

International Journal of Advanced Chemistry Research

ISSN Print: 2664-6781
 ISSN Online: 2664-679X
 IJACR 2024; 6(1): 216-220
www.chemistryjournals.net
 Received: 02-03-2024
 Accepted: 03-04-2024

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Evaluation the levels of female sex hormones (estrogen and progesterone) and kidney function in breast cancer patients

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DOI: <https://doi.org/10.33545/26646781.2024.v6.i1c.188>

Abstract

Breast cancer is currently a major public health problem in both developed and developing countries. BC is defined as the uncontrollable development of breast cells, whether malignant or benign. It is considered the second highest cause of cancer-related deaths in the world. In Iraq, breast cancer constitutes one third of the total number of cancers. The current work aims to measure the effectiveness of female sex hormones (estradiol and progesterone) in addition to kidney functions (urea and creatinine) in the blood serum of women with breast cancer compared to healthy women. Sixty women patients and thirty healthy women samples were used to conduct this study from the blood serum of healthy women, and the results obtained showed: a significant increase ($p < 0.01$) in the level of estrogen and kidney functions (urea and creatinine) in the affected women compared to the control group, a significant decrease ($p < 0.01$) in the level of progesterone in affected women compared to the control group. This study can be considered as a vital sign and a tool for diagnosing and detecting the disease.

Keywords: Breast cancer (BC), female sex hormones, creatinine, estrogen and progesterone

Introduction

Breast cancer is defined as the uncontrollable development of breast cells that may be malignant or benign [1]. Breast cancer is also known as a group of heterogeneous physiological and molecular diseases that begin in the breast (BC) [2, 3]. The cellular pathways of BC are intertwined with normal breast development. The proliferation of mammary epithelial cells is stimulated during adolescence by such as Primary sex - estrogen and progesterone. As they stimulate physiological changes during adolescence, menstruation, pregnancy, lactation, cessation of lactation, and menopause [4]. Breast cancer is associated with the second-highest cancer-related mortality rate worldwide [5]. Therefore, in Iraq, breast cancer accounts for a third of the total types of cancers. Because of hormonal puberty, women are more prone to infection [6]. Thus, Tumors develop from healthy tissue to cancer in situ, then the invasion of the lymph nodes, surrounding stroma, and distant organs. It is a metastatic illness after that. Breast cancers are known to originate primarily from the luminal cell compartment. Conversely, it is believed that the proliferating luminal epithelial cells are surrounded by muscular epithelial cells, which are a terminally differentiated cell type. The absence of epithelial cells MEPs indicate invasive cancer [7]. Almost all malignant breast tumour arise in the Terminal Ductal Lobula Unit. Regardless of the histological type of tumor. Thus, carcinomas are characterized by a loss of epithelial polarity and tissue organization. Cancer cells that remain within the BM of the ductal lobular system of the breast are classified as benign carcinomas in situ. Once tumour cells rupture the BM and invade the adjacent stroma: the tumour cell rupture the BM and invade the adjacent stroma the tumour becomes malignant [8]. The most prominent changes in cellular composition that accompany the progression from normal mammary gland to invasive carcinoma are the loss of myoepithelial cells, and the increase of Myofibroblasts and immune cells in Stroma and blood vessel enhancement [9]. Breast cancer can be eradicated in a few different methods. Age, the disease's class, chemicals, and early disease identification are some of the variables that affect treatment.

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Early identification could result in faster recovery and therapy. If the tumor is discovered early, coronary resection can be all that is needed instead of a surgical procedure like a mastectomy. Only treatment is available for the cancer cells that remain [10]. In many situations, surgical procedures are chosen. Others include radiation, hormonal and immunological (hormonal and chemotherapy), chemotherapy, and site-directed (Targeted) therapy [11].

Estrogen (E2) is the primary female sex hormone. The term "estrogen" refers to a group of female hormones, including estrone, estradiol and estriol. Its basic structure consists of 17 carbon-carbon bonds arranged as four rings. Fused (three cyclohexane rings and a Cyclopentane ring) [12]. Estrogen signalling is closely linked to breast cancer. Hormonal therapy with the usual treatment is an antiestrogen, however, resistance to these drugs nearly invariably develops through a variety of molecular reasons, including alterations in the function of the estrogen receptor, mutations in the estrogen receptor1 gene, and abnormal activation of the phosphoinositide 3-kinase pathway. Or an imbalance within the cell cycle. There have been novel treatments developed as a result of all these causes [13]. Hormonal therapy is the preferred treatment because estrogen receptor alpha activation by estrogen drives the proliferation of two-thirds of breast cancer cells to minimize BC recurrence and improve patient survival overall, this involves either depriving the tumor of estrogen or reducing estrogen receptor alpha activity [14].

