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Study of Serum Adiponectin, Leptin, and Galectin-3 in Breast Cancer

Aisha Abdulkareem Ibrahim (MSc)[1], Sardar Nori Ahmed (PhD)[2]
[1] College of Medicine, Hawler Medical University, Erbil, Iraq
[2] Clinical Biochemistry, University of Salahaddin, Erbil, Iraq

Abstract

Background: Breast cancer is the most common cancer that threatens the lives of women all over the world. Adipocytokines (adiponectin, leptin), and the β-galactoside-binding proteins (galectin-3) are new suggested parameters for the diagnosis and prognosis of breast cancer.
Objective: To find relationship between serum adiponectin, leptin, and galectin-3 and breast cancer diagnosis and prognosis factors.
Patients and Methods: A case-control study was done between (August 2021 to June 2022). Totally collected 111 female blood samples from patients that diagnosed with a breast cancer and healthy control, Samples were grouped into Group I (30 healthy control), Group II (43 patients pre-treatment), and Group III (38 patients post-treatment), from Rizgary Teaching Hospital, Nanakali Hospital, Hawler Teaching Hospital- General surgery and Neurosurgical Department, PAR Private Hospital, PAKY Hospital, and Rasul Private Hospital at Iraq-Erbil city and the age 18 up to 77 included in this study. Biochemical tests were performed (Adiponectin, Leptin, Galectin-3). These sample were analysed by using blood serum, statistically analysis the result.
Results: The post-treatment, pre-treatment, and control in respectively about (60.52%, 60.46%, and 63.34%) were the majority of the study population (38-57) age group. There is a statistically significant differences between case and control groups in residency, family history, and BMI with a P-vale of (0.08, <0.001, 0.015), respectively. Leptin, adiponectin, and galectin-3 were statistically significant (0.007, <0.01, and <0.01), in respectively. About cancer characteristic galectin-3 was significant with (ER/PR) receptor (P:0.037) and grade (P:0.034), also leptin was significant with the ee (P: 0.025).
Conclusion: We concluded that Adiponectin, Leptin, and Galectin-3 were new potential biochemical marker for diagnosis and prognosis the breast cancer, would be useful and important marker for assessing and evaluating grade, and receptor of the therapy plan.
Keywords: Breast cancer, Adiponectin, Leptin, Galectin-3

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Correspondence Address: Aisha Abdulkareem Ibrahim
College of Medicine, Hawler Medical University, Erbil, Iraq
Email: aesha.ibrahim95@gmail.com

Website: https://djm.uodiyala.edu.iq/index.php/djm

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Introduction

Breast cancer disease is cancer that develops from breast tissue. Signs of breast cancer may include a lump in the breast, a change in breast shape, dimpling of the skin, fluid coming from the nipple, a newly inverted nipple, or a red or scaly patch of skin. Risk factors for developing breast cancer include being female, genetic, environmental and nutritional factors, obesity, alcoholism, hormone replacement

