

Hormonal and Biochemical Factors in Serum of Pre- and Post-menopausal Iraqi Women with Breast Cancer.

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Abstract

Objective: Breast cancer is the most common cancer in women next to cervical cancer. Multiple factors are associated with an increased risk of developing breast carcinoma. The aim of this study was to evaluate the hormonal and biochemical parameters of pre- and postmenopausal women affected with breast cancer. **Methods:** This study included 30 patients with per-treatment BC stage III consisted of (15 premenopausal and 15 postmenopausal women), also 40 women (20 premenopausal and 20 postmenopausal) were age matched apparently healthy control subjects on routine checkup. Premenopausal women (patients and control) were age ranged (40 ± 8) years and postmenopausal women with mean age ranged (60 ± 10) years. Patients and control have biochemical assay of lactate dehydrogenase, alkaline phosphatase, γ -glutamyl transferase, superoxide dismutase, prolactin, estrogen and lipid profile (total cholesterol, triacylglycerol, high density lipoprotein-cholesterol, very low density lipoprotein and low density lipoprotein-cholesterol). Samples were collected from January 2017 to June 2017 of Tikrit Teaching Hospital. **Results and Conclusions:-** Levels of lactate dehydrogenase, alkaline phosphatase, γ -glutamyl transferase, prolactin, estrogen and lipid profile (except high density lipoprotein-cholesterol) were increased in serum of pre- and postmenopausal patients when compared with control but superoxide dismutase and high density lipoprotein-cholesterol, were decreased in serum of pre- and postmenopausal patients when compared with control. These data showed that lactate dehydrogenase, alkaline phosphatase, γ -glutamyl transferase, superoxide dismutase, estrogen and triacylglycerol will be reliable markers in breast cancer and can be used as differential diagnostic in both of pre- and postmenopausal women.

Key words:- Breast cancer, lactate dehydrogenase, alkaline phosphatase, γ -glutamyl transferase, superoxide dismutase, prolactin, estrogen, lipid profile.

Introduction:-

Breast cancer (BC) is a disease that internationally documented to be the most frequent malignant tumor ever and the main cause of cancer mortality amongst women⁽¹⁾, it originates either from the inner lining of milk ducts or the lobules⁽²⁾. Biochemical parameters have been studied for early detection of carcinoma and for evaluation malignancy.

Tumor markers reflect behavioral changes from tissue to blood, resulting in changes in enzymes and hormones levels in cancerous tissue and blood⁽³⁾. During proliferation, invading tumor causes tissue damage resulting in the release of intracellular enzymes, like lactate dehydrogenase (LDH) into the blood by the injured or dying cells, elevation in LDH could be brought about as it is an essential

enzyme for anaerobic glycolysis⁽⁴⁻⁵⁾, and associated with metabolic activities, inflammation, tissue injury and neoplasms. Hypoxia in tumor microenvironment leads to high LDH levels⁽⁶⁾. Alkaline phosphatase (ALP) comprises a group of enzymes that catalyze the hydrolysis of phosphate esters in an alkaline environment, generating an organic radical and inorganic phosphate⁽⁷⁾, elevated serum ALP. Hyperalkaline phosphatasemia is predominantly seen with specific disorders, including malignant such as BC in this view ALP evaluation cancer as a potential marker for early detection of cancer⁽⁸⁾. Oxidative stress markers such as γ -glutamyl transferase (GGT)⁽¹⁾, which may lead to tumor development, through modification of signaling pathways and Deoxyribonucleic acid (DNA) damage⁽⁹⁾, has a highly significant association with BC⁽¹⁰⁾. Various mechanisms involved in breast tumorigenesis, free radicals attack breast epithelium and lead to fibroblast proliferation, epithelial hyperplasia, cellular atypia and BC. Superoxide dismutase (SOD) catalyzes the dismutation of highly reactive oxygen species (ROS) such as O_2^- and H_2O_2 ⁽¹¹⁾. Imbalance between reactive oxygen species (ROS) and antioxidants reaction capacity stimulates the development of BC⁽¹²⁾.

