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The Role of Apolipoproteins A1 and B as Prognostic Indicators in Progression of Breast Cancer

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Abstract

Breast tumor is the most common lesion among women. This study was designed to investigate the role of apolipoproteins A1 and B (ApoA1 and B) as risk factors in the progression in blood serum of benign and malignant breast tumors patients. Commercial enzyme-linked immunosorbent assay (ELISA) kits were utilized to calculate apolipoproteins A1 and B levels in the serum of forty women with benign breast tumors (age range 16–65 years), forty women with malignant breast tumors (age range 33–75 years), and forty healthy women (age range 24 to 54 years) as a control group. The study included two groups of patients diagnosed with malignant breast tumors: stage II (low-level) and stages III and IV (high-level). The results of the current study showed a significant decrease ($p< 0.05$) in the levels of ApoA1 in patients with benign breast tumors and breast cancer (24.319±2.76 and 26.526±2.66 ng/ml, respectively) compared with the control group (32.89 ± 5.60 ng/mL). Also, the results of this study demonstrate there were no significant differences in the level of ApoB in women with benign breast tumors (4337 ±160 ng/ml) compared with the control group (4392±90.57 ng/ml) with a slight increase in the level of ApoB in women with malignant breast tumors (4603.9±102.4 ng/ml). Furthermore, there were no significant differences in levels of ApoA1 and ApoB in breast cancer patients at low-level and high-level stages compared to the control group. The results of the current study indicated that the concentrations of ApoA1 and ApoB in women's blood serum may be useful predictors for the early detection of breast cancer and serve as a prognostic indicator of its development.

Keywords: breast cancer, benign breast tumors, Apolipoprotein A1 and B

دور صميم البروتين الشحمي A1 و B كمؤشرات تشخيصية لتطور مرض سرطان الثدي

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الخلاصه

يعتبر ورم الثدي هو الآفة الأكثر شيوعا بين النساء. صممت هذه الدراسة لبحث دور صميم البروتين الشحمي A1 و B (ApoA1 و B) كعوامل خطر في تطورالمرض في مصل الدم لدى مرضى أورام الثدي الحميدة والخبيثة.. وقد استخدمت مجموعات اختبار الممتز المناعي المرتبط بالإنزيم (ELISA) لحساب

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مستويات البروتينات الدهنية A1 و B في مصل 40 امرأة مصابة بأورام الثدي الحميدة (في الفئة العمرية 16–65 سنة)، و40 امرأة مصابة بأورام الثدي الخبيثة (في الفئة العمرية 33–75 سنة)، و40 امرأة سليمة (في الفئة العمرية 24–54 سنة) كعينات ضابطة. وقد شملت الدراسة مجموعتين من المرضى الذين تم تشخيص إصابتهم بأورام الثدي الخبيثة: المرحلة الثانية (منخفضة الدرجة) والمرحلتين الثالثة والرابعة (عالية الدرجة). وأظهرت نتائج الدراسة الحالية انخفاضًا معنويًا ($p<0.05$) في مستويات ApoA1 لدى مريضات أورام الثدي الحميدة وسرطان الثدي (24.319±2.76 و26.526±2.66 نانوغرام/مل على التوالي) مقارنة بمجموعة التحكم (32.89±5.60 نانوغرام/مل). وأظهرت نتائج هذه الدراسة أيضًا عدم وجود فروق معنوية في مستويات ApoB لدى النساء المصابات بأورام الثدي الحميدة (4337±160 نانوغرام/مل) مقارنة بمجموعة التحكم (4392±90.57 نانوغرام/مل) مع زيادة طفيفة في مستويات ApoB لدى النساء المصابات بأورام الثدي الخبيثة (4603.9±102.4 نانوغرام/مل). علاوة على ذلك، لم تكن هناك فروق معنوية في مستويات ApoA1 وApoB لدى مريضات سرطان الثدي في مرحلتيه المنخفضة والعالية مقارنة بمجموعة التحكم. تشير نتائج الدراسة الحالية إلى أن تركيزات ApoA1 و ApoB في مصل النساء قد تكون مفيدة للتنبؤ بالكشف المبكر عن سرطان الثدي، فضلاً عن كونها بمثابة مؤشر تشخيصي لتقدمه.

