recently diagnosed** – breast cancer patients within 3 months of diagnosis who are either exposed (chemo) or not exposed (non-chemo) to chemical therapy; **FBG** – fasting blood glucose; **early stage** – stage I and II; **advanced stage** – III and IV (Sobin and Wittekind, 2002[26]); breast cancer stages (I–IV) according to tumor size (T), lymph node involvement (N), metastasis (M) classification system (TNM). Stage was classified as stage I (T0/T1and N0), stage II (T0/T1 and N1, or T2 and N0/N1, or T3/N0), stage III (T0/T1/T2 and N2, or T3 and N1/N2, or T4 and any N, or any T and N3), stage IV (any T, any N, M1) according to Bloom and Richardson (1957)[27].

Tab. 3. Prevalence of high FBG in the study sample according to BC stage and treatment exposure[1–3]

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among recently diagnosed (10.6% vs. 24.0%) and newly-diagnosed patient (10.5% vs. 20.0%) (Tab. 3).

Mean and frequency distribution of FBG in pre- and postmenopausal women according to treatment exposure are shown in Tab. 4. Compared with premenopausal, postmenopausal BC patients had significantly higher ($p < 0.05$) prevalence of abnormal FBG (21.0% vs. 11.1%).

The differences were also significant ($p < 0.05$) in the mean of FBG (103.0 ± 1.5 vs. 89.0 ± 0.0 mg/dL). In postmenopausal BC patients, FBG was higher ($p < 0.05$) in the recently diagnosed (105.6 ± 1.7 mg/dL vs. 126.2 ± 1.2 mm Hg) compared to the newly-diagnosed group (Tab. 4).

Age-controlled partial correlation coefficients between selected biochemical and obesity indices according to treatment exposure are shown in Tab. 5. In the whole study sample, FBG was significantly correlated ($p < 0.05$) with HOMA ($r = 0.34$) and C-peptide ($r = 0.16$). In newly-diagnosed patients FBG was significantly correlated ($p < 0.05$) with WHtR ($r = 0.27$), WHpR ($r = 24$) and WC ($r = 24$). FBG were also significantly correlated ($p < 0.05$) with BMI ($r = 0.20$). In recently diagnosed patients, WHtR was significantly correlated ($p < 0.05$) with FBG ($r = 0.14$) (Tab. 5).

Comparison between the mean of FBG, FBI and HOMA between the whole sample in the current study and previous study among non-cancer women in Jordan are given in Tab. 6. In the whole study sample, FBG was significantly lower ($p < 0.01$) compared with that found among non-cancer women (95.0 ± 0.9 vs. 119.15 ± 3.25)

Variable	Newly-diagnosed (*N* = 134)				Recently diagnosed (*N* = 262)				Whole sample (*N* = 396)			
	Premenopause (*N* = 80)		Postmenopause (*N* = 54)		Premenopause (*N* = 149)		Postmenopause (*N* = 113)		Premenopause (*N* = 229)		Postmenopause (*N* = 167)	
FBG* (mg/dL)	Mean	*SEM*	Mean	*SEM*	Mean	*SEM*	Mean	*SEM*	Mean	*SEM*	Mean	*SEM*
	88.5	1.6	98.0	2.5[a]	89.3	1.4	106.5	1.7[b]	89.0	1.1	103.0	1.5
FBG* >100 (mg/dL)	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
	16	11.9	22	16.4	28	10.7	61	23.4	44	11.1	83	21.0

Values are given as number of patients (*n*) and their percentages out of *N*, also values are given as mean ± *SEM*.
* Significant differences ($p < 0.05$) between pre- and postmenopausal women for treatment exposure groups and whole sample.
Values in rows with different superscripts are significantly different among newly and recently diagnosed groups ($p < 0.05$).
SEM – standard error of the mean; **newly-diagnosed** – breast cancer patients who are not exposed to any type of interventions; **recently diagnosed** – breast cancer patients within 3 months of diagnosis who are either exposed (chemo) or not exposed (non-chemo) to chemical therapy; **FBG** – fasting blood glucose.

Tab. 4. Mean and frequency distribution of FBG in pre- and postmenopausal women according to treatment exposure[1–4]

Character	Newly-diagnosed (*N* = 134)	Recently diagnosed (*N* = 262)			Whole sample (*N* = 396)
		Non-chemo (*N* = 86)	Chemo (*N* = 176)	Total (*N* = 262)	
	FBG (mg/dL)	FBG (mg/dL)	FBG (mg/dL)	FBG (mg/dL)	FBG (mg/dL)
C-peptide (ng/mL)	0.09	0.45***	0.20**	0.26***	0.16***
HOMA	0.43***	0.33**	0.30***	0.32***	0.34***
BMI	0.20*	–0.01	0.12	0.11	0.11*
WC	0.24**	–0.02	0.15*	0.11	0.15**
WHpR	0.24**	–0.04	0.06	0.03	0.09
WHtR	0.27**	–0.03	0.18*	0.14*	0.17***