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therapy during menopause, ionizing radiation, and a family history of breast cancer. Breast cancer is the most common cancer that threatens life of women all over the world [1].Adiponectin, is circulating protein hormone with 244-amino acid polypeptide protein. It is an insulin-sensitizing hormone secreted mainly by adipocytes of white adipose tissue, which play pivotal roles in regulation of energy homeostasis ("regulating glucose levels, and fatty acid breakdown"), insulin sensitivity, antioxidant, anti-atherogenic, cell proliferation, anti-inflammation, and promotes apoptosis in carcinogenic cells. [2,3]. It has suggested that the low serum adiponectin concentration was associated with hyperinsulinemia and increased vascular endothelial growth factor (VEGF) and insulin-like growth factor levels, which have been demonstrated to increase the risk of obesity-related malignancies, including breast cancer [4]. Adiponectin receptors (AdipoR1 and R2) are activated of AMPK related pathways, so its inhibition of cell proliferation and promotion of apoptosis, the regulation of tumorigenic-related factors, and the suppression of angiogenesis. The signalling pathways linking adiponectin with tumorigenesis might provide potential drug targets for the future [5]. Leptin is a peptide hormone contains 167 amino acids, 16kDa. Secreted from adipocytes in response to the nutritional status "regulator of food intake", and it signals to the central nervous system (CNS) and peripheral organs to coordinates energy homeostasis [6,7] Leptin is a pleiotropic molecule that play role in the regulation of energy homeostasis, metabolism homeostasis, stimulate cell proliferation, neuroendocrine function (regulates glucocorticoids, insulin hormone), fertility, hematopoiesis, regulates immunity, pro-inflammatory, anti-apoptotic proteins, TNF- α, and pro-angiogenic factor which promotes cancer cell survival and proliferation [8].Leptin exhibits potent oncogenic actions and acts on different stages of cancer, including cell proliferation, angiogenesis, metastasis, and drug resistance, via multiple mechanisms such as breast cancer proliferation by (LEP-R) activation of MEK/ERK1/2 and PI3K/Akt signalling pathways, autophagy induction, and NLRP3 inflammasomes activation [9]. Summarize leptin function ass exert neoplastic effects in breast cancer by acting directly on tumour growth, migration and invasion signalling pathways or by decreasing tissue sensitivity to insulin or regulating inflammatory responses and tumour angiogenesis [10].Galectins-3 are a family of β-galactoside-binding proteins that share a consensus sequence in the carbohydrate recognition domain (CRD) can be found in the cellular cytoplasm and nucleus, as well as extracellularly in various tissues. The 30-kDa molecule contains an (N-terminal proline-rich domain) that is important for its oligomerization and a (C-terminal CRD) for carbohydrate-binding activity. Plays a role in "cell-cell adhesion, cell matrix interaction, macrophage activation, angiogenesis, metastasis, and apoptosis". Galectin-3 expressed in tumour cells plays an important role in the processes relevant to tumorigenesis such as malignant cell transformation, invasion and metastasis [11]. Initiation tumor cell transformation through interactions with oncogenic Ras proteins (K-

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Ras) and activation of phosphatidylinositol 3-kinase (PI3K) and Raf1, may also influence tumorigenesis through the regulation of cell cycle. Downregulates the expression of cyclin E and cyclin A and upregulates the expression of cell cycle inhibitors p21(WAF1) and p27(KIPI) [12]. Galectin-3 plays an important role in neoplastic progression and is highly expressed by triple-negative breast cancer (TNC), for which it has been proposed as a potential therapeutic target. It has also suggested that it has a role in breast cancer development and progression [13]. The aim of the present study is to evaluate the serum adiponectin, leptin, and galectin-3 in breast cancer, and what are the factors affect those levels in breast cancer, and also the relation among them.

Patients and Methods

Study protocol

A case-control study, that was carried out from 28th of August 2021 to the 11th of June 2022, At - Erbil/ Iraq. Healthy controls (Group I) were volunteers randomly selected and had no evidence for any disease. Patients (Group II and Group III) were selected from Rizgary Teaching Hospital, Nanakali Hospital, Hawler Teaching Hospital- General surgery and Neurosurgical Department, PAR Private Hospital, PAKY Hospital, and Rasul Private Hospital).

Study population

Totally collected 111 female blood sample aged between 18 up to 77 included in this study from patients that diagnosed with a breast cancer and healthy control, Samples were grouped into Group I (30 apparently healthy control), Group II (43 patients pre-treatment), and Group III (38 patient post-treatment). Inclusion criteria [female, aged between (18 to 77), have another type of breast cancer (Paget's disease, Medullary BC, Colloid (Muclnous) BC, Tubular BC, and Phyllodest BC), all Patient were pathological diagnosed with BC]. Exclusion criteria (male, age less than 18 or older than 77, benign breast cancer, homolysis samples, alcoholic, have medication of hormone, chronic medical problems requiring medical treatment, did not complete their investigations and having unknown stage or lymph node, have another type of breast carcinoma (Sarcoma, adenocarcinoma) and the (recurrent breast cancer), didn't finish their treatment plan for (post-treatment) group.

Study design

A systematic interview With 31 questions includes the demographic variables (name, age, home address & phone number, marital status, paternity, level of education, residence, occupation, socioeconomic status, physical activity, smoking, drinking alcohol, dietary habits, wight, hight, family history,...ect.), along with access to medical records or records which contain intimate personal information, and are individually identifiable and are not publicly available that included descriptive characters of the BC groups (have surgery for tumor remove, have treatment, type of treatment, type of cancer, stage, grade, L.N. , receptor, duration of disease). Collection of blood sample totally collected 111 female blood sample from (81) patients that diagnosed with a breast cancer and (30) healthy control. Five milliliters (ml) of venous blood sample were obtained and put in serum separator tube (SST), then it remains stand about 20 minutes at room temperature then underwent a 10- minute

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centrifuge process at 3500 rpm, serum obtained transferred into sealed (Eppendorf tubes) and directly stored at -20 ℃. The separated blood serum used to preform biochemical tests (adiponectin, leptin, galectin-3) were done by ELIZA.

