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RELATIONSHIPS BETWEEN SERUM EXPRESSION OF IGF-1 AND METABOLIC SYNDROME METRICS IN SYRIAN WOMEN WITH BREAST CANCER

Husseina Khaddour [1,2]***, Yahya I. Elshimali*** [3]***,***
Rucsandra Dănciulescu-Miulescu [4,✉]***, Daniela Gradinaru*** [1]

[1] Department of Biochemistry, Faculty of Pharmacy, Carol Davila - University of Medicine and Pharmacy, Bucharest, Romania
[2] Department of Biochemistry, Faculty of Pharmacy, University of Damascus, Damascus, Syria
[3] Department of Pathology and Oncology, UCLA School of Medicine & Charles R. Drew, University of Medicine and Science, USA
[4] Department of Endocrinology, Faculty of Dentistry, Carol Davila - University of Medicine and Pharmacy; N. Paulescu - Institute of Diabetes, Metabolic and Nutrition Diseases, Bucharest, Romania

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Abstract

Background and aims*: Insulin-like Growth Factors (IGF-1) plays as mediator between metabolic syndrome (MetS), oxidative stress and breast cancer (BrCa) progression. The objective of this study was to examine the relationships between IGF-1 serum levels and metabolic profile biomarkers in a population group of BrCa patients.* ***Material and methods****: 126 Syrian women with breast lesions were assigned in 3 study groups: I. Malignant breast tumor group, II. Benign breast tumor group and a Normal (control) group. The following biochemical parameters were measured: IGF-1, HDL-cholesterol, LDL-cholesterol, triglycerides (TG) and glucose.* ***Results****: The mean levels of serum IGF-1 in patients with breast cancer was significantly higher than those with benign tumors but we did not find any correlation between IGF-1 serum levels and tumor stage or lymph nodes metastases. Total cholesterol and LDL-cholesterol levels, along with TG were significantly higher in patients with BrCa versus benign and normal subjects.* ***Conclusion****: Results support the link of metabolic dysregulation and oxidative stress in BrCa progression as elevation of serum IGF-1 levels in BrCa patients are associated with metabolic syndrome markers which eventually adds more risk in cancer progression.*

key words: *Obesity, Malignancy, Metabolic dysregulation*

Background and aims

Breast cancer (BrCa) in woman is the most frequent malignant tumor in incidence; about one in eight women are diagnosed with breast cancer in during their lifetime. The mortality rate from breast cancer yearly is still considered high. Most women diagnosed with breast cancer are between ages 45 – 55 with some differences

✉ N. Paulescu - National Institute of Diabetes, Nutrition and Metabolic Diseases, Ion Movilă 5-7, Bucharest, 030167; *corresponding author e-mail*: rucsandra_m@yahoo.com

between races and ethnicities, but younger women can also get breast cancer [1].

Metabolic syndrome (MetS) is a cluster of risk factors for cardiovascular disease, diabetes and cancer. BrCa is conditioned by genetic predisposition and environmental factors, such as obesity, diabetes, or metabolic syndrome. All these risk prognostic factors are associated with breast cancer (BrCa) and share several hallmarks, among which insulin resistance (IR) seems to have particular relevance. Importantly, IR is associated to impaired glucose tolerance, hyperinsulinemia and hypertension, consequently, it has been proposed as a putative underlying cause in the relationship of obesity, diabetes, and metabolic syndrome with higher BrCa risk prognosis, and survival [2]. There are significant differences in metabolism between normal cells and cancer cells proposing that MetS components play a part in carcinogenesis. However, MetS could affect the risk of BrCa through alterations in a number of interrelated hormonal pathways, including those involving insulin, sex hormones, cytokines, growth factors and Insulin-like Growth Factors (IGFs) [3,4].

The role of Insulin-like Growth Factor-1 (IGF-1) and its receptor (IGF1R) in breast cancer progression was studied worldwide, and every study added valuable data related to cancer etiology [5]. IGF-1/IGF1R pathway is involved directly or indirectly with multiple pathways that contribute to breast cancer such as Proto-oncogenes (C-myc, int-2, c-erbB2 (HER2, neu, NGL) along with Cyclin D, tumor suppressor genes (BRCA1, BRCA2, p53) and DNA repair genes [6-8]. The role of the IGF-1 as mediator between the metabolic syndrome, oxidative stress and breast cancer progression is complicated and not fully understood and many factors and cellular pathways are involved in this association.

