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Original Article

Adipocytokines, inflammatory, epigenetic instability & angiogenesis biomarkers in type 2 diabetic Egyptian women with breast cancer

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ABSTRACT

Obesity is the main determinant of type 2 diabetes. Some adipocytokines play important roles in diabetic complications. Lipid transport is an important aspect of lipid metabolism in cancer.

Present study aimed to evaluate the effect of some adipocytokines, inflammatory, epigenetic instability & angiogenesis biomarkers in type 2 diabetic Egyptian women with breast cancer.

Study Design was performed on eighty females divided into 20 healthy subjects (Group I), 20 patients with type 2 diabetes (Group II), 20 patients with breast cancer (Group III) & 20 patients with diabetes and breast cancer (Group IV). Demographic data & body mass index have been collected. Biochemical analysis included fasting & postprandial blood glucose, lipid profile, fatty acid-binding proteins-4 (FABP-4), tumor necrosis factor-α (TNF-α), vascular endothelial growth factor (VEGF), 8-hydroxy-2′-deoxyguanosine (8-OHdG) & thioredoxin reductase (TrxR) activity.

Results revealed significant increase in FABP-4, TNF-α, VEGF, 8-OHdG and significant decreased TrxR activity in diabetic patients with breast cancer in comparison with other groups. These changes were evident in breast cancer subjects than diabetic and healthy cases and in diabetic than healthy cases.

Conclusion: This study confirmed the role of FABP-4 in pathogenesis of type 2 diabetes & breast cancer via enhancing angiogenesis, inflammatory and epigenetic instability biomarkers.

1. Introduction

The balance in the lipid and carbohydrate metabolism is altered by environmental or metabolic stress, lifestyle, genetic or epigenetic factors, they can also become critical components of pathophysiological cascades that are highly damaging, leading to organelle dysfunction, chronic inflammation & cell death [1].

Obesity which is the main determinant of type 2 diabetes [2], leads to a local lipotoxic environment through dysregulated release of fatty acids, leading to an immune phenotype of adipose tissue characterized by increased release of cytokines such as Tumor necrosis factor-α (TNF-α) [3].

TNF-α are considered to be the main regulators of inflammatory cytokines in diabetes [4].

Additionally, TNF-α regulates lipid metabolism in adipocytes via increasing lipolysis [5]. Increased lipolysis from adipose tissue is also linked to secretion of fatty acid-binding proteins-4 (FABP-4), which is an important mediator of immunometabolic responses locally at the adipose tissue [6].

Fatty acid-binding proteins (FABPs) were originally described as intracellular proteins that can affect lipid fluxes, metabolism and signalling within cells. It has become evident that they are critical mediators of metabolism and inflammatory processes. FABP-4 plays a vital role in lipid-mediated biological processes associated with type 2 diabetes, obesity, and metabolic syndrome [7].

Moreover, Lipid transport and uptake are an important aspect of lipid metabolism in cancer. FABP-4 transports free fatty acids, which helps the regulation of triacylglycerol storage by decreasing

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its hydrolysis. In addition, it is becoming clear that lipid droplets are more than just passive storage components and are important in cancer as well, in particular for survival under stressful conditions [8].

Furthermore, reactive oxygen species (ROS) are regarded as the common denominator in the pathogenesis of hyperglycemic injury [9]. 8-hydroxy- 2′-deoxyguanosine (8-OHdG) is a product of DNA damage in the presence of high levels of ROS, with specific enzymatic cleavage and 8-hydroxylation of guanine bases. It is a biomarker of oxidative DNA damage in the pathogenesis of diabetic complications [10].

The breast carcinoma DNA contains high concentrations of base modifications. An increased level of 8-OHdG was observed in malignant tissues suggesting that ROS may play an important role in the early phases of carcinogenesis [11].

Moreover, ROS can promote the angiogenic switch in fibroblasts by the upregulation of vascular endothelial growth factor (VEGF), VEGF receptors, which are essential for angiogenesis-associated matrix remodeling [12]. ROS might play a role in cancer angiogenesis not only acting on tumor cells but also on tumor-infiltrated immune cells (i.e., macrophages) [13]. VEGF is involved in pathologic angiogenesis that occurs in tumor growth and metastasis [14].

