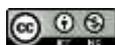


Dyslipidemia and CA15-3 serum level in Iraqi Women with Breast Tumor: A Comparative Study

DOI: <https://doi.org/10.32007/med.1936/jfacmedbagdad.v60i3.8>



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Aseel N. Kamil*

BSc, PhD

Basil O. Saleh **

MBChB, PhD

Kifah H. Alani ***

MBChB, PhD

Abstract:

Background: Lipids seem to have a direct influence in women breast cancer (BC) or dyslipidemia may be a consequence of this cancer.

Objective: the aim of this study is to define serum levels of lipid profile in women with breast cancer (BC) and to compare that with fibroadenoma benign breast tumor. Also, to assess the role of serum CA 15-3 in early diagnosis of breast cancer (BC).

Patients and Methods: This case study was carried out at Biochemistry Department, College of Medicine, University of Baghdad, during the period from February 2017 to November 2017. It included 38 Iraqi women diagnosed with primary breast cancer (BC, Group-I) and 25 women with Fibroadenoma of benign breast tumor (FA, Group-II). Women with BC were sub divided according to their stage of BC into: stage I (n=12), stage II (n=14), and stage III (n=12). Investigations included serum measurements of CA 15-3 and lipid profile (Total Cholesterol, Triglyceride, LDL-Cholesterol and HDL-Cholesterol).

Results: The mean value of CA15-3 in breast cancer women was found to be significantly higher ($p < 0.001$) as compared to benign group. The mean values of serum levels of TC, TG and LDL-C in breast cancer women were found to be significantly higher as compared to the benign women group (for all, $p = 0.001$).

Conclusion: This study concluded that breast cancer was more associated with dyslipidemia than FA benign tumor.

Keywords: breast cancer, benign breast tumor, lipid profile, CA15-3.

JFac Med Baghdad
2018; Vol.60, No .3
Received Aug. 2018
Accepted Oct. 2018
Published: Dec. 2018

Introduction:

Breast cancer (BC) is the second leading cause of women death from cancer in the world (1). Incidence of BC started to rises during the 2nd decade of life and peaks in the 4th and 5th decades, of women's life followed by the 6th, BC is by far the most frequent cancer among women worldwide, accounting for 25% of all cancers, with an estimated 1.57 million new cases in 2012 (2). Benign breast disease encompasses a heterogeneous group of breast lesions that include developmental anomalies, inflammatory diseases, epithelial and stromal proliferations and neoplasms (3). Fibroadenoma expands from the special stroma of the lobule. It usually occurs in approximately 25% of asymptomatic women. The most potent way to conflict cancer is its prevention and early detection. CA 15-3(also known as MUC1) is widely used as tumor marker and investigated in follow up of breast cancer.

It is a large transmembrane glycoprotein, which is over expressed (4,5) and aberrantly glycosylated in cancer (6). The main uses of CA 15-3 are detecting recurrence of breast cancer pre-clinically and monitoring the treatment of women with advanced stages (5, 7). During treatment of BC women, a decrease in CA 15-3 levels can indicate tumor response, while stable or increasing CA 15-3 levels can indicate that the tumor is not responding to treatment or recurrence of tumor despite adequate treatment (8,9). Lipids seem to have a direct influence in women breast cancer (BC), especially with increased body mass index (10). The role of lipids in cancer in the maintenance of cell integrity is well documented (11). Changes in serum lipid profile in BC cases can increase its risk status and its measurement may be useful in assessment of the prognostic and the diagnostic importance of the disease (12). The aim of this study was to define serum levels of lipid profile parameters in women with breast cancer (BC) and to compare that with fibroadenoma benign breast tumor. Also, to assess the role of serum CA 15-3 in early diagnosis of breast cancer (BC).