Therefore, the objective of this study is to examine the relationships between metabolic syndrome (MetS) and breast cancer (BrCa) progression, by the link between IGF-1 serum levels and metabolic profile biomarkers, in a population group of Syrian BrCa patients.

Material and method

Subjects and biological samples

This population study was conducted on 126 Syrian women with breast lesions assigned in 3 study groups:

I. Malignant breast tumor group: 61 women with invasive ductal carcinoma (IDC) or/and ductal carcinoma (DCIS);

II. Benign breast tumor group: 30 women with fibroadenomas or/and lipoma;

III. Normal group: 35 healthy women with no tumors (nor malignant neither benign) includes mastitis, fatty necrosis, fibrocystic changes or just normal tissue), considered as a control group. Study samples were collected in Syria between October 2016 and July 2017 from three hospitals: Albayrouni, Almouwasat, and the University Hospital from Damascus. The blood sample was drawn from every patient with breast lesion right before the surgical procedures.

Biochemical methods

The IMMULITE® 1000 system was used to analyze the levels target analyets from the serums of the collected subjects. Calibration, standardization and testing for the internal controls for the biochemical parameters were performed before the analyses. All blood samples were drawn from the cubital vein between 9:00 a.m. and 11:00 a.m. after an overnight fast. The samples were collected in a BD vacutainer without any anticoagulation. The samples were then centrifuged at 4000 rpm for 10 min at 4˚C, and the serum was transferred

into Eppendorf tubes (2 ml). All samples were immediately frozen at -80˚C until the measurements were performed. The following biochemical parameters were measured: IGF-1, total cholesterol (CHOL), HDL-cholesterol, triglycerides (TG), LDL-cholesterol and glucose. Serum IGF-1 was measured by an enzyme-labeled chemiluminescent immunometric assay (Immulite 1000; Siemens Medical Solutions Diagnostics). The Immulite IGF-1 assay has been calibrated to the old standard WHO. IGF-1 concentrations were compared with the age-specific normative range values for IGF-1.

Statistical analysis

Data resulting from demographic analysis and biomarkers measurements are represented as mean distribution (%) of women in the three study groups: Benign, Malignant and Normal (control), according to the studied parameter. Statistical analysis of the correlation between malignancies (Breast Cancer) and lipid-profile, serum glucose and IGF-1 were analyzed using different statistical tests such as the Mono-Variance (ANOVA) analysis and Multiple Comparisons. One is the Pearson Chi-Square test that was applied for calculation of P value, as well as the Likelihood Ratio and the Linear-by-Linear Association. After univariate analysis of each variable, bivariate associations were made between Breast Cancer and each independent variable using JMP 8.0.2 statistical software.

Results

Demographic and clinical characterization of the population study group

Age group distribution: Women in the age group between 41 - 50 years represent 27.8% of the whole group followed by age group of 51 – 60 years that represent 23%. For both age groups (31-40) and (61-70), each represents 5.9 % of the whole group, and for those whom are less than 30 years old (21-30) and less than 20, they represent 14.3% and 3.2% of the whole group respectfully. The mean age for those who have malignant diseases was 51 and for those who have benign tumors was 39.

Table 1. Serum levels of lipids, lipoproteins and glucose and BMI values of subjects included in all study groups

		Benign	Malignant	Normal
CHOL (100-200 mg/dl	Mean	219.12	242.01	117.03
	Std. Deviation	58.25	59.54	10.96
HDL (35-60 mg/dl	Mean	45.71	41.61	49.09
	Std. Deviation	12.89	13.90	11.19
TG (60-200 mg/dl)	Mean	128.60	162.77	78.82
	Std. Deviation	76.45	80.60	15.26
LDL (70-155 mg/dl)	Mean	147.63	167.87	52.14
	Std. Deviation	47.88	52.23	14.57
Glucose (80-120)	Mean	103.74	127.94	95.09
	Std. Deviation	48.71	48.14	7.28
Body mass index (BMI)	Mean	25.21	29.88	23.40
	Std. Deviation	4.73	5.10	3.10

Metabolic characteristics: Results obtained from one-way variant analysis (ANOVA) that revealed significant differences between measurements of blood testing for metabolic parameters and BMI for all subjects are shown in Table 1. Results were analyzed using the Mono-Variance (ANOVA) analysis and Multiple Comparisons (Tables 2 and 3). Significant

differences are present between variants means of all three groups (benign, malignant and normal) (P<0.05).

