Biochemical Study of Omentin-1 in Breast Cancer Patients of Mosul City-Iraq

Amna Ali Jajju* , Safaa A. Al-Ameen*
***Department of Chemistry, College of Science, University of Mosul, Mosul, Iraq**
Correspondence: safaalameen@uomosul.edu.iq

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ABSTRACT

Background: Breast cancer is one of the most common malignancies diagnosed in women, and its incidence is increasing every day**.** Omentin-1 is a new class of adipocytokine expressed in the intestines, vascular tissue, visceral adipose tissue, and goblet cells of the respiratory system. Researchers have demonstrated that omentin-1 plays a critical role in the processes of carcinogenesis**.**

Aim: To evaluate the levels of serum omentin-1, aromatase, other hormones, and enzymes of patients women with breast cancer in Mosul City. Also, biotechniques will study omentin-1 of normal human plasma.

Methods: This study comprised 50 patients at the beginning of diagnosis with breast cancer and follow-up after surgery by one month from the same ones in addition to 50 healthy women as control samples with ages between (25 and 75) years. The samples were classified into pre and postmenopausal women. Samples were collected from October 2023 to March 2024.

Results: Omentin-1 and other variables levels in breast cancer affected before or after menopause. Also, from biochemical techniques, the results indicated that omentin-1 has a low molecular weight of nearly 39810 Dalton with specific activity (5.25) and recovery (70%) with purification folds (40.38).

Conclusion: Breast cancer is affected by many factors, such as menopause, family history, old age as well as obesity. The concentration of Omentin-1 as adipokine is influenced by many types of cancer, such as breast cancer. It has been observed that postmenopausal women with breast cancer have high aromatase activity and thus increase the level of estradiol, which in turn can interact with its metabolites with DNA to cause carcinogenic mutations, which contribute to the development of breast cancer.

Keywords: Breast cancer, Omentin-1, Aromatase. Estradiol.

دراسة كيموحيوية للاومنتين-١ في المريضات المصابات بسرطان الثدي في مدينة الموصل – العراق

امنة علي خضر ججو* ، صفاء عبد العزيز طه الامين*
*قسم الكيمياء ، كلية العلوم، جامعة الموصل، الموصل، العراق

الخلاصة

الخلفية: سرطان الثدي هو واحد من أكثر الأورام الخبيثة شيوعا التي يتم تشخيصها لدى النساء ، ويتزايد معدل حدوثه كل يوم. الاومنتين-١ هو فئة جديدة من الشحوم الدهنية والتي توجد في الأمعاء والأنسجة الوعائية والأنسجة الدهنية الحشوية والخلايا الكأسية في الجهاز التنفسي. لقد اثبت الباحثون أن الاومنتين-١ يلعب دورا مهما في حدوث السرطان.

الهدف: لتقييم مستويات الاومنتين-١ وفعالية انزيم الاروماتيز وبعض الهرمونات والانزيمات الاخرى في مصل النساء المصابات بسرطان الثدي في الموصل ومقارنتها بمجموعة السيطرة لنساء سليمات. وكذلك دراسة الخواص الكيموحيوية للاومنتين-١ بواسطة التقنيات الحياتية.

المرضى والأساليب: شملت هذه الدراسة ٥٠ مريضة في بداية تشخيص إصابتهن بسرطان الثدي والمتابعة بعد الجراحة بشهر واحد لنفس المريضة بالإضافة إلى ٥٠ امرأة سليمة كعينات ضابطة تتراوح أعمارهن بين (٢٥-٧٥) سنة. تم تصنيف العينات إلى نساء قبل وبعد انقطاع الطمث. تم جمع العينات من أكتوبر ٢٠٢٣ إلى مارس ٢٠٢٤.