*Clinical Biochemistry, Ministry of Health.
Correspondence Author: aseelkamil83@yahoo.com

** Dept. of Biochemistry, College of Medicine,
University of Baghdad. Basil_omsal@yahoo.com

***Dept. of Pathology, College of Medicine,
University of Baghdad.

Email: kifahalani@yahoo.com

Patients and Methods:

This study was conducted at the Biochemistry Department, College of Medicine, University of Baghdad, and at the Main Referral Training Center for Early Detection of Breast Tumors/ Oncology Teaching Hospital/Medical City, Baghdad, Iraq, during the period from February 2017 to November 2017. Sixty-three Iraqi women were enrolled in the study. Thirty-eight women aged (30-65) years were diagnosed to have had breast cancer (BC, Group-I) based on the triple assessment techniques, i.e.; Clinical Breast Examination (CBE), Mammography and/or Ultrasonography and fine needle aspiration cytology (FNAC) or after mastectomy (13). Twenty-five women aged (20-65) years were diagnosed to have had benign breast tumor, all of fibroadenoma type (FA, Group-II). Women with BC were sub divided according to their stage of BC into: stage I (n=12) (T1N0M0), were defined as they have had breast tumor size < 2 cm, stage II (n=14) (T2N0M0, T2N1M0, T3N0M0), were defined as they have had breast tumor size (2 – 5) cm and stage III (n=12) (T2N2M0, T3N1M0, T3N2M0 and T4N2M0), were defined as they have had breast tumor size > 5 cm. Tumor classification and staging were performed depending on criteria of International Union against Cancer Tumor-Node-Metastasis (UICC-TNM) classification and the American Joint Committee on Cancer Staging (14). Histopathology investigations were performed by Consultant Histopathologic based on tissue biopsy of mammary tumor or after mastectomy. Women with breast cancer of advanced stage (stage IV), multiple types of cancers; female reproductive tract cancers (ovarian, cervical and endometrial cancers), hepatic, renal, colorectal, pancreatic, lung, head and neck tumors were excluded. Also, those women with a history of previous cancer (breast or others), smokers and alcoholic women were also excluded from this study. The staging procedure was performed using the physical examination and blood analysis, mammography, mammary ultrasound scanning (U/S), breast core biopsies and chest X-rays. None of the women with BC had received chemo- or radiotherapy prior to blood sample collection. Five milliliters (mls.) of blood sample was aspirated from each woman, allowed to clot for 15 minutes and then centrifuged at 2500 rpm to separate the serum which stored at - 40°C until assayed. Serum CA15-3 measurement was performed by using the quantitative sandwich Enzyme Linked Immunoassay (ELISA) technique. Kits were provided by (HUMAN CO./GERMANY). Also, serum lipid profile parameters including total cholesterol (TC), triglyceride (TG), high density lipoprotein-cholesterol (HDL-C), and low-density lipoprotein-cholesterol (LDL-C) were determined by enzymology methods kits were provided by (HUMAN CO./GERMANY).

Statistical Analysis:

Statistical Package for Social Sciences (SPSS) 20.0.0, used to make the statistical analysis, p value

considered to be significant if <0.05. Two independent groups were compared by Student's t-test. Differences among groups was evaluated by one-way ANOVA test. The degree of association between continuous variables was calculated by Spearman's correlation coefficient (r). Values were expressed as mean ±SD.

Results:

The mean (±SD) value of age of the studied BC women was (48.3±9.20 year) and that of body mass index was (29.3±4.1 Kg/m²). Also, the number of women who were married was 28 (74 %) and single (10;26 %). The results also revealed that the number of BC women of stage I was found to be (n=12), of stage II (n=14), and of stage III (n=12). Moreover, the mean (±SD) value of age of the studied FA benign women group was (32.3 ± 11.3 year) and that of body mass index was (25.4 ± 3.9 Kg/m²). Table 1 show that the mean (± SD) value of serum CA15-3 levels of Group-I was significantly higher compared to that of Group-II (27.3 ± 18.0 u/ml, 10.6 ± 3.3 u/ml; respectively, p<0.001). Raised value of CA15-3 was seen with advanced stage of breast cancer. Also, table1 shows the mean value of serum CA15-3 of BC patients (Group-I) according to their cancer stages (I, II and III). The mean (± SD) value of serum CA15-3 levels of BC women with stage III was significantly higher compared to that of stage II and stage I (37.2 ± 7.1 u/ml, 29.2 ± 15.2 u/ml and 15.1 ± 3.9 u/ml; respectively, p<0.05). However, there was no significant difference in the mean value of serum CA15-3 between stage II and stage I.

Table 1: Mean (±SD) value of serum CA15-3 of the studied groups.