Additionally, Selective increase in plasma VEGF may favor aberrant neovascularization and endothelial abnormalities. These abnormalities are closely linked to the pathophysiology of microvascular and atherosclerotic vascular complications in type 2 diabetes [15].

From another point of view, the antioxidant defense mechanism represented by thioredoxin reductase (TrxR), was suggested to modulate glucose and lipid metabolism [16]. Moreover, altered expression of TrxR, which has been described in various malignancies and cancer cells, is thought to be closely associated with tumor growth promotion, progression and metastasis [17].

2. Aim of the work

The aim of the present study is to evaluate the effect of some adipocytokines, inflammatory, epigenetic instability and angiogenesis biomarkers in type 2 diabetic Egyptian women with breast cancer.

3. Subject & methods

The study was performed on eighty female subjects aged from (50–65 years). The subjects were chosen from patients admitted to the Departments of Internal Medicine, & General surgery of the Tanta University Hospital between February 2016 & February 2017. They were divided into 20 patients with type 2 diabetes mellitus (Group II), 20 patients with breast cancer (Group III), 20 patients with type 2 diabetes mellitus and breast cancer (Group IV) and 20 healthy subjects (Group I) for comparison of assessed data. All patients were of matched menstrual state & socioeconomic status as control group. The breast cancer patients have primary invasive ductal carcinoma of the breast. All of them had mammary gland surgery.

A written consent was obtained from subjects under study in accordance with the principles of Ethical Committee of Faculty of Medicine, Tanta University, Egypt and was in accordance with the principles of the Declaration of Helsinki II.

A complete medical examination was performed for each participant. Based on the American Diabetes Association (2013), the diagnostic criteria of type 2 diabetes mellitus cases where glycemic control was evaluated showing plasma glucose $\geq$ 126 mg/dl or 2 h postprandial $\geq$ 200 mg/dl [18].

Patients with findings suspicious for breast cancer on mammography were confirmed by hitopathological biopsies were diagnosed with invasive ductal carcinoma. Among the cases, classification of malignant tumors (tumor size, nodal-status, and metastasis), grading (G), and hormone receptor status (estrogen receptor [ER] and progesterone receptor [PR]) were confirmed by the pathologists. Clinicopathological features such as age, tumor grade, tumor size, hormone receptor status, lymph node involvement and pathology reports were retrieved from the patients' records after obtaining all the relevant ethical approvals [19].

Exclusion criteria were histologically ductal carcinoma in situ, lobular carcinoma in situ, and patients with clinical manifestations of infections.

4. Data collection

The case subjected to:

Full history taking with past medical and family history.

Body weight by body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m^2) [20].

For breast cancer patients, investigations as chest X-ray, abdominal ultrasound & bone scan.

Demographic data were shown in Table 1.

4.1. Sample collection

After 12 h overnight fasting, 5 ml of venous blood was withdrawn from all subjects and separated into three portions. One portion was placed in plain tube and left to clot for 30 min at room temperature then centrifuged for 10 min at 3000 rpm to provide serum clear supernatant which is stored at −20 C until the time of assay. The second portion was placed into fluoride tube for blood glucose estimation (by enzymatic colorimetric test, using SPINREACT Diagnostics Company, Spain) [21].

4.2. Biochemical assessment included the following

4.2.1. Glycemic control

Fasting blood glucose (FBG) & 2 h postprandial blood glucose (PBG) were assayed using enzymatic colorimetric kit (Ref: 1001190) supplied by SPINREACT Diagnostics Company (Spain) [21].

4.2.2. Serum lipid profile

Serum total cholesterol (TC) level was assayed by enzymatic colourimetric test using commercial kit (CAT. No. CHSL 0490) supplied by ELITECH Diagnostics Company (France) [22] & serum triacylglycerol (TAG) level was estimated by enzymatic colourimetric kit (Ref: 1001310) using commercial kit supplied by SPINREACT Diagnostics company (Spain) [23], besides estimation of serum high density lipoprotein cholesterol (HDL-C) level by colourimetric test based on precipitation method using commercial kit (Ref: 10084) supplied by Human Diagnostics Company (Germany) [24] and serum low density lipoprotein cholesterol (LDL-C) level was calculated from the total cholesterol concentration (TC), the HDL cholesterol concentration (HDL-C) and triacylglycerol concentration (TAG) according to Friedewald et al. (1972) [25]. LDL-C = TC-[(HDL-C) + (TAG/5)] in mg/dl.