Statistical Analysis

All statistic data were analyzed using (SPSS, version 26) and GraphPad prism 9. The Shapiro-will test and Kolmogorov-Smirnov test were used to determine whether a random sample was normally distributed. The Chi-square test was used to test the significance of associations between independent and dependent variable. Compare between two independent sample group (e.g., case & control) using unpaired t-test, while measurement data among multiple group were done using one-way ANOVA (F-test) followed by multiple comparison post-hoc ANOVA LSD test or Kruskal-wallis. P value: 0.05 statistically significant (S), highly significant (HS) when the P value was 0.001, and non-significant (NS) when the P value was >0.05.

Results

A total of 111 female subjects from both groups were included, 72.97% of them were cases and 27.027% were controls and the mean age was 49.66 ± 11.34 with a range of 18-77 years old. The post-treatment, pre-treatment, and control in respectively about (60.52%, 60.46%, and63.34%) were the majority of the study population (38-57) age group, followed closely by the (58-77) age group (31.58%, 27.91%, and23.33), (7.90%, 11.63%, and 13.33%) were between (18-37) years of age.

In regards to the risk factors among case and control group of the study population, upon analysing the risk factor differences between patients and healthy individuals, the Chi-square test analysis observed that there is a statistically significant differences between the two groups of subjects in most of the risk factors including Residency, Family history, and BMI with a P-vale of (0.08, <0.001, 0.015), respectively. This information's are summarized in Table (1).

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Table (1): Social and demographic characteristics of study group

Parameter			Control group *n*=30	Patient group *n*=81	test	value	P value
paternity	Yes	*n* (%)	24 (80)	59 (72.8)	Chi-square	0.59	0.44
	No	*n* (%)	6 (20)	22 (27.2)			
Residency	Urban	*n* (%)	25(83.3)	54 (66.7)	Chi-square	2.96	0.08*
	Rural	*n* (%)	5 (16.7)	27 (33.3)			
Level of education	Illiterate	*n* (%)	12 (40)	27 (33.3)		1.10	0.77
	primary	*n* (%)	7 (23.3)	23 (28.4)	Chi-square		
	secondary	*n* (%)	6 (20)	21 (25.9)			
	College &above	*n* (%)	5 (16.7)	10 (12.3)			
Occupation	Employed	*n* (%)	6 (20)	12 (14.8)	Fisher's Exact	----	0.56
	Unemployed	*n* (%)	24 (80)	69 (85.2)			
Socio-economic status	Low	*n* (%)	4(13.3)	24 (29.6)			
	Middle	*n* (%)	18(60)	47 (58)	Chi-square	5.08	0.079
	High	*n* (%)	8(26.7)	10 (12.4)			
smoking	Yes	*n* (%)	1(0.3)	11(13.6)	Fisher's Exact	----	0.17
	No	*n* (%)	29(96.7)	70(86.4)			
Family history	Yes	*n* (%)	0 (0.00)	39 (48.1)	Chi-square	22.26	<0.001*
	No	*n* (%)	30(100)	42(51.9)			
Age (year)		mean± SD	49.66±11.34	51.11±11.60	t.test	- 0.59	0.55
BMI (Kg/m²)		mean± SD	32.10±5.54	29.02±6.19	t.test	2.51	0.015*

*Significant difference

There was a significant difference between the mean level of leptin among the cases and controls. Unsurprisingly, the cases (pre-treatment & post-treatment) had a higher leptin level (1797.21±125.70 & 1628.41±146.62), respectively. Compared to the control (1170.33±135.82). This was significant with a P-value of 0.007. The controls had higher adiponectin levels (139.36±0.72) compared to the pre-treatment cases (132.82±0.62) but the post-treatment had the highest level (140.79±0.67), this was also significant, P = <0.001. The cases had higher mean galectin-3 levels in (pre-treatment & post-treatment) (2.64±0.11 & 1.30±0.12), respectively. Then the control (1.15±0.12) and this was highly significant, with P<0.001. This information's are summarized in Table (2).