	CA15-3 (u/ml)
Total BC Group-I (n=38)	27.3 ± 18.0*
(BC Stage I; n=12)	15.1 ± 3.9
(BC Stage II; n=14)	29.2 ± 15.2 ^{NS}
(BC Stage III; n=12)	37.2 ± 7.1**
FA Group-II (n=25)	10.6 ± 3.3

*t-test revealed significant increase in CA15-3 levels in Group-I compared to Group-II (p<0.001). ** ANOVA and t-test revealed: a significant increase in CA15-3 levels in stage III compared to each of stage I and II, (p<0.05); ^{NS}: no significant difference in CA15-3 levels in stage I & II, (p>0.05).

Table2 reveals the mean (±SD) value of lipid profile parameters [Total cholesterol (TC), triglyceride (TG), HDL-C and LDL-C] in BC women (Group-I) and FA benign women (Group-II). The mean (±SD) value of serum TC level was significantly higher in Group-I in comparison to p of Group-II (180.3 ± 20.0 mg/dl, 166.8 ± 22.3 mg/dl; respectively, p<0.05). Similarly, the mean (±SD) value of serum TG level was significantly higher in Group-I compared to that of Group-II (97.4 ± 22.8 mg/dl, 85.6 ± 19.5 mg/dl; respectively, p=0.001). Moreover, the mean (±SD) value of serum HDL-C of Group-I was significantly lower compared to that of Group-II (65.4 ± 17.3 mg/dl, 78.3 ± 11.1 mg/dl; respectively, p=0.001). Also, the mean (±SD) value

of atherogenic lipid, the serum LDL-C, of Group-I was significantly higher when compared with that of Group-II (93.0 ± 28.9 mg/dl, 80.3 ± 17.4 mg/dl; respectively, p<0.05). Table 3 depicts the mean (±SD) values of serum TC, TG and LDL-C (188.6 ± 23.6 mg/dl, 95.1 ± 22.6 mg/dl, 88.9 ± 24.2 mg/dl, respectively) in menopausal FA benign women were significantly higher than those of FA benign menstruated women (162.2 ± 25.6 mg/dl, 63.9 ± 24.5 mg/dl, 78.3 ± 13.8 mg/dl; respectively, p<0.05). Also, the mean (±SD) value of serum HDL-C of FA menstruated women was significantly higher than that of menopausal FA benign women (79.4 ± 19.7mg/dl, 73.4 ± 14.7mg/dl; respectively, p<0.05). Similarly, in table 4 the mean (±SD) values of serum TC, TG and LDL-C (192.2 ± 12.6 mg/dl, 133.0 ± 21.0 mg/dl, 111.3 ± 27.3 mg/dl; respectively) of menopausal BC women were significantly higher than those of BC menstruated women (172.5 ± 20.2mg/dl, 118.7 ± 20.5mg/dl, 81.1 ± 23.5mg/dl; respectively, p<0.05). Moreover, the mean (±SD) value of serum HDL-C of BC menstruated women was significantly higher than that of menopausal BC women (70.4 ± 15.9mg/dl, 57.7 ± 17.0 mg/dl; respectively, p<0.05).

Table 2: Mean (±SD) Value of Lipid Profile Parameters of BC Women and FA Benign Women

Parameters	BC Group-I (n=38)	FA Group-II (n=25)
Total-Cholesterol (TC) (mg/dl)	180.3 ± 20.0 *	166.8 ± 22.3
Triglyceride (TG) (mg/dl)	97.4 ± 22.8 *	85.6 ± 19.5
HDL-C (mg/dl)	65.4 ± 17.3	78.3 ± 11.1 **
LDL-C (mg/dl)	93.0 ± 28.9 *	80.3 ± 17.4

*ANOVA and t-test revealed significant increase in TC, TG and LDL-C levels in Group-I compared to Group-II (p<0.001), (p<0.05)
 **: significant increase in HDL-C level in Group-II compared to Group-I (p=0.001).

Table 3: Mean (± SD) value of lipid profile comparison according to menopausal status in FA benign (Group-II)

Parameters	Menses (n=18)	Menopause (n=7)
TC (mg/dl)	162.2 ± 25.6	188.6 ± 23.6 *
TG (mg/dl)	63.9 ± 24.5	95.1 ± 22.6 *
HDL-C (mg/dl)	79.4 ± 19.7 **	73.4 ± 14.7
LDL-C (mg/dl)	78.3 ± 13.8	88.9 ± 24.2 *

*ANOVA and t-test revealed significant increase in TC, TG and LDL-C level in menopausal women of Group-II compared to menstruated women of Group-II, (p<0.05)

** : significant increase in HDL-C level in menstruated women of Group-II compared to menopausal women of Group-II (p<0.05).