النتائج: الاومنتين-١ ومستويات المتغيرات الأخرى في سرطان الثدي تتأثر بمستوى قبل أو بعد انقطاع الطمث. ومن خلال التقنيات الكيميائية الحيوية, أشارت النتائج إلى أن الاومنتين-١ له وزن جزيئي منخفض تقريبا ٣٩٨١٠ دالتون مع نشاط محدد (٥.٢٥) واستعادة (٧٠٪) مع عدد مرات التنقية (٤٠.٣٨).
الاستنتاج: يتأثر سرطان الثدي بالعديد من العوامل مثل انقطاع الطمث والتاريخ العائلي والشيخوخة فضلا عن السمنة. يتأثر تركيز الاومنتين-١ كأديبوكاين بالعديد من أنواع السرطان مثل سرطان الثدي. لوحظ ان النساء المصابات بسرطان الثدي بعد انقطاع الطمث لديهن نشاط مرتفع في انزيم الأروماتيز وبالتالي زيادة مستوى الاستراديول الذي بدوره يمكن أن تتفاعل مستقلباته مع الحمض النووي لإحداث طفرات مسرطنة ، والتي تساهم في تطور سرطان الثدي.

الكلمات المفتاحية: سرطان الثدي، الاومنتين-١، الاروماتيز، الاسترادايول.

INTRODUCTION

According to the World Health Organization(WHO), breast cancer is one of the most common malignancies diagnosed in women, and its incidence is increasing every day. There are many variables, such as old age, obesity, late menopause, hormone therapy, usage of contraception, and family history, that can cause breast cancer. [1].

Numerous biological processes, such as the development of sex organs, pregnancy, bone density, cholesterol mobilization, brain function, cardiovascular system, and more, are regulated by steroid hormones and their receptors. They contribute significantly to the onset and spread of breast cancer. The formation and progression of breast cancer are significantly influenced by estrogen and its receptor, with about 70% of cases being hormone receptor-positive. These cases involve cells expressing positive expression of estrogen receptor ER and/or progesterone receptor PR, which are linked to the growth and spread of cancer cells [2].

Omentin-1 is a protein with 313 amino acids and a molecular weight of about 35 kDa. It is located on chromosome 1q22–q23. In healthy individuals, the level of omentin-1 in the blood can vary greatly, ranging from a few ng/mL to 300–600 ng/mL. This adipokine is generally more concentrated in women's plasma and serum than men's. [3]. Omentin-1 is a new class of adipocytokine expressed in the intestines, vascular tissue, visceral adipose tissue, and goblet cells of the respiratory system. The properties of omentin-1 include preserving body metabolism, improving insulin sensitivity, lowering inflammation, and preventing atherosclerosis. Omentin-1 has been connected to autoimmune diseases and anti-inflammatory disorders such as systemic sclerosis, psoriasis, rheumatoid arthritis, and acute respiratory distress syndrome [4].

Omentin-1 is a pro-apoptotic and anti-inflammatory adipokine that aids in communication between adipocytes and surrounding tissues to regulate glucose and fat metabolism [3].

Researchers have demonstrated that omentin-1 plays a critical role in carcinogenesis, as shown in Figure 1, cell differentiation, and apoptosis process acceleration in cancer cells [5].

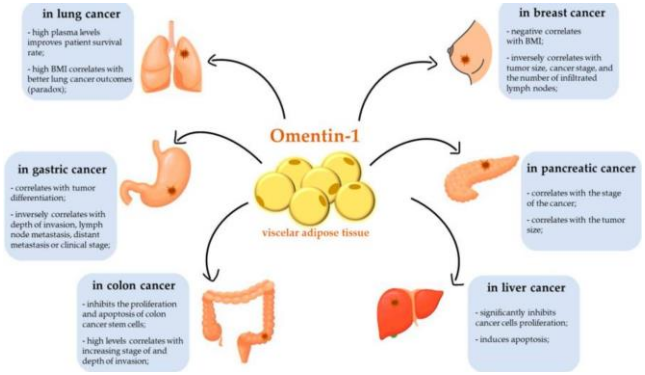

Figure 1: Influence of omentin-1 on carcinogenesis [3]

Obesity is a global epidemic that is putting people's lives in danger. An excessive and abnormal accumulation of body fat causes it. Despite growing knowledge of the harmful impacts on health, the prevalence of obesity is gradually rising. People with abdominal obesity are particularly susceptible to the harmful consequences of being overweight. The immunological response, as well as the paracrine and endocrine functions of adipose tissue, are impacted by obesity [6]. Adipose tissue, or endocrine organ, is a complex structure involved in fat storage and releases a variety of bioactive polypeptides known as "adipokines." These adipokines can control appetite, body weight, glucose homeostasis, blood pressure, and inflammation. [7].