Table 2. Results of Analysis of Mono-Variance (ANOVA).

		Sum of Squares	Df	Mean Square	F	Sig.
CHOL (100-200 mg/dl)	Between Groups	359142.531	2	179571.265	70.078	.000
	Within Groups	315183.112	123	2562.464		
	Total	674325.643	125			
HDL (35-60 mg/dl)	Between Groups	1286.510	2	643.255	3.829	.024
	Within Groups	20662.762	123	167.990		
	Total	21949.271	125			
TG (60-200 mg/dl)	Between Groups	157034.119	2	78517.060	17.028	.000
	Within Groups	567170.180	123	4611.140		
	Total	724204.300	125			
LDL (70-155 mg/dl)	Between Groups	308862.654	2	154431.327	80.013	.000
	Within Groups	237398.203	123	1930.067		
	Total	546260.857	125			
Glucose (80-120 mg/dl)	Between Groups	27415.597	2	13707.798	8.042	.001
	Within Groups	209650.278	123	1704.474		
	Total	237065.875	125			
Body mass index (BMI)	Between Groups	1055.204	2	527.602	25.604	.000
	Within Groups	2534.567	123	20.606		
	Total	3589.771	125			

Table 3. Results of Multiple Comparisons Analysis.

Dependent Variable	I	J	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
CHOL (100-200 mg/dl)	Benign	Normal	102.09276*	12.59479	0.000	77.1621	127.0234
	Malignant	Benign	22.88817*	11.28818	0.045	0.5439	45.2324
		NA	124.98094*	10.73410	0.000	103.7334	146.2284
HDL (35-60 mg/dl)	Benign	NA	-3.376904762	3.22481	0.297	-9.7602	3.0064
	Malignant	Benign	-4.100191257	2.89026	0.159	-9.8213	1.6209
		Normal	-7.47710*	2.74839	0.007	-12.9174	-2.0368
TG (60-200 mg/dl)	Benign	NA	49.77786*	16.89531	0.004	16.3346	83.2211
	Malignant	Normal	34.17418*	15.14256	0.026	4.2004	64.1479
		Normal	83.95204*	14.39928	0.000	55.4495	112.4545

Table 3. *Continued.*

Dependent Variable	I	J	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
LDL (70-155 mg/dl)	Benign	Normal	95.49048*	10.93071	0.000	73.8538	117.1271
	Malignant	Benign	20.23552*	9.79673	0.041	0.8435	39.6276
		Normal	115.72600*	9.31586	0.000	97.2858	134.1662
Glucose (80-120 mg/dl)	Benign	Normal	8.654285714	10.27205	0.401	-11.6786	28.9872
	Malignant	Benign	24.19770*	9.20641	0.010	5.9742	42.4212
		Normal	32.85199*	8.75451	0.000	15.5230	50.1810
Body mass index (BMI)	Benign	Normal	1.801703386	1.12944	0.113	-0.4339	4.0374
	Malignant	Benign	4.67485*	1.01227	0.000	2.6711	6.6786
		Normal	6.47655*	0.96258	0.000	4.5712	8.3819
*. The mean difference is significant at the 0.05 level.							

The cholesterol levels in patients with breast cancers were higher than those with benign tumors and normal control ($P < 0.05$). Also, women with benign tumors showed higher cholesterol levels than those with normal control (Table 2). Expectedly, the differences between HDL levels between women with breast cancer and those in control were significant ($P < 0.05$). Lower levels of HDL were observed in cancer patients. No significant differences were seen between patients with benign tumors and normal control ($P > 0.050$) (Table 2).

On the other hand, the triglyceride (TG) levels and the low density lipoprotein (LDL) levels in patients with breast cancer were higher than those with benign tumor and normal control: Malignant Tumors > Benign Tumors ($P < 0.05$) and Benign Tumors > normal ($P < 0.05$). Nevertheless, with regard to glucose levels, there was a significant difference between patients with breast cancers and those with benign tumors or normal control. Where the glucose levels in cancer patients with high IGF-1 is ranked at range of high normal (Tables 4 and 5).

Table 4. ANCOVA analysis according to serum glucose levels.

		Sum of Squares	Df	Mean Square	F	Sig.
Glucose (80-120 mg/dl)	Between Groups	27415.6	2	13707.8	8.042	0.001
	Within Groups	209650.3	123	1704.474		
	Total	237065.9	125			

Table 5. Multiple Comparisons analysis according to serum glucose levels.