Role of estrogen in iron manipulation is a well proven mechanism of free radical induced tumorigenesis in estrogen target tissue like breasts⁽¹³⁻¹⁵⁾. Prolactin (PRL) implicated in growth and differentiation of breast epithelial cells and the differentiation of alveoli⁽¹⁶⁻¹⁷⁾. Several BC risk factors, such as nulli-parity and high mammographic breast density, have been identified to be correlated with increased levels of serum PRL⁽¹⁸⁻¹⁹⁾.

Numerous studies have suggested that changes in serum lipid profile and lipoproteins, including total cholesterol (TC), triacylglycerol (TAG), high density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C), played a potential role in cancer risk, and its measurement may be helpful in evaluation of diagnostic and prognostic of the disease⁽²⁰⁻²³⁾. Cholesterol has an important role in cellular structure and function and as a

steroid hormone precursor which is the vast majority of BC is known to be hormone responsive⁽¹³⁾. The primary metabolite of cholesterol, oxysterol 27-hydroxycholesterol promotes estrogen receptor-positive BC growth⁽²⁴⁾. Higher level of TAG plays an important role in carcinogenesis and that the elevated LDL-C, which is more susceptible to oxidation, may increase in lipid peroxidation⁽²⁵⁾. Lipoproteins are responsible for the cholesterol transportation⁽²³⁾. It has been postulated that changes in serum lipid concentrations of BC patients could result in an increase production, of tumor necrosis factor and inhibit adipose lipoprotein lipase activity by the action of insulin and these changes impair the catabolism of very low density lipoprotein (VLDL)⁽²⁶⁾.

The aim, of this, study, was to evaluate of certain biochemical markers like enzymes, hormones, and lipid profile for early detection and monitoring of BC during pre and post menopause.

Material and Methods:-

This study included 30 women with pre-treatment of invasive ductal carcinoma BC stage III which consisted of (15 pre- and 15 post-menopausal), also 40 women (20 pre- and 20 postmenopausal) were age matched apparently healthy control subjects on routine checkup. Premenopausal women (patients and controls) with mean rang (40 ± 8) years and postmenopausal women mean age (60 ± 10) years. All the patients and controls were non-smoker, had no familial history of BC, hypertensive, diabetes, thyroid or renal diseases. Samples were collected from BC patients admitted to Tikrit Teaching Hospital from January 2014 to June 2014. Studies were performed on peripheral venous blood samples withdrawn from the cubical vein after 12 hours fasting condition, serums were separated and stored at -20°C until the assay time.

The separated serum samples were analyzed for LDH, ALP, GGT and lipid profile were measured by enzymatic methods, SOD estimated according to Marklund and

Marklund ⁽²⁷⁾. Serum PRL and Estrogen were determined by using Biomerieux mini VIDUS automated immunoassay kits ⁽²⁸⁾.

Statistical Analysis:-

Minitab statistical program was used to analyze the results statistically using (t) test. The arithmetic means of the characteristics were compared to calculations of the application Duncan's multiple range test by probability level $p \leq 0.05$ and $p \leq 0.01$.

Results:-

Table (1) shows the Mean \pm SD of the studied parameters in BC pre-menopausal women and controls. There was a significant increase in serum enzyme levels (LDH, ALP, and GGT) in BC pre-menopausal women as compared to controls ($p \leq 0.01$) while, there was a significant decrease in serum SOD in BC pre-menopausal women as compared with controls ($p \leq 0.01$). There was a significant increase in serum hormones levels (estrogen and PRL) in BC pre-menopausal women as compared to controls ($p \leq 0.05$ and $p \leq 0.01$ respectively). Also there was a significant increase in serum lipid profile except HDL-C in BC pre-menopausal, women as compared to controls ($p \leq 0.01$).

Table (2) shows the Mean \pm SD of the studied parameters in BC post-menopausal women and controls. There was a significant increase in serum enzyme levels (LDH, ALP, and GGT) in BC post-menopausal women as compared to controls ($p \leq 0.01$) while, there was a significant decrease in serum SOD in BC post-menopausal women as compared with controls, ($p \leq 0.05$). There was a significant increase in serum hormones levels (estrogen and PRL) in BC post-menopausal women as compared to controls ($p \leq 0.05$ and $p \leq 0.01$ respectively). Also there was a significant increase in serum lipid profile except HDL-C in BC post-menopausal women as compared to controls ($p \leq 0.05$).