Adipokines regulate a number of physiological functions, including the development of cancer, issues with angiogenesis and hemopoiesis, and immune system dysfunction. Adipokines have pleiotropic effects, meaning they can both slow down and speed up the process of carcinogenesis [3], as shown in Figure 2.

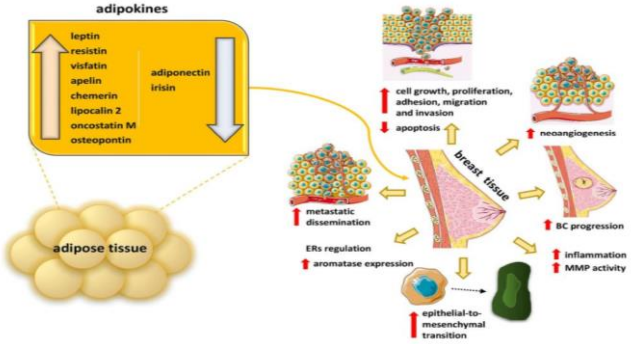

Figure 2: Mechanisms of serum adipokine in breast cancer [8]

One of the final steps in the production of estrogens is the conversion of 19-carbon steroids, like testosterone and androstenedione, to 18-carbon steroids, like estrone and estradiol, which is catalyzed by the microsomal enzyme Cytochrome P450 aromatase, or P450arom, which is expressed in the endoplasmic reticulum. A variety of tissues, including the brain, adipose tissue, placenta, blood vessels, skin, bone, and breast tissue, are known to contain aromatase. Its expression in breast adipose tissue is thought to be important in developing estrogen-dependent breast cancer after menopause. There are nine coding exons (II-X) and a 93 kb regulatory domain in the approximately 123 kb long aromatase (CYP19A1) gene. This chromosome is 15q21.2. [9]. Aromatase Inhibitors (AIs) are an effective targeted therapy for individuals with Estrogen Receptor positive (ER+) breast cancer because the enzyme aromatase catalyzes crucial steps in estrogen manufacture. As AIs inhibit both ER's genomic and nongenomic functions, they are more efficacious than Selective Estrogen Receptor Modulators (SERMs) [10].

For breast cancer patients to survive and maintain their quality of life, customized treatment is necessary. Radiation, surgery, chemotherapy, or a mix of the three are common forms of treatment. Anti-hormonal therapy (AHT), which is recommended for a minimum of five years and significantly increases survival, is recommended for 80% of breast cancers in women under 50 who test positive for estrogen receptors. There are presently two estrogen deprivation treatments available: 1) selective modulators of estrogen bioavailability, such as tamoxifen, and 2) aromatase inhibitors (AIs), which obstruct the main endogenous estrogen supply directly; it is possible to provide these two therapies one after the other [11].

Numerous factors are associated with obesity, such as alterations in the inflammatory mediator and adipokine profiles, which regulate the expression of the aromatase gene, leading to its overexpression.

Aromatase action can produce high local estrogen levels with significant biological influence without considerably altering circulating levels because tissue-specific promoters regulate aromatase expression in extragonadal tissues like adipose [12].

EXPERIMENTAL

Blood samples were collected from many hospitals in Mosul city from (1 October 2023 to 1 March 2024), from patients veins after sterilizing the area with heptane, where (5ml) blood was drawn from healthy people and breast cancer patients at the beginning of diagnosis and after a month of the operation by the same patient aged (25-75) years. All women while they were fasting. Then, the serum samples were collected after centrifugation for (10 min) at 4000 rpm. The samples were divided into several parts and stored in clean, dry plastic tubes at (-20 ˚C) until further experimental tests.