Progesterone (PR) is a secondary female sex hormone it consists a steroid precursor molecule with 21 carbons that predisposes women to the manufacture of steroids. Progesterone was applied to breast tissue to provide a general protective effect [15]. The report stated that progesterone in normal breasts encourages differentiation at the expense of growth, and they claim that it is challenging, if not impossible, to emphasize in their conclusion that progesterone cannot cause breast cancer and that the notion needs to be disproved [16].

Urea is considered the metabolic product that contains ammonia nitrogen, which is the product of protein metabolism in the organism's body. It belongs to the non-protein nitrogenous compounds, which include creatine, urea, ammonia, and amino acids. Blood urea nitrogen represents 45% of the non-protein nitrogenous compounds. Urea is produced in liver cells inside the human body, from ammonia, and is considered the final product of the process of removing ammonia from amino acids [17]. More than 90% of urea is filtered by the renal glomeruli [18]. Normally, the level of urea in blood serum/plasma is in the concentration range, 3.3-6.7 mmol, while its level > 30 mmol indicates the requirement of dialysis, in addition to other possible factors such as Brine, water depletion, and destruction of the gastrointestinal tract [19]. Destruction of the gastrointestinal tract.

Creatinine is the result of creatine and creatine phosphate metabolism [24]. Creatine is a nitrogenous organic acid synthesized primarily by the kidneys, liver, and pancreas from three amino acids: glycine, arginine, and methionine. Methionine this process consumes up to 10% of the daily glycine intake, 22% of arginine, and 42% of methionine. Creatine is formed when aminotransferase pine L-arginine and glycine react to produce ornithine and guanidinoacetate in the liver, pancreas, and kidneys [25].

Materials and Methods

The study was conducted in the city of Tikrit during the period from 1st of Dec.to the end of -Jan. Blood samples were obtained from sixty women with breast cancer and thirty healthy women as control, Blood samples were gathered from women with breast cancer at the Medical City Department - Oncology Teaching Hospital - Baghdad, in collaboration with the National Pioneer Center for Breast Cancer Research. During this investigation, sixty blood samples were taken, with ages ranging from 25 to 35 years. Blood samples were taken from the veins of one of the forearms for these patients who were clinically diagnosed by specialist's and who visited the hospital on a regular basis, seven milliliters of blood have been taken from patient, using a medical syringe. They were placed in special test tubes, then in the centrifuge at 3500 rpm for at least 15 minutes, then the serum was stored in plain plastic test tubes at refrigerator at -20 °C.

Estimation of progesterone hormone in blood serum

Progesterone hormone levels were measured depending on binding competitive between progesterone hormone and progesterone antibodies that conjugated with Horseradish peroxidase in binding solution. The levels of hormones determined according to the protocols that included with the special ELISA kit after ending the steps the intensity of colour for the ultimate solution was recorded at 450 nm. The concentration measured by standard curve.

Estimation of Estradiol hormone in blood serum

Estradiol hormone levels were measured depending on binding competitive between Estradiol hormone and progesterone antibodies that conjugated with Horseradish peroxidase in binding solution. The levels of hormones determined according to the protocols that included with the special ELISA kit after ending the steps the intensity of colour for the ultimate solution were recorded at 450 nm. The concentration measured by standard curve.

Estimation of urea level in blood serum

The level of urea in the samples were determined through FUJI DRI-CHEM SLIDE BUN-PII) by dissociation of urea by urease enzyme into ammonia and carbon dioxide. The protocol including many steps where in the ultimate step the density of optical reflection was recorded at 625 nm, the concentration determined automatically.

Estimation of Creatinine levels in blood serum

The level of urea in the samples were determined through FUJI DRI-CHEM SLIDE BUN-PII) by dissociation of creatinine by creatinine deaminase into ammonia gas that detected by bromophenol indicator where the yellow color converted into blue color in the ultimate step the density of optical reflection was recorded at 600 nm, the concentration determined automatically.

Statistical analysis

The statistical analysis was performed by utilizing the statistical program (MINI TAP-17) and the analysis of variance test (T-test) was used to clarify the difference between the arithmetic means of the groups included in the study and to determine the significant differences between them at a probability level of $p \geq 0.01$ or $p \geq 0.05$.

Results and Discussion

This study including measuring the level of Estrogen hormone, Estradiol hormone, Urea and creatinine in the

blood of women with breast cancer compared with control women. As recording in the following Table.