4.3. Assessment of adipocytokines & inflammatory cytokines

Serum Fatty acid binding protein-4 (FABP-4) was determined (after dilution of serum samples to 1:2) by ELISA technique performed according to commercial kits supplied by SUNRED Company, Changhai (Catalog No. 201-12-2037).

Table 1
Demographic data of the studied groups.

	Group I (n:20)	Group II (n:20)	Group III (n:20)	Group IV (n:20)	F	P
Age	57.53 ± 4.29	58.27 ± 3.83	57.27 ± 4.48	59.67 ± 4.03	1.001	0.399
BMI	22.49 ± 1.7	29.68 ± 3.5	26.53 ± 3.57	31.39 ± 3.6	22.401	<0.001*
Obese	(0%)	(80%)	(55%)	(85%)		
Non Obese	(100%)	(20%)	(45%)	(15%)		
Family History of DM						
Yes	(0%)	(65%)	(10%)	(20%)		
No	(100%)	(35%)	(90%)	(80%)		
Family History of Breast cancer						
Yes	(0%)	(10%)	(20%)	(10%)		
No	(100%)	(90%)	(80%)	(90%)		
Tumor size						
≤5	None	None	(60%)	(55%)		
>5	None	None	(40%)	(45%)		
Histological Grade						
I	None	None	(25%)	(15%)		
II	None	None	(50%)	(40%)		
III	None	None	(25%)	(45%)		
ER status						
Positive	None	None	(65%)	(80%)		
Negative	None	None	(35%)	(20%)		
PR status						
Positive	None	None	(55%)	(65%)		
Negative	None	None	(45%)	(35%)		
LN involvement						
Positive	None	None	(25%)	(45%)		
Negative			(75%)	(55%)		
Clinical stage						
I	None	None	(20%)	(15%)		
II			(55%)	(40%)		
III			(25%)	(45%)		

*P-value was considered significant at <0.05.

Serum tumor necrosis factor-α (TNF-α) was determined by ELISA technique performed according to manufacture instruction of commercial kits supplied by Sigma-Aldrich, Inc. Company, USA (Catalog No. CKH-200 A).

4.4. Assessment of angiogenic marker

Serum vascular endothelial growth factor (VEGF) was determined by ELISA technique performed according to manufacture instruction of commercial kits supplied by SUNRED Company, Changhai (Catalog No. 201-12-0081).

4.5. Assessment of epigenetic instability & DNA damage marker

Serum 8-Hydroxy 2-Deoxyguanosine (8-OHdG) was determined by ELISA technique performed according to commercial kits supplied by Chongqing Biospes Company, China (Catalog No. BYEK1218).

4.6. Assessment of antioxidant marker

Serum Thioredoxin reductase (TrxR) activity were measured by commercial kits (Catalog No. #K763-100) according to the manufacturer's instructions provided by Bivision (Milpitas, USA). Absorption at 412 nm was measured in a spectrophotometer. Serum TrxR activity is expressed in mU/ml [26].

4.7. Statistical analysis

Results represented mean ± SD, multiple comparisons were performed by one-way analysis of variance (ANOVA) followed by Tukey's post hoc test. Correlations between variables were assessed by Pearson's correlation test. All calculations were made using the computer program SPSS 23 (SPSS, Chicago, Ill, USA). The difference was considered statistically significant at $P < 0.05$.

5. Results

5.1. Adipocytokines & inflammatory markers

Serum FABP-4 showed statistically significant increase in Group II, III & IV patients as compared to control group ($P < 0.05$). Further, its level was statistically significantly increased in Group IV when compared to Group II &III as well as in Group III when compared to Group II (Table 2).

5.2. Angiogenic markers

Serum VEGF showed statistically significant increase in Group II, III & IV patients as compared to control group ($P < 0.05$). Further, its level was statistically significantly increased in Group IV when compared to Group II &III as well as in Group III when compared to Group II (Table 2).