Table 4: Mean (± SD) value of lipid profile comparison according to menopausal status in BC women (Group-I)

Parameters	Menses (n=23)	Menopause (n=15)
TC (mg/dl)	172.5 ± 20.2	192.2 ± 12.6 *
TG (mg/dl)	118.7 ± 20.5	133.0 ± 21.0 *
HDL-C (mg/dl)	70.4 ± 15.9 **	57.7 ± 17.0
LDL-C (mg/dl)	81.1 ± 23.5	111.3 ± 27.3 *

* ANOVA and t-test revealed significant increase in TC, TG and LDL-C level in menopausal women of Group-I compared to menstruated women of Group-I, (p<0.05)

** : significant increase in HDL-C level in menstruated women of Group-II compared to menopausal women of Group-I (p<0.05).

Linear regression analysis test depicts that there was significant positive correlation between age and each of serum TC, TG and LDL-C (r=0.460, r=0.348, r=0.487, for all p<0.05) and significant negative correlation between age and serum HDL-C (r= - 0.418, p<0.05). Similarly, there was significant positive correlation between BMI and each of serum TC, TG and LDL-C (r=0.727, r=0.571, r=0.660, for all p<0.001) and significant negative correlation between BMI and serum HDL-C (r= - 0.554 p<0.001). Also, there was significant positive correlation between tumor size and serum CA15-3 (r=0.411, p=0.010), while there was no significant correlation between tumor size and the values of lipid profile parameters, as illustrated in table (5).

Table 5: Correlation between age, BMI and tumor size with lipid profile in BC women

Parameters	CA15-3 (U/ml)		TC (mg/dl)		TG (mg/dl)		HDL (mg/dl)		LDL (mg/dl)	
	r	p-value	r	p-value	r	p-value	r	p-value	r	p-value
Age (year)	-0.257	0.119	0.460	0.004	0.348	0.032	-0.418	0.002	0.487	0.002
BMI (kg/m ²)	-0.209	0.209	0.727	<0.001	0.571	<0.001	-0.554	<0.001	0.660	<0.001
Tumor size (cm)	0.411	0.010	-0.279	0.089	-0.237	0.153	0.215	0.194	-0.164	0.325

Linear regression analysis

Discussion:

The present study shows that the mean value of CA15-3 levels of total BC women group (Group-I) was significantly higher compared to that of FA benign women group (Group-II (table 1), these results confirmed that of previous studies (8,15,16,17). The biochemical marker CA 15-3 (MUC1) is widely used and measured in breast cancer follow-up. Initial studies found that CA 15-3 is abnormal in patients

with metastatic breast cancer and levels of this antigen are associated with the developments in the clinical status of breast cancer females (18,19). The CA 15-3 is mainly used to monitor the response of breast cancer women to treatment and for early BC recurrence or metastasis. In agreement with previous studies (15,16,20, 21,22). This study observed that the levels of CA 15-3 of BC women with stage III was significantly higher compared to that of stage II and stage I, while there was no significant difference

between stage I and stage II (table 1). This revealed, that CA 15-3 in all the analyzed groups were statistically significantly higher with more advanced stages of cancer in comparison to benign disease. In general, high expression of serum CA 15-3 are correlated with a larger tumor burden and more advanced stages. In metastatic breast cancer, CA 15-3 with high levels are found when the cancer has metastasized to liver and /or to bone. Regarding to the result observed in table (2), the mean value of serum TC, TG and LDL-C was significantly higher in total BC women compared to FA benign women. While, the mean value of serum HDL-C was significantly higher in FA benign women compared to total BC women this might basically be attributed to difference in age and menopausal status (23,24,25,26). This study revealed that the mean values of serum TC, TG and LDL-C were significantly higher in menopausal FA benign women compared to FA benign menstruated women, table 3. While, there was significant increase in mean value of serum HDL-C menstruated women of FA benign group compared to menopausal women. Similarly, table 4 shows that the mean values of serum TC, TG and LDL-C were significantly higher in menopausal women of BC Group-In comparison to menstruated women of BC group. Moreover, the mean value of serum HDL-C of menopausal women of BC group was significantly higher in comparison to menstruated women of same group. These results agreed with previous results obtained by Dixit et al. (26) and Shah et al. (27). One of the indirect associations between serum lipid levels and breast lesions could be attributed to association of lifestyle factors with serum lipid levels (26). Among the aspects classically considered as risk factors for developing breast cancer are advanced age, low parity, early menarche, late menopause, obesity and dyslipidemia, alcoholism and increased height (28). Among those linked to nutritional status, those related to body composition, such as obesity and/or overweight and inadequate distribution of body fat, especially in the post- menopause, are noteworthy (29). Lipid peroxidation is one of the most important factors which involves cell membrane integrity and causation of cancer (30). It has been postulated that changes in the concentration of serum lipids in the breast cancer patients could result in an increase production of tumor necrosis factor and inhibit adipose lipoprotein lipase activity by the action of insulin (31). These changes impair the catabolism of very low-density lipoprotein (VLDL), leading to an increase in high density lipoprotein-cholesterol (HDL-C). However, it has been reported that HDL-C level was either elevated or depressed in women with the breast cancer (29,30,31). Furthermore, this study showed that both age and BMI significantly positively correlate with each of serum (TC, TG and LDL-C) in total BC women. Similar results were obtained by Gorial et al. (32). In contrast, there was significant negative correlation between serum HDL-C with both age and BMI in total BC women group. Also, CA15-3 was significantly positively