Table (2): Chemical parameters of the studied groups

Parameters (Mean ± SE)	Control	Pre-treatment	Post-treatment	F test value	P value
Leptin(pg/ml)	1170.33 ±135.82	1797.21 ±125.70	1628.41 ±146.62	5.15	0.007*
Adiponectin(ng/ml)	139.36 ± 0.72	132.82 ± 0.62	140.79 ± 0.67	43.92	<0.01*
Galectin-3 (ng/ml)	1.15 ± 0.12	2.64 ± 0.11	1.30 ± 0.12	47.65	<0.01*

*Significant difference

By using post-hoc ANOVA-LSD test to observed the level of significant differences between the control and cases (pre-treatment & post-treatment). Leptin level of significant between (Control & pre-treatment), and (Control & post-treatment) P-value (0.02,

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0.026) in respectively. (P:0.364) there was no significant different between (pre-treatment & post-treatment). Adiponectin there was a significant differences P-value (<0.01, <0.01) between (Control & pre-treatment) and (pre-treatment & post-treatment), in respectively. There was no significant different between (Control & post-treatment) (P:0.153). Galectin-3 was significant between (Control & pre-treatment) and (pre-treatment & post-treatment) with P-value (<0.01, <0.01), in respectively. There was no significant different between (Control & post-treatment) (P:0.405). This information's are summarized in Table (3).

Table (3): Chemical parameters between the studied groups

Parameters	Groups	P value
Leptin	Control **V** Pre-treatment	٠.002*
	Control **V** Post-treatment	0.026*
	Pre-treatment **V** Post-treatment	0.364
Adiponectin	Control **V** Pre-treatment	<0.01*
	Control **V** Post-treatment	0.153
	Pre-treatment **V** Post-treatment	<0.01*
Galectin-3	Control **V** Pre-treatment	<0.01*
	Control **V** Post-treatment	0.405
	Pre-treatment **V** Post-treatment	<0.01*

*Significant difference

By using (Kruskal-Wallis) of nonparametric test of non-normal distribution to find the level of significant in case group of the study population, upon analyzing the cancer characteristic in patients, the analysis observed that there is a statistically significant difference in some of cancer characteristic including (ER/PR) receptor in galectin-3 with P-value (0.037). Also, the grade was significant in leptin, galectin-3 with P-value (0.025, 0.034), in respectively. This information's are summarized in Table (4).

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Table (4): Descriptive characters of the breast cancer patients studied group and parameters

Cancer characteristic	(N)	(%)	(P value)
Cancer stage **Leptin** **Adiponectin** **Galectin-3**			 0.067 0.916 0.663
0 IA IB IIA IIB IIC IIIA IIIB IIIC IV	2 6 3 17 23 1 9 4 7 9	2.47% 7.40% 3.70% 20.00% 28.40% 1.23% 11.11% 4.93% 8.65% 11.11%	
Lymph node involvement status(N) **Leptin** **Adiponectin** **Galectin-3**			 0.108 0.868 0.447
PNx PN0 PN1 PN2 PN3	6 27 25 15 8	7.40% 33.30% 30.90% 18.50% 9.90%	
Receptors **Leptin** **Adiponectin** **Galectin-3**			 0.48 0.77 0.037*
Her2 Triple negative Triple positive ER/PR	13 6 20 42	16.05% 7.40% 24.70% 51.85%	
Grade **Leptin** **Adiponectin** **Galectin-3**			 0.025* 0.158 0.034*
1 2 3	14 46 21	17.3% 56.80% 25.90%	
Type of cancer **Leptin** **Adiponectin** **Galectin-3**			 0.613 0.341 0.208
DCIS ILC IDC Metastatic IBC IDC & DCIS IDC & ILC IBC & Metastatic ILC & IBC & Metastatic	2 2 64 4 1 3 3 1 1	2.50% 2.50% 79.00% 4.91% 1.20% 3.70% 3.70% 1.20% 1.20%	
Duration of disease 1>Year (1-5) Year 5<Year	 39 21 21	 48.10% 25.95% 25.95%	
Surgery Yes No	 53 28	 65.40% 34.60%	