5.3. Epigenetic & DNA damage marker

Serum 8-OHdG showed statistically significant increase in Group II, III & IV patients as compared to control group ($P < 0.05$). Further, its level was statistically significantly increased in Group IV when compared to Group II &III as well as in Group III when compared to Group II (Table 2).

5.3.1. Antioxidant marker

As shown in (Table 2), **Serum thioredoxin reductase activity** was statistically significant decrease in Group II, III & IV patients as compared to control group ($P < 0.05$). Further, its level was

Table 2
Comparison of biochemical findings among the studied groups.

Parameters	Groups				F	P-value
	Group I n = 20	Group II n = 20	Group III n = 20	Group IV n = 20		
FABP-4 (ng/ml)	14.28 ± 4.95	26.09 ± 6.25[a]	37.48 ± 10.82[a,b]	51.45 ± 13.63[a,b,c]	41.301	<0.001*
VEGF (ng/l)	95.97 ± 20.19	126.17 ± 21.42[a]	150.74 ± 25.35[a,b]	175.6 ± 25.32[a,b,c]	32.399	<0.001*
8-OHdG (ng/l)	25.89 ± 2.34	32.26 ± 4.60[a]	39.490 ± 4.30[a,b]	46.74 ± 7.55[a,b,c]	47.684	<0.001*
TNF-α (pg/ml)	4.79 ± 1.78	8.93 ± 3.38[a]	14.29 ± 5.39[a,b]	20.40 ± 5.16[a,b,c]	39.095	<0.001*
TrxR activity (mU/ml)	19.26 ± 2.76	15.44 ± 2.099[a]	12.67 ± 2.72[a,b]	10.06 ± 2.25[a,b,c]	37.946	<0.001*
FBG (mg/dl)	84.72 ± 6.82	165.17 ± 19.73[a]	85.78 ± 7.71 [b]	174.56 ± 22.92[a,c]	141.228	<0.001*
PBG (mg/dl)	117.15 ± 10.41	296.01 ± 57.599[a]	119.99 ± 11.07 [b]	323.14 ± 85.29[a,c]	68.107	<0.001*
TC (mg/dl)	167.12 ± 25.48	282.49 ± 25.48[a]	242.16 ± 35.61[a,b]	306.25 ± 24.53[a,c]	80.461	<0.001*
TAG (mg/dl)	123.59 ± 19.00	213.34 ± 38.496[a]	168.65 ± 29.83[a,b]	233.22 ± 54.6[a,c]	25.084	<0.001*
HDL-C (mg/dl)	73.74 ± 9.86	35.45 ± 6.11[a]	47.47 ± 8.53[a,b]	34.24 ± 6.91[a,c]	79.172	<0.001*
LDL-C (mg/dl)	68.66 ± 16.696	204.37 ± 23.004[a]	160.95 ± 35.97[a,b]	225.39 ± 25.59[a,c]	105.183	<0.001*

Data presented as mean ± SD n; number of cases.
Comparison between the studied groups was performed using one-way analysis of variance (ANOVA) with post hoc test. *P value was considered significant at<0.05. Group I: control group, Group II: Diabetic patients Group III: Breast cancer patients & Group IV: Diabetic patients with breast cancer. [a] Significantly different as compared with control group. [b] Significant different as compared with Group II. [c] Significant different as compared with Group III. FABP-4: Fatty acid binding protein-4, VEGF: Vascular endothelial growth factor, TNF-α: Tumor necrosis factor-α, 8-OHdG: 8-Hydroxy 2-Deoxyguanosine, TrxR: Thioredoxin reductase, FBG: Fating blood glucose, PBG: PTC:, Total cholesterol, TAG: Triacylglycerol, HDL-C: High density lipoprotein cholesterol, LDL-C: Low density lipoprotein cholesterol.

statistically significantly decreased in Group IV when compared to Group II &III as well as in Group III when compared to Group II (Table 2).

5.4. Glycemic control & lipid profile

FBG & PBG showed statistically significant increase in Group II & IV patients as compared to Group III & control group (P < 0.05) (Table 2).