correlate with tumor size, table 5. Similar results were obtained by previous study of Valić et al. (33).

Authors' contributions:

Aseel N. Kamil: Student

Basil O Saleh : First supervisor

Kifah H Alani: Second supervisor

Conclusion:

The value of TC, TG, LDL-C were high in BC women compared to FA benign women suggesting the association of dyslipidemia with BC is more than with FA benign tumor. Also, CA 15-3 serum levels was high in BC women compared to FA benign women suggesting the association of CA15-3 with BC is more than with FA benign tumor.

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دسليبيديميا (زيادة نسبة الدهون) ومصل الدم لمتبسط السرطان (CA15-3) في النساء العراقيات المصابات بورم الثدي:
دراسة مقارنة

د. اسيل نبيل كامل

أ.د. باسل عويد

أ.د. كفاح العاني

الخلاصة:

الخلفية: للدهون تأثير مباشر في سرطان الثدي . كما ان زيادة الدهون في الدم قد يكون احد الاسباب او العوامل التي تؤدي الى زيادة خطر الاسباب بمرض السرطان.

الهدف: ان الهدف او الغرض من هذه الدراسة هو تحديد مستويات مصل الدم لمعلقات الدهون في النساء المصابات بسرطان الثدي ومقارنة ذلك مع النساء المصابات بورم الثدي الحميد . ايضا تهدف هذه الدراسة الى تقييم دور مصل الدم لمتبسط السرطان (CA15-3) في التشخيص المبكر لسرطان الثدي

المواد وطرق العمل: اجريت هذه الدراسة في قسم الكيمياء الحياتية / كلية الطب / جامعة بغداد ، خلال الفترة من شباط 2017 إلى تشرين الثاني 2017. وشملت 38 امرأة عراقية مصابات بسرطان الثدي (Group I, BC) و 25 امرأة مصابة بالورم الليفي من ورم الثدي الحميد (Group II, FA benign). وتم تقسيم النساء المصابات بسرطان الثدي إلى مجموعات فرعية على أساس مراحل السرطان ؛ المرحلة الأولى (n=12) ، والمرحلة الثانية (n=14) ، والمرحلة الثالثة (n=12). حيث تم قياس مصل الدم لمعلقات الدهون و متبسط السرطان (CA15-3) .

النتائج: وجدت النتائج ان متوسط قيمة CA15-3 في النساء المصابات بسرطان الثدي يكون أعلى بكثير ($P < 0.001$) بالمقارنة مع مجموعة النساء المصابات بورم الثدي الحميد. كما وظهرت النتائج على ان القيم المتوسطة لمستويات مصل الدهون (TC، TG و LDL-C) في النساء المصابات بسرطان الثدي تكون أعلى بكثير بالمقارنة مع النساء المصابات بورم الثدي الحميد ($p=0.001$ ، لكل القيم).

الاستنتاج: تم التوصل في هذه الدراسة إلى أن زيادة نسبة الدهون في مصل الدم اكثر ارتباطا مع سرطان الثدي من ورم الثدي الحميد.
المفاتيح: سرطان الثدي، ورم الثدي الحميد ، مستوى الدهون، متبسط السرطان (CA15-3)