The level of serum Omentin-1 was estimated using a kit from (BT- LAB, China) by enzyme-linked immunosorbent assay (ELISA) technique; it is an immune method of quantification based on the sandwich principle.

Estradiol and Prolactin hormone concentrations were estimated using an industrial assay using a solution Elecsys Estradiol III and a device Cobas e 411. The assessment was carried out in a private laboratory in Mosul city.

Serum aromatase activity was estimated using a kit from (BT- LAB, China)) by enzyme-linked immunosorbent assay (ELISA) technique, while the activities of GOT and GPT were estimated by using a kit from GIESSE in a Smart 150 (Geno TEK) device. Also, the activity of GGT was estimated by using a Fuji device.

Isolation and Partial Purification of Omentin-1 from Normal Human Plasma

This part includes isolation and partial purification of omentin-1. Normal human plasma was taken from a healthy woman aged 28 years; the steps of isolation and purification were carried out by using various biotechniques as follows:

Precipitation and Separation of Protein by (75%) Ammonium Sulfate

Ammonium sulfate was used as a precipitating agent of plasma proteins with a saturation of 75% at 4ºC with slow stirring for 60 min. Water is associated with ammonium sulfate molecules, and the amount of water that interferes with the Protein decreases, so it aggregates protein molecules together and precipitates. Then, the mixture was left in the refrigerator for (24 hours) to complete the deposition process completely [13].

After completing the deposition process, cooling centrifugation at (10000 rpm) was used to separate the precipitate from the filtrate for (45 min). After that, the precipitate was taken and stored in a dry and clean tube, then kept at (-20 ˚C) for the next steps [14].

Dialysis technique was used to rid the solution of salts and substances with small molecular weights. This process uses cellophane tubing, a semi-permeable membrane that allows small molecules to pass, not large ones. This process was performed at (4 ˚C) with slow continuous stirring by the magnetic stirrer for (24 hours) with exchanging of (0.1 M) ammonium bicarbonate solution from time to time. Then, the solution is applied in a lyophilizer to concentrate the solution.

Sephadex (G-75) was used to fill the separation column (90 × 1.5 cm). The gel was placed at a height of 80 cm as a stationary phase. Proteinous precipitate and known molecular weights (standards), which have (204-2000000 D), were applied to the same column to determine the properties of the column, such as internal volume and void volume(vi, v^o), respectively. Also, to isolate omentin-1 and to determine its comparative molecular weight with a flow rate of (4ml/ 5min) for each part. The protein content was monitored by reading the absorbance at wavelength (280 nm) by using an ultraviolet & visible spectrophotometer.

The diluted protein peaks resulting from the gel filtration technique were dried and concentrated by lyophilizer, then kept in the freezer at (-20˚C) until further steps.

A modified lowery method was used to estimate the protein concentration [15]**.** Bovine serum albumin (BSA)was used as a standard protein, and the absorbance was read at (650 nm). The standard BSA has an extinction coefficient ($0.67M^{-1}$ cm^{-1}). The absorption intensity is proportional to the concentration of the protein [16].

RESULTS

Part One: Clinical Study

Table 1: Concentration of Hormones as (Mean ± S.E) in patients before and after surgery compared to controls in pre and postmenopausal women.

Sample / Hormones	Controls		Patients Before surgery		Patients After surgery	
	Premenopausal (22-46)	Postmenopausal (47-79)	Premenopausal (22-46)	Postmenopausal (47-79)	Premenopausal (22-46)	Postmenopausal (47-79)
Omentin-1 (ng/L) Mean ± S.E	171.458±32.417	160.557±19.166	162.501±12.712	198.302±12.848	149.935±15.994	161.538±16.809
Estradiol (pg/mL) Mean ± S.E	161.576±17.393	34.146±6.199	109.303±25.141	42.103±9.660	74.872±10.892 *	35.908±7.909
Prolactin (ng/mL) Mean ± S.E	8.888±0.710	7.689±0.789	20.626±2.221 *	19.394±2.233 *	41.146±4.055 *	42.883±3.621 *

* Mean Significant at ($p < 0.05$)

Table 2: Activity of Enzymes as (Mean ± S.E) in patients before and after surgery compared to controls in pre and postmenopausal