Serum TC, TAG, LDL-C showed statistically significant increase in Group II, III & IV patients as compared to control group (P < 0.05). Group IV showed statistically significant increase in comparison to Group III. Also they showed statistically significant increase in Group II as compared to Group III (Table 2).

Serum HDL-C showed statistically significant decrease in Group II, III & IV patients as compared to control group (P < 0.05) (Table 3). Group IV showed statistically significant decrease in comparison to Group III. Also they showed statistically significant decrease in Group II as compared to Group III (Table 2). There is also positive correlation between VEGF & TNF-α (Table 4).

6. Discussion

Oxidative stress associated with insulin resistance induced obesity is the main determinant of type 2 diabetes [2]. Obesity is associated with adipose tissue inflammation and increased secretion of pro-inflammatory adipokines such as fatty acid-binding protein-4 (FABP-4), & tumor necrosis factor-alpha (TNF-α) [27].

This study found significant elevation in serum FABP-4 level in breast cancer subjects with type 2 diabetes compared with breast cancer, diabetic & normal subjects. Moreover, it was significantly elevated in breast cancer subjects compared with diabetic & normal subjects. Additionally, it was significantly elevated in diabetic subjects in comparison with normal subjects.

These findings aligned with Lehmann F et al. (2004) who stated that FABP-4 acts at the interface of metabolic and inflammatory pathways and plays a significant role in the development of obesity, insulin resistance and type 2 diabetes [28]. As well as, these findings are compatible with Garin-Shkolnik T et al. (2014) who reported that FABP-4 impairs insulin sensitivity and decreases expression of insulin-sensitizing adiponectin [29].

Consistently, Hancke K et al. (2010) confirmed that Circulating FABP-4 is higher in patients with breast cancer than in healthy individuals. Moreover, they reported that breast cancer patients with high serum levels of FABP-4 have a worse prognosis [30].

FABP-4 is an important protein which transports free fatty acids that are involved in lipid metabolism in different breast cancer subtypes [31]. In addition, this study revealed positive correlation between FABP-4 & BMI and this aligned with Hancke K et al. (2010) who also showed significant higher mean serum FABP-4 levels in obese over non-obese breast cancer patients and controls [30].

Considerable emphasis has been placed on the relationship of FABP-4 with anthropometric indices and factors associated with insulin resistance & obesity [32]. BMI of breast cancer patients was higher than in women with benign lesions particularly for post-menopausal women demonstrating the link between obesity and breast cancer [33].

The current study showed also positive correlation between serum FABP-4 & serum TC, TAG, LDL-C & negative correlation with serum HDL-C. This agreed with Kralisch S et al. (2013) who stated

Table 3
Correlations between Serum FABP-4 & different studied parameters among Group II, III & IV patients (n = 60).

Correlations		
	Serum FABP-4	
	r	*P-value*
Serum VEGF	.491	.001*
Serum TNF-α	.512	<.001*
Serum 8-OHdG	.454	.002*
Serum TrxR activity	-.411	.005*
Serum TC	.358	.016*
Serum TAG	.406	.006*
Serum HDL-C	-.319	.033*
Serum LDL-C	.330	.027*
BMI	.569	<.001*

*P value was considered significant at <0.05.

Table 4
Correlations between Serum FABP-4 and serum VEGF among Group II, III & IV patients (n = 60).

Correlations		
	Serum TNF-α	
	r	*P-value*
Serum VEGF	.313	.036*

*P value was considered significant at <0.05.

that total FABP-4 promotes insulin resistance, hypertriacylglycerolaemia and atherosclerosis [34].

The present study revealed significant elevation in serum TNF-α level in breast cancer subjects with type 2 diabetes compared with breast cancer, diabetic & normal subjects. Moreover, it was significantly elevated in breast cancer subjects compared with diabetic & normal subjects. Additionally, it was significantly elevated in diabetic subjects in comparison with normal subjects.

Also the present study confirmed positive correlation between serum FABP-4 & TNF-α levels. This agreed with Niu G et al. (2016) who reported that chronic inflammation is considered to be associated with obesity and insulin resistance [2]. FABP-4 participates in regulating the production of inflammatory cytokines [5]. Terra X et al. found that FABP-4 was positively correlated with inflammatory cytokines in obese subjects with newly diagnosed type 2 diabetes. Also, positive association of serum FABP-4 with inflammatory factor TNF-α, has been observed in morbidly obese women [32].