* $p < 0.05$); ** $p < 0.01$; *** $p < 0.001$.
Newly-diagnosed – breast cancer patients who are not exposed to any type of interventions; **recently diagnosed** – breast cancer patients within 3 months of diagnosis who are either exposed (**chemo**) or not exposed (**non-chemo**) to chemical therapy; **FBG** – fasting blood glucose; **HOMA** – homeostasis model assessment according to the following formulas: Log (HOMA) as log [FBG (mmol/L) × FBI (μU/mL)/22.5] (Matthews et al., 1985)[31]; **BMI** – body mass index; **WC** – waist circumferences (cm); **WHpR** – waist to hip ratio; **WHtR** – waist to height ratio.

Tab. 5. Age-controlled partial correlation coefficients between FBG and selected biochemical and obesity indices according to treatment exposure[1–2]

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in previous study[32]. While, the FBI and HOMA were significantly higher ($p < 0.01$) compared with that found among non-cancer women in previous study (14.5 ± 0.8 vs. 10.5 ± 0.5 and 10.5 ± 0.5 vs. 0.4 ± 0.0, respectively) (Tab. 6).

DISCUSSION

Diabetes mellitus type 2 is a common metabolic disorder, affecting people in the whole world. It is caused by insulin secretary defect and resistance[1]. Insulin is a possible factor linking DM II to BC[7]. To the best of our knowledge, studies that investigate the prevalence of DM II and its risk components such as FBG, C-peptide, HOMA in relation to stage, menopausal status and type of treatment exposure among BC patients in Jordan and Arab, are not available. In present study, 21% of BC patients were diagnosed as diabetic and 32% of studied BC patients had high FBG >100 mg/dL. These results are in line with a study by Agnoli et al.[14], who have reported that 30.3% of BC patients had high FBG level. In a review of literature, Gouveri et al.[7] have reported that DM II and BC frequently coexist as diabetes increased risk of BC up to 20%, and 18% of patients with BC have diabetes; these results are also consistent with our results. However, in a meta-analysis, serum insulin has not been associated with BC risk when insulin-BMI was controlled[33]. Other studies have found no relation between diabetes and BC[34,35].

The prevalence of DM II and high FBG level in present study were not significantly higher than in BC patients who were expose to BC treatments either chemotherapy or other treatment interventions (recently diagnosed) compared to treatments of naïve BC patients (newly-diagnosed).

The possible explanation for such result variations is the interchangeable effects of BC and DM II therapy on each other, it has been supposed that DM II may be affected by BC treatments, while antidiabetic drugs have a minor influence on cancer risk, drugs used to treat cancer may worsen pre-existing diabetes[18]. Treatments of BC can exacerbate underlying insulin resistance as dexamethasone, which is commonly used anti-emetic agent before chemotherapy, causes hyperglycemia[7]. In premenopausal overweight women, using tamoxifen, hormonal estrogen modulators therapy, have decreased insulin sensitivity by almost seven times compared to women not taking tamoxifen[36] and in older BC survivors, tamoxifen has been associated with an increased incidence of diabetes[16].

In Jordan, studies that link BC and DM II are non-existent, this study is a first. In Jordan, the prevalence of non-BC patients with diabetes has been shown to be 17%[4] and more than 40% of women had elevated FBG[6]. Furthermore, Khader et al.[5] has showed that the prevalence of elevated FBG almost 25%, which is low, compared with our study and the mean FBG is significantly lower (95.0 ± 0.9 vs. 119.15 ± 3.25) compared with previous Jordanian study by Obeidat et al. (2016) among 322 female without BC[32], this may due to low dietary intakes during first 3 months of BC diagnosis.

In present study the prevalence of high FBG tends to be higher in recently diagnosed than in newly-diagnosed patients and it was significantly more prevalent in advanced stage than early stage BC. This coincide with a study by Kabat et al.[37], where FBG have been associated with increased BC risk in time dependent analysis. These findings harmonize also with a study by Lipscombe et al.[16] where medical interventions of BC as chemotherapy and dexamethasone have been linked with exacerbation of underlying insulin resistance and hyperglycemia. Furthermore, a study by Goodwin et al.[18] have established that drugs used to treat cancer may worsen pre-existing diabetes. Whereas, Healy et al.[9] have found that prevalence of high FBG was insignificantly different with respect to tumor size which doesn't not agree with our findings as the FBG is significantly related BC stages severity.

This inconsistency may be due to sample categorization of early and advanced BC stage or due to the differences among populations of both studies. Considering that DM II is a modifiable risk factor depending on lifestyle and dietary behaviors[25].

The prevalence of elevated FBG in this study, was higher in postmenopausal than in premenopausal women. This coincides with observations of Lipscombe et al.[16] who have shown a significant increase in BC risk among the postmenopausal women with diabetes. Similar results have been shown by other studies[7,38].