Sample / Enzyme	Control		Patients Before surgery		Patients After surgery	
	Premenopausal (22-46)	Postmenopausal (47-79)	Premenopausal (22-46)	Postmenopausal (47-79)	Premenopausal (22-46)	Postmenopausal (47-79)
Aromatase (ng/L) Mean ± S.E	11.486±0.809	10.524±0.906	9.632±0.953	11.971±0.833	10.977±0.654	11.221±0.708
GPT (U/L) Mean ± S.E	21.4±1.995	18.12±1.992	15.625±1.451*	16.235±1.548	25.437±4.183	19.735±2.020
GOT (U/L) Mean ± S.E	8.04±0.508	8.56±0.506	8.437±0.790	8.588±0.409	8.875±0.531	8.764±0.307
GGT (U/L) Mean ± S.E	16.08±1.377	18.28±1.237	21.687±2.526 *	28.882±2.349 *	31±3.427 *	41.088±4.312 *

* Mean Significant at ($p < 0.05$)

Part Two: Isolation and Partial Purification of Omentin-1

Gel Filtration Chromatography

A type of partition chromatography called gel-filtration chromatography is used to separate molecules with varying molecular sizes [17].

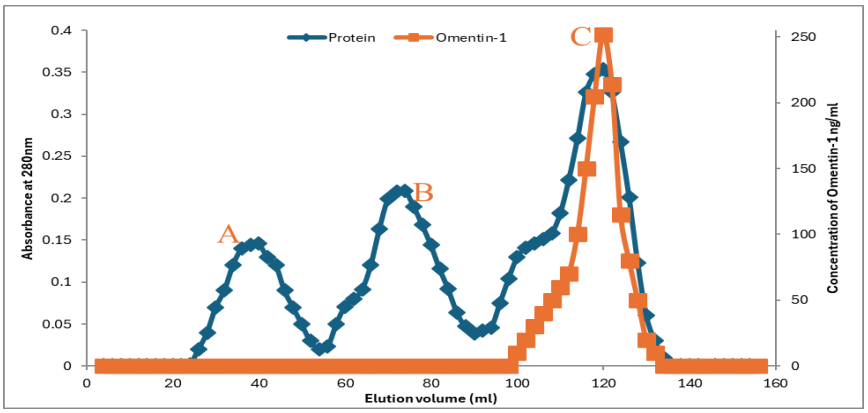

Figure 3: Elution volume of partially purified omentin-1 from normal human plasma by ammonium sulfate (75%) by gel filtration on the column (1.5 x 90) cm Sephadex G-75

Table 3: Steps of partial purification of Omentin-1 from normal plasma by gel filtration

Purification Steps	Total Volume (ml)	Total Protein (mg)	Total Conc. Of Omentin-1 (ng/ml)	Specific concentration	Recovery %	Purification folds
Plasma	40	1891.73	249.67	0.13	100	1
Proteinous Precipitate solution	15	1132.40	204.09	0.18	82	1.38
Dialysis	30	773.06	185.02	0.23	74	1.76
Gel filtration / Sephadex G-75 (peak C) after Lyophilizer	32	33.06	173.62	5.25	70	40.38

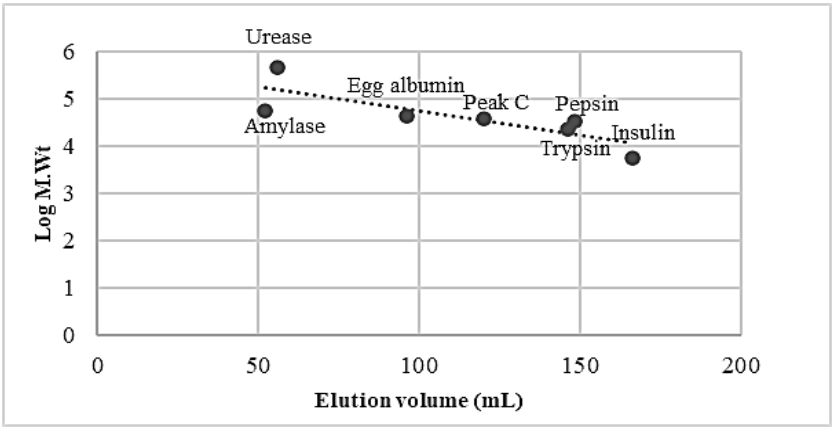

Figure 4: A plot of logarithm molecular weight of standard proteins versus elution volumes on Sephadex G-75.