Less significant difference (LSD)							
Dependent Variable	I	J	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Glucose (80-120 mg/dl)	Benign	NORMAL	8.654286	10.27205	0.401	-11.6786	28.9872
	Malignant	Benign	24.19770*	9.20641	0.01	5.9742	42.4212
		NORMAL	32.85199*	8.75451	0.000	15.523	50.181

Serum IGF-1 analysis: The mean levels of serum IGF-1 in patients with breast cancer was 156.49 ng/ml which is higher than those with benign tumors, but without significant differences between subjects with benign tumors and the normal group. Since the mean levels of serum IGF-1 is different between age groups, a new method of analyzing IGF-1 levels was applied, and the results are shown in Tables 6 and 7.

Table 6. ANCOVA analysis evaluating the comparison of serum IGF-1 levels.

Control	Mean	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound
Benign	108.377[a]	13.181	82.284	134.470
Malignant	156.490[a]	9.340	138.000	174.979
Normal	107.238[a]	11.974	83.535	130.941

a. Covariates appearing in the model are evaluated at the following values: Age of Patient at DX2018 = 45.5397.

Table 7. ANCOVA test analysis for serum levels of IGF-1

Dependent Variable: IGF-1					
Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	108983.172[a]	3	36327.724	7.409	.000
Intercept	455866.074	1	455866.074	92.979	.000
Age	84052.459	1	84052.459	17.143	.000
control	64256.746	2	32128.373	6.553	.002
Error	598152.122	122	4902.886		
Total	2881096.010	126			
Corrected Total	707135.294	125			

a. R Squared = .154 (Adjusted R Squared = .133)

Table 8. Statistical analysis of serum IGF-1 levels in all study groups based on Estimated Marginal Means

(I) control		Mean Difference (I-J)	Std. Error	Sig .[b]	95% Confidence Interval for Difference [b]	
					Lower Bound	Upper Bound
Malignant	Benign	48.113*	16.667	0.005	15.119	81.106
	Normal	49.252*	15.495	0.002	18.578	79.926
Benign	Normal	1.139	17.478	0.948	-33.459	35.738

*. The mean difference is significant at the 0.05 level

b. Adjustment for multiple comparisons: Least Significant Difference (equivalent to no adjustments) Covariates appearing in the model are evaluated at the following values: Age of Patient at DX 2018 = 45.53

As demonstrated in Tables 6 and 7 and from the comparison of IGF-1 values in the designated three groups (malignant, benign and normal) the differences in IGF-1 levels were significant between the three groups ($P < 0.05$). In order to be more accurate in approaching the differences in study group levels of IGF-1, less significant difference (LSD) was applied as shown in Table 8.

Discussions

As mentioned in the introduction, BrCa is the most common cancer and the leading cause of cancer death among females worldwide, accounting for 25% of all cancer cases and 15% of all cancer-related deaths among females [1].

Increased body weight and metabolic disorder including insulin resistance, type 2 diabetes and cardiovascular complications together constitute metabolic syndrome. In

addition to changes in fuel availability and the adipocyte-derived hormones leptin and adiponectin [9,10]. Recent studies indicate that abnormalities in cellular lipid metabolism are involved in the pathogenesis of the metabolic syndrome. The pathogenesis of metabolic syndrome involves multitude of factors. Many studies however indicate, with some conformity, that oxidative stress along with chronic inflammatory condition pave the way for the development of metabolic diseases [10].

IGF-1 plays as mediator between the metabolic syndrome, oxidative stress and breast cancer progression. IGF-1 and IGF-2 through binding their receptors and other thyrosine kinase receptors induce signaling networks leading to fundamental cellular processes, such as cell growth, proliferation, differentiation and survival [11]. Aberrations in the generation or action of IGFs play an important role in several pathological conditions such as metabolic disorders and cancers. Therefore, we aimed to study the correlation between IGF-1 and some parameters according to MetS in a population study including 126 Syrian women. Substantial evidence indicates that the socioeconomic status (SES) of breast cancer patients has a significant impact on prognosis through its associated influence on the cancer stage at diagnosis. Previous findings suggest people with lower incomes have a later cancer stage at point of diagnosis and a worse overall prognosis. Also, Socioeconomic status is significantly associated with education level and occupation, both of which can greatly influence patients' perception of the tumor, thereby affecting the level of early detection, diagnosis, and treatment [12]. This observation was noted also in our study and we found that 87% of those subjects with malignant diseases have intermediate educational level or have never been to the school. This is in fact very important observation that may contribute to the lack of preventive measures that women may practice to decrease the risk of breast cancer progression.