*Significant difference

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Discussion

Although there are many available recent used serum/plasma biomarkers (CEA, CA15-3, and CA125) but were not supported to be used alone for diagnosis of BC patient due to inaccurate diagnosis. We have set out to assess the serum adiponectin, leptin, and galectin-3 in patient with BC. Many studies suggest that adiponectin, leptin, and galectin-3 may serve as a biochemical indicator of breast cancer disease. The present case-control study aimed to shed light on these chemical parameters to the patients before having treatment (pre-surgery & post-surgery), as well as patients after finishing treatment plan, and healthy control. Also, focusing on cancer characteristic that help through diagnosis and prognosis the disease, in addition it has been proposed as a potential therapeutic target. Based on finding most of patients diagnosed with BC were among old aged groups (postmenopausal women), in line with this finding, Pan H and his colleagues reported that menopausal status subgroup analysis revealed a significant association in postmenopausal women [14]. The finding demonstrated that mean leptin was significantly higher among BC patients in comparison to control group (P:0.07). The finding shown (control & pre-treatment) were significant (P:0.02). Similar results have been reported by (Assiri, A. M. A *et al*, 2015) [15] and (control & post-treatment) were also significant (P: 0.026). Which was supported with other study (Delort, L *et al*., 2019) [16]. But there was no significant relationship between (pre-treatment & post-treatment) (P: 0.364) Nadia Obi and her colleagues reported that overall, post-diagnosis adipokines (leptin) were not associated with long-term outcomes after breast cancer [17]. The leptin also was statically significant with grade (P: 0.025) So it may help to detect patient's grade without going through biopsy procedure, similar results have been reported by (Liu, C.-L., 2007) that those with breast cancer, the serum leptin concentration was higher in women with high-grade cancers [18]. The results of serum adiponectin indicate the association of adiponectin levels with BC. We found that adiponectin was highly significant in BC patient compering to healthy control (P: <0.01). This study emphasize that serum adiponectin mean was higher in (control than pre-treatment) and the results was highly significant (P: <0.01). These results were in agreement with the result of (Peña-Cano, M. I. *et al.*, 2019) [19]. On another said the mean of (post-treatment was higher than control, that is why we found there was no significant different between (control & post-treatment) (P: 0.153) Nadia Obi and her colleagues reported that overall, post-diagnosis adipokines (adiponectin) were not associated with long-term outcomes after breast cancer [17]. However, (pre-treatment & post-treatment) were highly significant (P:<0.01) similar outcomes were reported (Ozmen, H. K., *et al*., 2017) [20]. The available data have shown a highly significant positive relationship between mean galectin-3 and BC (P:<0.01) in patient it was higher than control. These results are also supported by (Topcu TO, *et al*., 2018), and (Shafiq, A., *et al*., 2020) it indicates a highly significant relationship between (control & pre-treatment), as well as, (pre-treatment & post-treatment) [21,22].

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However, our results found no significant relationship between (control & post-treatment) (P:0.405) the study (Patel, S. R., 2021) supported the outcome of this study and reached similar results [23]. Another important factor that have been detect through this investing the clinically significant of serum galectin-3 and BC of cancer grade (P: 0.034) and receptors (P: 0.037) which were supported by other studies that have similar results (Zhang, H., *et al*., 2020) (Zhang, H., *et al*., 2014) (Koo, J. S., & Jung, W., 2011) (K. Sujathan, *et al*., 2011). [24-27]) which may by a highly remarkable marker in diagnosis and treatment plan as well as potential therapeutic target.

Conclusions

This is the first study assessing serum Adiponectin, Leptin, and Galectin-3 among breast cancer patients in this region. Our study has identified link between (adiponectin, leptin, and galectin-3) with BC patient. Under the findings of this study, we conclude that serum (adiponectin, leptin, and galectin-3) shows significant relationship with all (control & pre-treatment) patients when there was no contradiction of treatment when the cancer still inside the body or untreated, so we can use these parameters as biochemical markers for diagnosis BC. According to this study (Galectin-3 & leptin) were significant with the histological grade due to that doctor may use these markers for detecting the grade without having to go through biopsy procedure that most of people afraid to go through. Moreover, serum galectin-3 shows significant relationship with the receptors and most of published studies find out it was significant with triple negative receptor. So, these parameters may be effective to detect breast cancer, lowering the high incidence and mortality rates, in many studies it was suggest that adiponectin and galectin-3 can be potential treatment target so it may reduce the high cost of treatment and improve health outcomes.

Recommendations

Have a larger sample size to avoid any false positive results, and in order to have a narrower scope for the results (e.g., post-treatment patient) should be divided into subgroup based on their treatment plan wither having (surgery only, or chemotherapy, hormone/endocrine therapy, targeted/ biological therapy, radiotherapy). In addition, if the sample size was larger the hormone receptor (ER/PR) can study in separated way, because some patient use to Obtained only (ER positive) and it may effect on treatment plan.