1. Introduction

A breast tumor is an abnormal mass of tissue in the breast due to neoplasia. A breast neoplasm may be benign, as in fibrocystic and fibroadenoma, or malignant, termed breast cancer (BC). Either case commonly presents as a breast lump. Approximately 7% of breast lumps are fibroadenomas, and 10% are breast cancer, the rest being other benign conditions or no disease [1-5]. Benign breast tumors can occur at any age, but they are most common in women of childbearing age because of the fluctuation of hormone levels, such as fibroadenoma, which can occur at any age but is most common between the ages of 14 and 35. As for breast cancer, it is most common in women between the ages of 50 and 70. However, it can affect younger women [6].

Apolipoproteins are the protein constituents of high-density lipoproteins (HDL), low-density lipoproteins (LDL), very low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), and lipoproteins (a) [7]. They play a fundamental role in the transportation and redistribution of lipids and lipoproteins across different tissues. As an example, apolipoprotein B (ApoB) specifically attaches to LDL, VLDL, and IDL, but it does not bind to HDL. The remaining components generally attach to the outer layer of HDL, including apolipoprotein A1 (ApoA1) [8].

Apolipoproteins control cancer progression by influencing key malignancies' characteristics such as resistance to apoptosis, inflammation promotion, angiogenesis induction, metastasis activation, and proliferation viability [9]. Researchers have also investigated the new therapeutic potential of these APOs against tumors [10]. ApoA1 functions as a cofactor for lecithin-cholesterol acyltransferase (LCAT) and is involved in reverse cholesterol transport from peripheral tissues to the liver. In addition, subtypes of apolipoprotein synthesis in the liver and small intestine [11]. ApoA1 profoundly suppresses the proliferation and infiltration of malignant cells during the formation and progression of malignancies [12]. The lipid transfer into cells in the human body is facilitated by ApoB [13]. However, the mechanism underlying the pathogenesis of breast tumor remain incompletely understood. Therefore, this study was designed to investigate the role of ApoA1 and ApoB as risk factors in the progression of blood serum samples of benign and malignant breast tumors diseases.

2. Materials and methods

2.1 Study subjects

In accordance with the most recent edition of the Declaration of Helsinki, the research met the established standards. The Ethical Committee of the Department of Biotechnology, College of Science, University of Baghdad (CSEC/0623/0044 dated June 8, 2023) granted approval for the study after obtaining written informed permission from all participants. A total of 120 Iraqi women were enrolled in this study. Eighty women diagnosed with breast tumors (pre-treatment) were randomly selected during their attendance at Al-Hussein Teaching Hospital's Oncology Center/ Karbala, Iraq and Al-Karama Hospital's Oncology Center/Wasit. Forty women with benign breast tumors ranged from 16 to 65 (30.00 ± 1.99) years, and forty with breast cancer ranged from 33 to 75 (52.17 ± 1.48) years. In addition, 40 healthy women aged 24-54 (39.50 ±2.77) participated in this study.

2.2 Data collection

Clinical data relevant to this study were collected retrospectively from patients' medical records from Al-Karama Hospital-Oncology Center/Wasit and Al-Hussein Teaching Hospital-Oncology Center/Karbala, from December 2022 to August 2023. All women participating in the study were handed a questionnaire including age, weight, height, smoking, family history, location of breast injury, and use of contraceptive pills.

2.3 Measurement of apolipoprotein A1 and apolipoprotein B levels

The ApoA1 and ApoB (Cata. No. E-EL-H0125 and E-EL-H0464, respectively) were tested using the Sandwich-ELISA method from Elabscience, USA. Catalogue numbers E-EL-H0125 and E-EL-H0464, respectively. The micro ELISA plate was pre-coated with an antibody specific to Human ApoA1 and ApoB. The samples were introduced into the wells of the ELISA microplate and mixed with the corresponding antibody. A biotinylated detection antibody specific to human ApoA1 and ApoB, along with an Avidin-Horseradish peroxidase (HRP) conjugated antibody, was applied to each well of the microplate and allowed to incubate. Unbound components have been removed by washing. Substrate solution was added to each well. Only the wells containing Human ApoA1 and ApoB, biotinylated detection antibodies, and Avidin-HRP conjugate will appear blue. The enzyme's reaction with the substrate was terminated by adding a stop solution, and the color was turned yellow. The optical density (OD) is measured spectrophotometrically at 450 nm wavelength.

2.4 Statistical analysis

The statistical analysis was conducted using the statistical package of social science (SPSS) version 23. The data were presented as the mean ± standard error. The t-test was employed to conduct statistical comparisons between groups, and a p-value of ≤ 0.05 was considered significant. An analysis of variance (ANOVA) was employed to compare the differences between more than two groups.