Our study revealed significant correlation between malignancies and body mass index (BMI), 77% of those with breast cancer being obese or overweight. Expression of IGF-1 in breast cancer was significantly associated with high BMI, it appears likely that sensitivity to insulin in obesity plays a central role in the GH-IGF axis response, by inhibiting pituitary GH, increasing hepatic GH responsiveness and suppressing hepatic IGFBP-1 secretion. Our result revealed that there is a correlation between IGF1 and BMI in all age groups. This is confirming that obesity is associated with an increased IGF-1 response to GH and increased GH-binding protein levels so that an increase in expression of GH receptor may explain lack of suppression of total IGF-I levels. Some studies report an inverse relationship between total IGF-I concentrations and measures of adiposity, such as waist circumference [13].

Elevations in LDL-cholesterol and triglycerides (TG) levels with low levels of HDL cholesterol can predict development and prognosis in metabolic syndrome and eventually in cardiovascular diseases and malignant diseases in general. In our studies, the cholesterol and LDL levels in patients with breast cancers along with TG were higher in breast cancer patients than those with benign tumors and normal controls ($P < 0.05$). While lower levels of HDL were observed in cancer patients as expected ($P < 0.05$). In regard to glucose levels and BMI, there was no significant differences between patients with breast cancers and those with benign tumors or normal control. Interestingly the patients with normal controls have glucose levels and BMIs higher than those in breast cancer patients.

In summary, the mean levels of serum IGF-1 in patients with breast cancer was 156.49 ng/ml which is higher than those with benign tumors, but without significant differences between subjects with benign tumors and the normal group.

From the above findings the indicators of metabolic syndromes (TG, Cholesterol, LDL, HDL) and remarks of oxidative stress (tobacco smoking and others) are associated with elevation or high expression of IGF-1 which is eventually linked to breast cancer progression.

It appears that the binding of IGF-1 to its receptor activates the tyrosine kinase and initiates a cascade of phosphorylations that activate intracellular kinases and nuclear transcription factors, including the estrogen receptor (ER). There is increasing evidence for a complex mechanism of cross-talk between peptide and steroid pathways. The emerging model of cross-talk between IGF-1 and estrogens suggests that estrogens, acting through the estrogen receptor (ER), induce the expression of IGF-1. IGF in turn exerts its actions through binding to the IGF receptor I, a transmembrane protein with tyrosine kinase activity. On the other hand, the inhibition of IGF-1 receptor signaling with anti-IGF receptor antibodies, may restricts breast cancer cell growth *in vivo*. Previous studies revealed that similar effect is also observed in breast tumor xenografts *in vivo* [11,14]. Since, it would be interesting to investigate a possible correlation between IGF-1 and ER Expression, as antiestrogens, inhibit IGF-1 receptor dependent growth by down-regulating the IGF autocrine pathway and modulating the expression of IGF binding protein. In addition, antiestrogens decrease the expression of IGF-1 binding sites and suppress the activation.

Recent studies have shown that the levels of estrogens and other steroid hormones in breast fluids are much higher than in serum, which may be the result of local synthesis or increased uptake from the circulation. No differences in estrogen levels of breast fluid have been found between normal women and those with breast disease. A possible explanation may be differences in the levels of estrogen antagonists, such as progesterone.

Finally, we did not find any correlation between IGF-1 serum levels and tumor stage or lymph nodes metastases as have been demonstrated in breast cancer and other cancer types [15-17]. Subjects samples, age groups and geographic distribution as well as genotypes may explain this contradictory.

Conclusions

Our studies showed that the elevation of serum IGF-1 levels in breast cancer patients are associated with high levels of metabolic syndrome markers such as LDL-cholesterol, triglycerides, glucose, body mass index (BMI) and low levels of HDL which eventually adds more risk in cancer progression, that support the link of metabolic dysregulation and oxidative stress on breast cancer progression.

Interestingly, this study revealed remarkable link between malignant subjects and their educational levels which may have reflected in many aspects on their lifestyles such as low physical exercises, diet type and high carbohydrates uptake that increase the risk of breast cancer.

Nevertheless, we did not find in this study any correlation between serum IGF1 levels and tumor stage or lymph nodes metastases in patient's breast tumors as have been mentioned in previously published reports in breast cancers and other cancer types.

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