C-peptide is a single chain polypeptide consisting of 31 amino acids. In insulin biosynthesis, C-peptide facilitates the formation of the proper secondary and tertiary structure of the insulin. During insulin secretion, the precursor molecule (proinsulin) is cleaved into equimolar amounts of insulin and C-peptide. The C-peptide is more stable and has a longer half-life compared with insulin[39]. Therefore, measurements of C-peptide reflect

Character	Current study ($n = 396$)		Previous study ($n = 322$)	
	Mean	± *SEM*	Mean	± *SEM*
FBG (mg/dL)*	95.0	0.9	119.15	3.25
FBI (MU/mL)*	14.5	0.8	10.5	0.5
HOMA*	3.6	0.2	0.4	0.0

* Significant differences ($p < 0.01$) between the current study and previous study among non-cancer women in Jordan (Obeidat et al., 2016)[32].
SEM – standard error of mean; **FBG** – fasting blood glucose; **FBI** – fasting blood insulin; **HOMA** – homeostasis model assessment according to the following formulas: Log (HOMA) as log [FBG (mmol/L) × FBI (μU/ml)/22.5] (Matthews et al., 1985)[31].

Tab. 6. Comparison between the mean of FBG, FBI and HOMA between the whole sample in the current study and previous study among non-cancer women in Jordan[1–3]

pancreatic insulin secretion rates more accurately than insulin itself[40]. Many studies have observed null[21], non-significant positive[20] and inverse[19] associations between BC and C-peptide or insulin levels.

In present study the mean values of C-peptide and FBI level in the whole studied sample was 1.4 ng/mL and 14.5 MU/mL, respectively with no significant differences among study groups. Similar finding has been observed by Eliassen et al.[12] in a nested case-control study within the Nurses' Health Study II among predominantly premenopausal women among 317 cases and 634 matched controls. The study has shown that the median C-peptide and insulin levels were similar between cases and controls[12]. In the study by Irwin et al.[41] a 1 ng/mL increase in serum C-peptide level, was associated with a 35% increased risk of death as a result of BC and the associations were stronger among women with advanced stage BC. Although the level of C-peptide in both studies were almost similar (1.4 vs. 1.36 ng/mL), it is clearly that FBI level was higher in current study (14.5 MU/mL) compared with a previous study (7.22 MU/mL). Previous study by Goodwin et al.[38] have revealed a three-fold increased risk of death in BC women with higher fasting blood insulin collected 3 months after diagnosis. The high level of FBI in our results may be because the stress during this critical period (first 3 months of diagnosis). Eliassen et al.[12] have examined the associations of insulin with BC risk in predominantly premenopausal women. Studies have shown conflicting findings regarding menopausal status[20,21].

Homeostasis model assessment estimated insulin resistance (HOMA)-IR, which is a score used to define insulin resistance[31]. Although HOMA index is a reliable indicator of insulin resistance, however, it is less affected by life style modification than insulin level itself[22]. In this study the mean (3.6 ± 0.2) and frequency of high HOMA (42.2%) were not significantly different with respect to treatment exposure in newly and recently diagnosed BC patients but they were notably high compared with a study by Duggan et al.[23] on 527 BC patients where lower mean of HOMA-IR was observed (2.55). Furthermore, FBI and HOMA were high compared with that found among non-cancer women in previous study (14.5 ± 0.8 vs. 10.5 ± 0.5 and 10.5 ± 0.5 vs. 0.4 ± 0.0, respectively)[32]. Interestingly, the above study has shown that increasing HOMA-IR, after adjustment for covariates, were associated with reduced BC survival[23]. The variation between results may be due to differences in sample size, sampling technique, target group and ethnicity.

Obesity was prevalent (>50%) among study participants using BMI and FBG, which is significantly correlated with HOMA and C-peptide. These present study results were consistent with that observed in a study by Al-Zeidaneen et al.[42] about interactive role of obesity indices on BC severity in Jordanian women. Many studies have also confirmed similar results[8,9,43]. Insulin and related growth factors are possible factors linking obesity, DM II and BC. It has been reported that heavier women tend to have higher levels of insulin compared to leaner women[11,44]. Insulin has diverse metabolic functions and can act as a growth factor influencing cell proliferation and cell death, and it is a powerful mutagenic agent in normal mammary tissue as well as in BC cells[7]. However, the role of obesity and DM II in BC etiology may differ by ethnicity suggesting metabolic differences related to obesity[45].

In conclusion, diabetes mellitus II was prevalent among BC patients and increased with age and BC severity. The mechanisms underlying the association between BC and DM II are not fully understood, as many confounding factors share the two conditions such as obesity[8] and insulin resistance which are associated with BC severity and mortality[20,33,38]. The burden of diabetes on society continues to increase and warrants closer attention by healthcare provider for both BC prevention and improved outcomes after diagnosis.

Conflict of interest

The authors do not report any financial or personal links to any persons or organizations who could adversely affect the content of this publication and/or claim any rights thereto.

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