DISCUSSION

The results in Table 1 show that omentin-1 concentration before and after surgery is decreased in premenopausal patients and increased in postmenopausal patients compared to controls. The differences in omentin concentration were likely related to the hormonal and metabolic changes associated with menopause.

Estradiol (E_2) concentration before and after surgery is decreased in premenopausal patients, while it increases in postmenopausal patients compared to controls. Also, estradiol after surgery appears to significantly decrease ($p<0.05$) in premenopausal patients as compared to controls, as shown in Table 1.

Numerous studies have shown that people with breast cancer often have high levels of serum estradiol, and they have also shown that estrogen may serve as a risk factor for the disease, particularly in postmenopausal women. Because it has been linked to the development of breast cancer, estradiol (E_2) is the most active form of estrogen. The theory that showed estrogen and its metabolites play a multifaceted role in the development and progression of breast cancer in the human body; estrogen metabolites called catechol estrogen quinone four and catechol estrogen-3,4-quinones react with DNA to cause carcinogenic mutations, which in turn contribute to the development of breast cancer [18].

Prolactin (PRL) concentration before and after surgery appears to have significantly increased ($p<0.05$) in pre and postmenopausal patients as compared to controls, as shown in Table 1.

Prolactin stimulates cell proliferation and inhibits apoptosis, which plays essential roles in the onset and progression of breast cancer. Prolactin promotes cell motility and angiogenesis, which may play a significant role in cancer metastasis. Elevated levels of plasma prolactin are, in fact, frequently detected in patients with advanced or metastatic malignancies [19].

The results in Table 2 show that Aromatase activity before and after surgery is decreased in premenopausal patients compared to controls. While it increased in postmenopausal patients compared to controls.

GPT activity before surgery is decreased in pre- and postmenopausal patients, while after surgery, it is increased in pre- and postmenopausal patients, as compared to controls. Also, GPT decreases significantly ($p<0.05$) in premenopausal patients compared to controls, as shown in Table 2.

GOT activity before and after surgery is the same between pre and postmenopausal patients as compared to controls, as shown in Table 2.

GGT activity before and after surgery is significantly increased ($p<0.05$) in pre and postmenopausal patients compared to controls, as shown in Table 2.

It was discovered that patients with breast cancer had much higher activities of the liver enzymes GPT and GGT than controls in every group. The most reliable indicators of prognosis for breast cancer both before and after treatment [20].

The proteinous precipitate was separated into three peaks, A, B, and C, according to molecular weights. Peak C has high activity of Omentin-1 and low molecular weight, as shown in Figure 3. Total Protein, omentin-1 concentration, specific concentration, and purification folds are shown in Table 3.

The known molecular weight of standard materials and the approximate molecular weight of omentin-1 are shown in Figure 4. The comparative molecular weight of Omentin-1 was found to be nearly (39810 D) with specific activity (5.25) and recovery (70%) with purification folds (40.38) from biochemical techniques. This is consistent with the results found by Celia and others, who found an apparent molecular weight of 38000 Da [21].

CONCLUSION

Breast cancer is affected by many factors, such as menopause, family history, old age as well as obesity. The concentration of Omentin-1 as adipokine is influenced by many types of cancer, such as breast cancer. It has been observed that postmenopausal women with breast cancer have high aromatase activity and thus increase the level of estradiol, which in turn can interact with its metabolites with DNA to cause carcinogenic mutations, which contribute to the development of breast cancer.

Omentin-1 concentration varies between pre and postmenopausal groups before and after surgery. So, it is decreased in pre-menopausal before and after surgery, while the results showed an increment in postmenopausal patients women before surgery.

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