Table1: The Mean \pm SD of all the studied parameters in serum of pretreatment women BC stage III premenopausal and control.

Parameters	Pre-menopausal patients Mean \pm SD	Control Mean \pm SD	P Value
Number	15	20	
Age (year)	40 \pm 8	40 \pm 8	
LDH(IU/L)	235.2 \pm 47.04	172 \pm 23.5	$p \leq 0.01$ *
ALP (IU/L)	242.16 \pm 68.36	120 \pm 18.2	$p \leq 0.01$ *
GGT (IU/L)	174.3 \pm 38.52	80 \pm 22.6	$p \leq 0.01$ *
SOD (U/ml)	43.5 \pm 11.76	60.5 \pm 14.8	$p \leq 0.01$ *
Estrogen (pg/ml)	63.5 \pm 39.2	22. 4 \pm 8.6	$p \leq 0.05$ *
PRL(ng/ml)	53 \pm 32.3	20.8 \pm 7.4	$p \leq 0.01$ *
TC (mg/dl)	220 \pm 30.2	182.8 \pm 25.8	$p \leq 0.05$ *
TAG (mg/dl)	180 \pm 23.5	118 \pm 36.2	$p \leq 0.01$ *
HDL-C (mg/dl)	40 \pm 4.2	48 \pm 5.3	$p \leq 0.01$ *
VLDL (mg/dl)	40 \pm 5.7	23.6 \pm 7.24	$p \leq 0.01$ *
LDL-C (mg/dl)	144 \pm 40.3	117.2 \pm 13.26	$p \leq 0.01$ *

LDH: lactate dehydrogenase; ALP:alkaline phosphatase; GGT: γ -glutamyl transferase ;PRL: prolactin; TC: total cholesterol; TAG: triacylglycerol; HDL-C: high density lipoprotein- cholecterol; VLDL: very low density lipoprotein; LDL-C: low density lipoprotein-cholesterol.*:significant difference at $p \leq 0.05$ or $p \leq 0.01$.

Table 2: The Mean \pm SD of all studded parameters in serum of postmenopausal women BC stage III and control.

Parameters	Postmenopausal patients Mean \pm SD	Control Mean \pm SD	P value
Number	15	20	
Age (years)	60 \pm 10	60 \pm 10	
LDH(IU/L)	298.3 \pm 48.48	220 \pm 35.3	$p \leq 0.01$ *
ALP (IU/L)	343.4 \pm 77.47	184 \pm 20.6	$p \leq 0.01$ *
GGT (IU/L)	242.8 \pm 46.55	110 \pm 30.4	$p \leq 0.01$ *
SOD (U/ml)	30.95 \pm 13.2	52.4 \pm 20.7	$p \leq 0.05$ *
Estrogen (pg/ml)	31.3 \pm 13.1	10.1 \pm 3.6	$p \leq 0.01$ *
PRL (ng/ml)	18.4 \pm 14.0	11.5 \pm 5.7	$p \leq 0.05$ *

TC (mg/dl)	240±30.5	228±20.4	p≤0.05*
TAG (mg/dl)	200±30.8	142.4±28.2	p≤0.01*
HDL-C (mg/dl)	35.8±5.8	40.8±5.9	p≤0.05*
VLDL (mg/dl)	36±6.16	28.48±5.64	p≤0.01*
LDL-C (mg/dl)	164.2±18.54	159.72±8.86	p≤0.05*

LDH: lactate dehydrogenase; ALP: alkaline phosphatase; GGT: γ -glutamyl transferase; PRL: prolactin; TC: total cholesterol; TAG: triacylglycerol; HDL-C: high density lipoprotein-cholesterol; VLDL: very low density lipoprotein; LDL-C: low density lipoprotein-cholesterol.*:significant difference at $p \leq 0.05$ or $p \leq 0.01$.