Table 1: Mean \pm standard deviation of the level of female sex hormone Estrogen, Progesterone, Urea, creatinine

Groups	Estrogen E2 (pg/mL) Mean \pm SD	Progesterone PR (ng/mL) Mean \pm SD	Creatinine (Mg/dl) Mean \pm SD	Blood urea (Mg/dl) Mean \pm SD	Estrogen E2 (pg/mL) Mean \pm SD
Patients (60)	573.96 \pm 210.93	0.195 \pm 0.0811	0.843000 \pm 0.279	30.8237 \pm 11.680	573.96 \pm 210.93
Control (30)	91.928 \pm 71.210	0.609 \pm 1.270	0.558000 \pm 0.180	16.6617 \pm 5.982	91.928 \pm 71.210
P-Value	0.000004	0.02	0.000001	0.005	0.000004

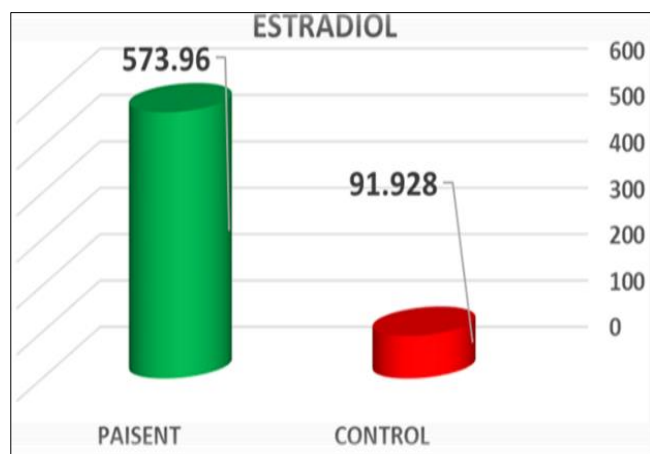


Fig 1: Estradiol hormone level (pg/mL) \pm standard deviation in the studied groups