3. Results and Discussion

3.1 Serum levels of ApoA1 and ApoB of BC patients according to age, BMI, and menopause

The results of Table 1 showed the distribution of BC patients at low and high stages according to age, BMI, and menopause. The results indicated that BC patients less than 50 years had higher levels of ApoA1 at low-level stages (I+II) (31.1131±3.4 ng/ml), but there was no significant difference ($p \leq 0.418$) between less and more than 50 years in BC patients (24.6616±1.5 ng/ml) at the level of the same stages. Similar results were found with ApoA1at high-level stages. Also, the results of Table 1 showed similar outcomes, with no significant

differences in ApoB levels at low and high-level stages according to age groups. In regard to BMI, the results of ApoA1 and ApoB levels showed there were no significant differences among BC patients at both low and high-level stages, as shown in Table 1.

The patients who through menopause had higher mean ApoA1 levels in the low-level stage with no significant differences and higher mean ApoA1 levels in the high-level stages (III + IV) with significant differences ($p \leq 0.05$). On the other hand, the postmenopausal group had higher mean ApoB levels in both low and high-level stages, as shown in Table 1.

Table 1: Serum levels of ApoA1 and ApoB at low and high-level stages of BC patients according to age, BMI, and menopause.

Age groups			
Variable		**ApoA1 (ng/ml)**	**ApoB (ng/ml)**
Low L. (I+II)	<50	31.1131±3.4	4199.55±256
	>50	24.6616±1.5	4207.32±325
P-value		**0.418**	**0.988**
High L.(III+ IV)	<50	32.23±2.8	3746.09±451
	>50	25.94±3.4	4445.24±201
P-value		0.394	0.209
BMI			
Low L. (I+II)	Underweight 15-19.9	--	--
	Normal weight 20- 24.9	16.47±2.8	4787.98±171.5
	Over weight 25- 29.9	27.64±4.1	4640.22±213.1
	Obesity weight 30- 39.9	30.27±6.9	3757.36±129.1
	Morbid weight ≥ 40	31.68±2.9	4602.08±156.3
P-value		**0.739**	**0.230**
High L.(III+ IV)	Underweight 15-19.9	--	--
	Normal weight 20- 24.9	23.84±3.9	4056.49±152
	Over weight 25- 29.9	28.95±4.7	4194.09±217
	Obesity weight 30- 39.9	30.18±8	4789.43±121
	Morbid weight ≥ 40	--	--
P-value		**0.657**	**0.430**
Menopause groups			
Low L. (I+II)	premenopausal	29.5318±6	3901±352
	postmenopausal	26.121±4.9	4482±343
P-value		**0.551**	**0.285**
High L.(III+ IV)	premenopausal	35.57±2.1	3746±451
	postmenopausal	25.29±4.3	4445±301
P-value		**0.03**	**0.143**

Breast cancer is very prevalent among women in their middle and senior years. 30% of breast cancers are exhibited individuals aged 60 and beyond, while those aged 50 are estimate to be 82% [14].

Metabolic dyslipidaemia significantly contributes to the development of postmenopausal breast cancer [15]. Adipose tissue in postmenopausal women produces the majority of

estrogen due to reduced ovarian estradiol levels. Hypertrophy of adipose tissue in women after menopause may result in elevated levels of estrogen, thereby compromising the prognosis of breast cancer [16, 17]. Recently, researchers have conducted several studies to evaluate the relationship between body mass index (BMI) and breast cancer [18].

3.2 Serum levels of apolipoprotein A1 in patients and controls

ApoA1 levels showed a significant decrease in sera of benign breast tumor patients compared to control (24.319±2.76 and 32.895±5.60 ng/ml, P≤0.05, respectively). The decrease in ApoA1 levels was also significant in breast cancer patients compared to healthy controls (26.526±2.66 ng/ml). When comparing protein levels in the two groups of patients, the results indicated no significant difference between benign tumors compared to breast cancer patients (Table 2).

Table 2: Changes in ApoA1 levels in breast tumors patients

Group	Mean ± SE
	ApoA1 (ng/ml)
Control	32.895±5.60 a
Benign	24.319±2.76 b
Malignant	26.526±2.66 b
P-value	0.05
Means having the different letters in the same column differed significantly * (P≤0.05).	

ApoA1 is involved in a number of physiological activities, some of which include anti-apoptotic function, antioxidant function, and anti-inflammatory function. Furthermore, studies have shown that it can impede the growth of cancer cells [19, 20]. ApoA1 is involved in the development and progression of malignancy. Numerous studies have verified that low ApoA1 levels are associated with pancreatic cancer, gastric cancer, liver cancer, colorectal cancer, renal cancer, and acute lymphoblastic leukaemia [15, 21].