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Ethical clearance: By Hawler Medical University's Research Ethics Committee, College of Medicine. Also, verbal approval was obtained from each Hospital. As well as verbally Informed consent was taken from each patient. A Complete explanation of the

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nature and aim of the study was given to each participant, and reassure about the confidentiality of the data and their anonymity.

Conflict of interest: Nil

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دراسة مصل الأديبونيكتين، اللبتين، والجالكتين-٣ في سرطان الثدي

عائشة عبدالكريم إبراهيم[١] ، سردار نوري احمد [٢]

الملخص

خلفية الدراسة: سرطان الثدي هو أكثر أنواع السرطانات شيوعًا التي تهدد حياة النساء في جميع أنحاء العالم. الأديبوسيتوكينات)اللبتين، الأديبونيكتين)، والبروتينات المرتبطة)الجالكتين-٣) β- جالاكتوزيد هي علامات مقترحة جديدة لتشخيص سرطان الثدي والتنبؤ به.

اهداف الدراسة: لإيجاد علاقة بين مصل الدم الأديبونكتين واللبتين الجالكتين-٣ وعوامل التشخيص والتشخيص لسرطان الثدي.

المرضى والطرائق: تم إجراء دراسة الحالات والشواهد بين (أغسطس ٢٠٢١ إلى يونيو ٢٠٢٢). تم جمع ١١١ عينة دم من الإناث من المرضى الذين تم تشخيص إصابتهم بسرطان الثدي والأشخاص الاصحاء، وتم تجميع العينات في المجموعة الأولى (٣٠ اشخاص اصحاء)، والمجموعة الثانية (٤٣ مريضًا قبل العلاج) ، والمجموعة الثالثة (٣٨ مريضًا بعد العلاج)، من مستشفى رزكاري التعليمي ، ومستشفى نانكلي ، ومستشفى هولير التعليمي - قسم الجراحة العامة وجراحة الأعصاب، ومستشفى PAR الخاص ، ومستشفى PAKY الخاص ، ومستشفى الرسول الخاص في مدينة أربيل - العراق، والأعمارالمدرجة في هذه الدراسة هي من ١٨ إلى ٧٧سنة . تم إجراء الاختبارات البيوكيميائية (الأديبونيكتين، اللبتين، الجالكتين-٣). تم تحليل هذه العينة باستخدام مصل الدم وتحليل النتيجة إحصائيا.

النتائج: كانت أغلبية الفئة العمرية الخاضعة للدراسة هي (٥٧-٣٨) سنة سواء من االمرضى بعد العلاج، والمرضى قبل العلاج العلاج، والاشخاص الاصحاء وكانت النسبة على التوالي هي (٦٠,٥٢٪، ٦٠,٤٦٪، ٦٣,٣٤٪). توجد فروق ذات دلالة إحصائية بين مجموعات المرضى والاشخاص الاصحاء في مكان الإقامة ووجود تاريخ العائلي للمرض ومؤشر كتلة الجسم مع (٠,٠٠١>، ٠,٠٨، ٠,٠١٥ =P قيمة) على التوالي. كان كل من اللبتين والأديبونيكتين والجالكتين-٣ ذا دلالة إحصائية (٠,٠٠٧، و <٠,٠١ و <٠,٠١) على التوالي. حول خصائص السرطان كان الجالكتين-٣ معنويا مع المستقبلات الهرموني (ER/PR)هي (P: 0.037) ودرجة السرطان هي (P: 0.034) ، كما كان اللبتين معنويا مع درجة السرطان(P: 0.025).

الاستنتاجات: خلصنا إلى أن الأديبونيكتين واللبتين والجالكتين-٣ كانت مؤشر كيميائية حيوية جديدة محتملة لتشخيص سرطان الثدي والتنبؤ به، وستكون مؤشرات مفيدة ومهمة لتقييم درجة السرطان ومستقبلات لأجل الخطة العلاجية.

الكلمات المفتاحية: سرطان الثدي، الأديبونيكتين، اللبتين، الجالكتين-٣

البريد الالكتروني: aesha.ibrahim95@gmail.com

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[١] كلية الطب – جامعة هولير الطبية – اربيل - العراق

[٢] جامعة صلاح الدين - ربيل - العراق