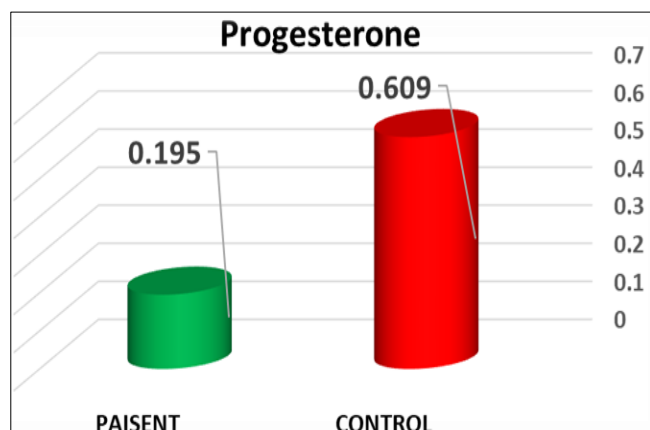


Fig 2: Progesterone level (ng/mL) \pm standard deviation in the studied groups

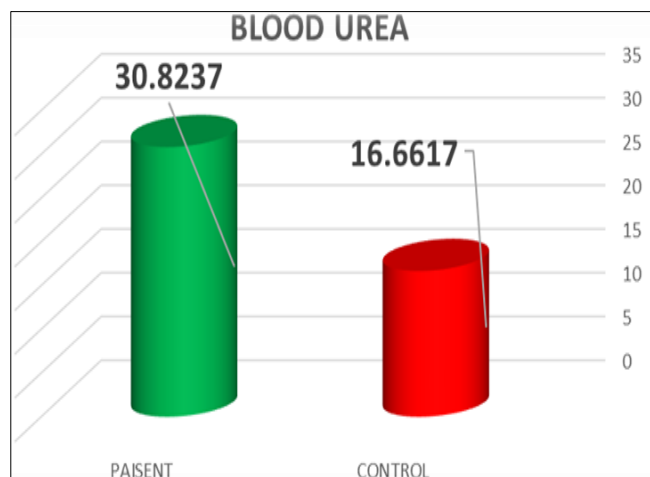


Fig 3: Urea level \pm mg/dl (standard deviation) in the studied group

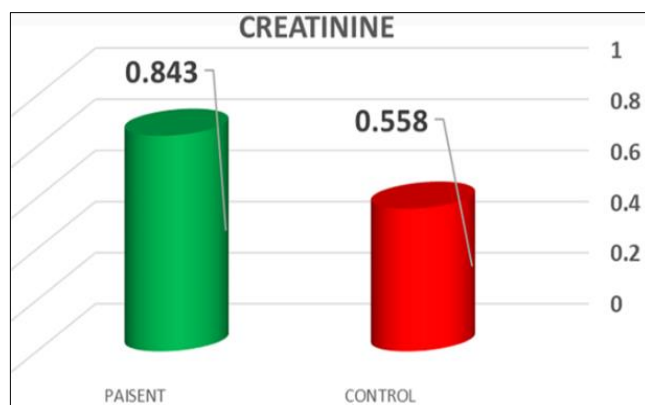


Fig 4: Creatinine level \pm mg/dl (standard deviation) in the studied groups

The results revealed increase in the level of estradiol (E2) table-1, fig (1) in women with breast cancer compared with control group. The current study agrees with some studies [20] that confirmed the existence of a correlation between a high level of estrogen E2 in women's plasma and the risk of breast cancer, as high estrogen stimulates it to regulate the growth of many breast tumors [21, 22] This has been confirmed recently by epidemiological studies on Suspected role of estrogen E2 as a breast carcinogen. Three main mechanisms are postulated to be involved in the carcinogenic effects: stimulation of cellular proliferation through receptor-mediated hormonal activity, direct genotoxic effects via increased mutation rates through cytochrome P450-mediated metabolic activation, and induction of aneuploidy [23] Some studies on the causes of breast cancer risk before and after menopause, as after menopause the subcutaneous adipose tissue turns into endocrine glands, This causes the secretion of estradiol derivatives to increase. Furthermore, because cholesterol is a precursor to steroid hormones like estradiol E2, excessive cholesterol levels may either cause these hormones to be released at a higher rate or be more closely linked to the development of early-stage tumors [24].

The results revealed decrease in the level of progesterone table-1, fig (2) in women with breast cancer compared with control group. The current study agrees with the following studies [25, 26]. The reason for a decrease in the level of progesterone in the blood of women with breast cancer is that progesterone acts as a precursor to androgens and estrogens, so the tumor tissue in the mammary gland absorbs plasma steroid from the cycle. These tumors do not depend on circulating steroid levels but produce steroid hormones locally from circulating precursors. Progesterone level appears to be a risk factor for pre- and postmenopausal breast cancer, with a significant inverse relationship between progesterone level and breast tumor risk [27]. Some

studies [28] indicated that progesterone stimulates the development of lobules and alveoli in the breast. Progesterone plays an important role in breast cancer by inhibiting the growth and proliferation of breast cancer cell lines. In one study, Patients with early-stage breast cancer were treated with progesterone alone; following a brief course of progestin therapy for breast tumors, tumor development was decreased and the cell cycle was suppressed. Additionally, it was discovered to have varying impacts on tumor growth, supporting the idea that progesterone influences tumor grade in BC develops and that progesterone's presence reroutes the ER with a decrease in the action of oncogenic genes in conjunction with a decrease in cell or tumor growth [20, 21].

The results revealed increase in the level of urea table-1, fig (3) in women with breast cancer compared with control group the current study agrees with the results of Chauhan *et al.* [22] who indicated a significant increase in the level of urea in the blood serum of women with breast cancer compared to healthy women. The reason for the increase in urea in the serum of women with breast cancer is an increase in the metabolism of cellular proteins resulting from increased cell destruction. Cancerous and some healthy cells as a result of chemotherapy. Urea is considered an important chemical tool for monitoring cancer, and the results of the study by Abu Zaid *et al.* [23] showed a slight increase in the concentration of urea in the affected group compared to the healthy group. Breast cancer patients often have pre-existing comorbidities or other risk factors that increase the likelihood of developing renal insufficiency before receiving potentially nephrotoxic treatments [24]. Most elderly people have chronic kidney disease, which is a common disease overall, regardless of age. The presence of cancer [25].

The results revealed increase in the level of Creatinine table-1, fig (4) in women with breast cancer compared with control group. This results consistent with the following studies [26] the results showed that creatinine levels elevated in women with breast cancer compared to healthy women, and that high creatinine levels may be due to the kidneys being affected by chemotherapy. They found that there is a relationship there is a significant relationship between creatinine and breast cancer BC, as biochemical variables in the blood indicate an important diagnostic tool in monitoring the disease and metastasis. Thus, the Super fan study [27] indicates that one frequently utilized method for assessing renal function in breast cancer patients is creatinine clearance. In accordance with other results reported by Montoya [28], which indicated that the level of creatinine in the blood is considered more sensitive to renal function compared to BUN. The current study does not agree with some studies that showed that all patients maintained renal function, as evidenced by no change in Serum creatinine levels throughout the study period [28] The results of the current study are not consistent with Chauhan and his group [22] who showed that creatinine levels are within the normal range in breast cancer patients and healthy subjects

Conclusion

The present investigation showed that women with breast cancer had reduced levels of progesterone and increased levels of estrogen, urea, and creatinine in comparison to the

control group. These findings indicate a possibility of breast cancer.

Acknowledgment

I extend my thanks and gratitude to, Dr. Firas. T. Maher, and to chemistry department/ College of Science/ University of Tikrit.

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