Discussion:-

In this study serum LDH, ALP and GGT levels were increased significantly in BC patients compared, with control, but further increased in BC cases of post-menopausal women, our results were consistent with other studies⁽²⁹⁻³⁰⁾. Elevated levels of LDH were seen in malignancies occurred due to glycolysis induction by tumor cells.⁽³¹⁾ Also, a significant elevation in serum LDH levels in BC post-menopausal women when compared with control which is in agreement with the study of Agrawal A et al⁽⁴⁾. Elevation in LDH levels with age and following menopause may be due to the release of the intracellular enzyme from dead cells into circulation since aging is a degenerative process associated with tissue breakdown and necrosis^(4, 32). Serum ALP levels were significantly increased in BC patients when compared with control further increased was seen in cases of postmenopausal women. Most data indicate that the elevation of serum ALP occurs because of the accelerated de novo synthesis of the enzyme and subsequent regurgitation into the serum⁽⁷⁾. The present study is in agreement with other study⁽³³⁾. Serum GGT was significantly increased in BC patients compared with control, a further increased in BC cases of postmenopausal group was observed, these findings were in accordance with Rajeswari et

al study⁽²⁹⁾. The increment may be due to response of increased reactive oxygen production in the blood⁽³⁴⁻³⁵⁾ which can be confirmed by the significant decreased in SOD activity in sera of pre- and postmenopausal BC patients group than healthy control, further decrease was observed in postmenopausal group due to high production of free radicals that lead to accumulation of reactive oxygen metabolites^(36, 12).

Increased PRL was found in both pre- and post-menopausal BC patients groups compared with control, highest increment was observed in pre- compared with post-menopausal group, this result was in agreement with previous studies^(37-39, 14). The presence of abnormal high level of PRL in circulation or the extracellular matrix, could lead to aberrant stimulation of the PRL receptor(PRLR).Prospective studies demonstrate up to 95% of female breast carcinomas express prolactin and/or PRLR⁽⁴⁰⁾. PRL levels, increase at, menarche and, decrease after, menopause as, estrogen levels do⁽¹⁶⁾. In this study, high circulating levels of estrogen also been associated with an increased risk in pre- and post- menopausal BC women, these findings were in agreement with other studies⁽⁴¹⁻⁴⁴⁾. In pre-menopausal women, estrogens are synthesized from androgens by the granulosa cells in the ovaries. The main source of steroids in the ovaries is cholesterol. When ovaries are no longer functional, the source of estrogens in postmenopausal women comes, from the peripheral, conversion of androgens by the aromatase which is present in multiple organs, including breast tissue. Estrogens exert their activity by binding to the specific high affinity for estrogen receptors⁽⁴³⁾ that target to regulation of gene expression and plays an important biologically role in normal and malignant cells^(14, 45).

Multiple epidemiological studies exploring the causal associations between dyslipidemia and BC⁽⁴⁶⁻⁵⁰⁾. In this study, it has been demonstrated a statistically significant difference in the levels, of TC, TAG, VLDL, and LDL-C, which were higher in pre- and post-menopausal BC patients as compared with control, but the result in case HDL-C was conflicting. These results were in agreement

with other studies^(51-53, 20). A plausible explanation for the association between TC and BC that the production of mutagenic cholesterol epoxides in breast nipple fluid aspirates, might lead to breast carcinogenesis⁽⁴⁶⁾. It has been postulated that under, conditions of, high, cholesterol demand, as occurs, during rapid, proliferation, cells must be, able to disengage, the processes that function, to maintain Cholesterol, homeostasis⁽⁵⁴⁾. The potential biological role of TAG in BC has been suggested that increased level of TAG were closely related to decreased concentrations of sex hormone-, binding, globulin, which increased the amount of free estradiol and developed BC risk. The lipoproteins, (VLDL and LDL-,C), fostered tumor growth and metabolic abnormality of lipoproteins occurred in malignant tissue. Owiredo *et al*⁽²¹⁾ found that the, elevated, LDL-C level, which is, more susceptible, to oxidation may, result in, high lipid peroxidation, stress leading, to molecular and cellular damage, thereby, resulting, in cellular malignant conversion⁽²¹⁾. An association between HDL-C levels and increased BC risk has been reported by some others studies^(45-46, 54), while others show no association⁽⁴⁸⁻⁵⁸⁾. Decreased level, of, HDL-,C has, associated with ,increased, levels of low-grade inflammation and proinflammatory cytokines, which might increase risks of BC by stimulating breast cell hormone-independent proliferation^(21,58). Menopausal status effects on the association, between HDL-,C level, and risk, for BC ,so it, has been shown, that premenopausal, cases have, mean HDL-,C levels lower, than, matched controls⁽⁵⁹⁾.