In Swedish patients with breast cancer, the study showed no association between ApoA1 and breast cancer risk [22]. This study was consistent with His *et al*. finding that ApoA1 was inversely associated with breast cancer risk. The study conducted by Martin *et al*. found an association between breast cancer and levels of apolipoprotein A1 [23].
ApoA1 inhibits tumors' growth and progression via two essential mechanisms. First, ApoA1 suppresses tumor-associated angiogenesis, and then it lowers the protein expression of matrix metalloproteinase-9 (MMP-9), an essential matrix-degrading enzyme required for metastasis [12, 24]. By promoting the expression of the estrogen receptor (ER), ApoA1 contributes more to hormone receptor-positive IDC than it does to hormone receptor-negative IDC. It has been proven that ERa, a protein encoded by the estrogen receptor 1 (ESR1) gene, can regulate the expression of proteins in regulating the metabolism of plasma lipids [25]. Plasma apoA1 interacts with ATP-binding cassette (ABC) lipid transporters, which modulate breast cancer ER/PR expression in vitro and in vivo by inducing Cdc42 and PAK-1 signalling. This may be accomplished by stimulating Cdc42 and PAK-1 signalling [26, 27].

ApoA1 selectively binds to and eliminates lysophosphatidic acid, a compound associated with an advanced stage of cancer and an unfavorable prognosis, thereby suppressing the growth of cancer cells. Moreover, ApoA1 controls the tumor's immune environment. ApoA1 may cause tumor-associated macrophages to change from an M2 phenotype that helps the tumor to an M1 phenotype that fights the tumor, which slows down tumor invasion [28].

According to previous studies, it can be suggested an explanation for the associations between ApoA1 and breast cancer, as HDL has been found to have antioxidant and anti-inflammatory properties. HDL acts by blocking the dopamine oxidation pathway of LDL and may reduce oxidative stress. Furthermore, HDL is inversely associated with some inflammatory biomarkers, and higher levels of HDL in the bloodstream are associated with increased levels of IL-10, a cytokine that fights inflammation. As seen in vascular smooth muscle cells, apoA1's potential to inhibit cell proliferation and promote cell cycle progression may have a significant impact [29-31].

3.3 Serum levels of apolipoprotein B in patients and controls

The results of the current study demonstrated non-significant ($p \leq 0.234$) in the level of ApoB of benign breast tumors women (4337 ±160 ng/ml) and a slight increase in the level of ApoB in breast cancer women (4603.9 ±102.4 ng/ml) as compared with the control group (4392±90.57 ng/ml) as shown in Table 3.

Table 3: Changes in ApoB levels in breast tumors patients.

Group	Mean ± SE
	ApoB (ng/ml)
Control	4392±90.57
Benign	4337 ±160.6
Malignant	4603.9 ±102.4
P-value	0.234

Apolipoprotein B is the main component of low-density lipoprotein (LDL). There is a specific protein part called ApoB-100 on LDL that finds and binds to the ApoB (LDL) receptor. This interaction sets off the receptor-mediated breakdown of LDL. There is also one molecule of ApoB in every LDL particle. Researchers have extensively studied this relationship with cardiovascular problems [32, 33]. Furthermore, increased circulating ApoB concentrations have been associated with diabetes, atherosclerotic disease, and metabolic syndrome, all of which have the potential to influence cancer development [34-36]. Previous research has investigated the relationship between circulating Apo B levels and breast cancer incidence, with inconclusive results. However, there is a lack of studies examining the relationship between circulating Apo B levels and cancer development.

The current study is consistent with Martin *et al*. which showed that there were no significant associations of serum ApoB level with breast cancer risk [23]. Another study showed a non-significant positive association of serum ApoB with breast cancer risk [37]. The relationship of ApoB to 27-HC and LDL may explain the potential mechanism that links ApoB levels to worse outcomes in breast cancer, 27-HC is primarily transported by LDL and is associated with increased breast tumor growth and metastasis in estrogen receptor-positive breast cancer [38]. ApoB is the major protein component of LDL; therefore, ApoB reflects serum LDL levels [39].