Moreover, dendritic cells that are FABP4-deficient produce lower levels of cytokines including TNF-α, and have reduced capacity to activate T cells [35]. Confirmatively, fat cells may also promote inflammation linked cancer through tumor growth regulators and tumor necrotic factors. Adipose tissue secretes TNF-α leading to inflammation promoting cancer [36].

Consistently, it is also well established that ROS is a common denominator in the pathogenesis of diabetic complications. This study found significant elevation of serum 8-HdOG level and significant decrease in TrxR activity in breast cancer subjects with type 2 diabetes compared with breast cancer, diabetic & normal subjects. Moreover, these significant changes occurred in breast cancer subjects compared with diabetic & normal subjects. Additionally in diabetic subjects in comparison with normal subjects. This confirms the negative correlation between serum 8-HdOG & TrxR activity.

Increased ROS activity can result from increased oxidant production and/or decreased antioxidant function. 8-OHdG levels are increased in diabetes patients and involved in the pathology of diabetes [37]. There was an increased level of 8-OHdG in the DNA of early-stage cancer tissue which suggests that ROS may play an important role in the early phases of carcinogenesis [11].

From another point of view, high glucose in diabetic subjects diminished TrxR activity. Restoration of TrxR activity may be a potentially beneficial therapeutic strategy for the prevention of diabetes-induced vascular complications [38]. Additionally, it was found a novel chemopreventive mechanism in cancer therapy is proposed involving Se catalysis of reversible cysteine/disulfide transformations that occur in a number of redox-regulated proteins, including TrxR [39].

Moreover, this study also revealed significant elevation of serum VEGF level in breast cancer subjects with type 2 diabetes compared with breast cancer, diabetic & normal subjects. Moreover, it was significantly elevated in breast cancer subjects compared with diabetic & normal subjects. Additionally, it was significantly elevated in diabetic subjects in comparison with normal subjects. One of the primary factors in the development of diabetic complications is pathological release of VEGF [40]. Increased VEGF release results in pathological angiogenesis that is irregularly distributed and features poorly constructed vessels that are prone to leak, leading to increased vascular leakage which is a serious risk factor for diabetic complications [41].

VEGFA may induce the production of matrix metalloproteinases (MMPs), such as MMP-2 and MMP-9, in breast cancer [42]. VEGF has been implicated in breast cancer susceptibility and aggressiveness. High VEGF expression was correlated with the presence of axillary nodal metastasis and lower overall survival rates [43].

Furthermore, this study showed positive correlation between FABP-4 & VEGF. It was reported that treatment of endothelial cells with VEGF via VEGF-receptor-2 or basic fibroblast growth factor induced FABP-4 expression. Also, FABP-4 in endothelial cells has also been reported to promote angiogenesis [44]. Consistently, the serum VEGF increments assessed herein may be influenced by expression of other cytokines (as TNF-α) regulating vascular permeability related to angiogenesis and this aligned with Pluda JM et al., 1997 [45]. Thus the current result confirmed positive correlation between VEGF & TNF-α.

7. Conclusion

This study confirmed the role of FABP-4 as an adipokine in pathogenesis of type 2 DM, breast cancer & diabetic subjects with breast cancer via enhancing angiogenesis (increased serum VEGF), inflammatory biomarkers (increased serum TNF-α) and oxidative stress (increased serum 8-OHdG & decreased serum ThxR activity). This can gives strong guidelines in management of type 2 DM, breast cancer & diabetic subjects with breast cancer by anti-FABP-4 therapy.

Conflicts of interest

This study confirmed the role of FABP-4 in pathogenesis of type 2 diabetes & breast cancer.

The role of FABP-4 via enhancing angiogenesis, inflammatory and epigenetic instability biomarkers.

This study evaluated the effect of some adipocytokines, inflammatory, epigenetic instability & angiogenesis biomarkers in type 2 diabetic Egyptian women with breast cancer.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.dsx.2018.08.005.

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