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المتغيرات الكيميوحيوية والهرمونية في مصل مرضى سرطان الثدي للنساء العراقيات قبل وبعد سن الياس

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الخلاصة:

المبدأ:- سرطان الثدي اكثر انواع السرطان شيوعا لدى النساء بعد سرطان الرحم وهناك عدة عوامل ترتبط مع ارتفاع خطورة الاصابة بهذا المرض. الدراسة الحالية تهدف الى تقييم المتغيرات الكيميوحيوية والهرمونية لدى النساء المصابات بسرطان الثدي قبل وبعد سن الياس. **الطريقة:-** تضمنت الدراسة 30 عينة لنساء قبل وبعد سن الياس مصابة بسرطان الثدي المرحلة III حيث تألفت من (15 مصابة قبل سن الياس و 15 مصابة بعد سن الياس) كذلك شملت 40 امرأة غير مصابة (20 قبل سن الياس و 20 بعد سن الياس) بعمر مطابق لعينة المصابات واعتبرت مجموعة سيطرة. ترواح عمر النساء قبل سن الياس (40±8) سنة اما عمر النساء بعد سن الياس فكان (60±10) سنة ولكل من مجموعة المرضى والسيطرة. اجريت لكل من مجموعة المرضى والسيطرة الاختبارات الكيميوحيوية التي تضمنت قياس مستويات اللاكتيت ديهيدروجينيز، الفوسفاتيز القاعدي، كاما-كلوتاميل ترانسفيريز، سوپراوكسايد ديسميوتيز، البرولاكتين، الاستروجين وتراكيز الدهون (الكوليستيرول الكلي، كلسيريدات ثلاثية الاسيل، البروتينات الدهنية عالية الكثافة- كوليستيرول، البروتينات الدهنية منخفضة الكثافة جدا والبروتينات الدهنية واطنة الكثافة- كوليستيرول). جمعت العينات في الفترة بين كانون الثاني 2017 الى يونيو 2017 في مستشفى تكريت التعليمي. **النتائج والاستنتاجات:-** وجد ارتفاع في مستويات اللاكتيت ديهيدروجينيز، الفوسفاتيز القاعدي، كاما-كلوتاميل ترانسفيريز، البرولاكتين، الاستروجين وتراكيز الدهون (عدا البروتينات الدهنية عالية الكثافة- كوليستيرول) لدى عينة المرضى قبل وبعد سن الياس مقارنة مع مجموعة السيطرة بينما انخفض مستوى كل من سوپراوكسايد ديسميوتيز وتركيز البروتينات الدهنية عالية الكثافة- كوليستيرول في مصل المرضى قبل وبعد سن الياس مقارنة مع مجموعة السيطرة. يستنتج من الدراسة الحالية ان كل من اللاكتيت ديهيدروجينيز، الفوسفاتيز القاعدي، كاما-كلوتاميل ترانسفيريز، البرولاكتين، الاستروجين و الكلسيريدات ثلاثية الاسيل يمكن ان تعتبر دالات في تشخيص ومتابعة سرطان الثدي في النساء قبل وبعد سن الياس.

الكلمات المفتاحية: سرطان الثدي، اللاكتيت ديهيدروجينيز، الفوسفاتيز القاعدي، كاما-كلوتاميل ترانسفيريز، سوپراوكسايد ديسميوتيز، البرولاكتين، الاستروجين، تراكيز الدهون.