Multiple studies have examined the possible processes that contribute to the development of breast cancer caused by 27-HC. In MCF-7 cells, 27-HC initially suppressed the p53 protein and its function via the estrogen receptor (ER). Oxysterol caused the level of the p53 regulator mouse double minute 2 (MDM2) to rise, which made the connection between p53 and MDM2 stronger. This suggests that MDM2 mediates p53 degradation, which is necessary for the proliferation of 27-HC. It is noteworthy that estradiol, the primary natural

ligand for ER, had comparable effects to 27-HC on cell proliferation but did not affect p53 activity. This suggests that 27-HC may help ER-positive breast cancer grow in ways that are different from how estrogens are known to work [40, 41]. Several research studies have shown that 27-HC makes the Myc protein more stable. The Myc protein is an important oncogene that can help cancer cells grow, move, and invade other cells. This was achieved by reducing the process of dephosphorylation and ubiquitination, which leads to protein breakdown via proteasomes [42]. STAT-3 is an important transcription factor that can help cancer grow by targeting c-Myc, VEGF, cyclin D1, MMP 2, and MMP9. This leads to tumor proliferation, invasion, metastasis, and angiogenesis [43]. The substance 27-hydroxycholesterol turned on STAT-3, which helped breast cancer cells make new blood vessels through a signaling pathway involving ROS, STAT-3, and VEGF [44]. It also started the epithelial-mesenchymal transition (EMT), a process that helps cells move and invade by turning on the STAT-3/MMP9 and STAT-3/EMT pathways [45]. It did this in breast cancer cells that had estrogen receptors and cells that did not have estrogen receptors. In addition, 27-HC increases the number of macrophages that enter the cell and makes inflammation worse when cholesterol levels are high [46].

3.4 Assessment of Serological Marker ApoA1 According to Low and High Levels of Breast Cancer Stages

The breast cancer patients at high levels showed no significant difference ($p \leq 0.515$) increase in ApoA1 level 27.204± 3.9 ng/ml compared with the control group 32.895± 4.8 ng/ml. Furthermore, no significance was found in BC patients at low-level stage 26.758± 2.4 ng/ml in comparison with control; furthermore, there was no significance between low-level and high-level, as seen in Table 4.

Table 4: Comparison between low and high-level stages of BC patients according to ApoA1 levels.

Groups	Mean ± SE
	ApoA1(ng/ml)
Control	32.895± 4.8
Low level	26.758± 2.4
High level	27.204± 3.9
P-value	0.515

Reduced levels of ApoA1 and increased levels of circulating tumor cells were associated with higher rates of recurrence and shorter survival durations. The findings indicate that ApoA1 has a significant function in suppressing tumor development and invasion. Numerous studies have demonstrated a strong correlation between low levels of ApoA1 and breast cancer [47].

3.5 Assessment of Serological Marker ApoB According to Low and High Levels of Breast Cancer Stages

The breast cancer patients at high levels showed no significant difference ($p \leq 0.798$) increase in ApoA1 level 4545±117.2 ng/ml compared with the control group 4392±90.57 ng/ml. Furthermore, no significance was found in BC patients at low-level stage 4204 ±148.0 in comparison with control; furthermore, there was no significance between low-level and high-level, as shown in Table 5.

Table 5: Comparison between low and high-level stages of BC patients according to ApoB levels.

Groups	Mean ± SE
	ApoB (ng/ml)
Control	4392±90.57
Low level	4204 ±148.0
High level	4545±117.2
P-value	0.798

The present results are consistent with those of Sawada *et al*. who reported an increase in ApoB at a high level in BC [49]. However, in the current investigation, there was no statistical significance, while the difference was not statistically significant, the level of ApoB in the low stage was lower than in the high stage, and all levels were lower than those seen in the control group. Tumors with a more aggressive clinical course, poorer survival rate, and higher metastasis rate may exhibit higher disease progression rates and higher levels of ApoB. This could be due to their ability to utilize lipids as an energy source and structural components for tumor growth [48]. The homologous tumor model has shown that as a tumor grows, it changes the host's lipid metabolism. This alters the production of low-density lipoproteins (LDL) while stopping their breakdown, thereby providing the tumor with more energy [49]. When examining the connection between ApoB and breast cancer, it is important to consider these parameters.

4. Conclusion

The incidence of breast cancer has been increasing in recent years; in contrast, the survival of breast cancer patients is also increasing, which can be attributed to the development of early detection methods such as radiography, adjuvant chemotherapy, hormonal therapy, and targeted therapies. However, improving early diagnosis rates is essential to reduce or predict early breast cancer. Several studies suggest that lipoproteins interact with conventional oncogenic pathways. This study demonstrates that ApoA1 is a risk factor for breast benign tumors and breast cancer patients. However, no association was found with ApoB. These two parameters are potential targets for the treatment of breast cancer patients. Future research could investigate potential molecular mechanisms underlying the antitumor effects of ApoA1 and ApoB. Further research on the relationship between plasma lipid transporters and breast cancer should consider these criteria.

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