Steroid Hormones, Immunoglobulins and Some Biochemical Parameters Changes in Patients with Breast Cancer

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Abstract

Background: Breast cancer is one of the diseases that a woman may have to face during her lifetime. Hormones play a role in breast cancer spread, determining the association between plasma hormones and breast cancer risk may provide insight into the etiology of breast cancer.

Objective: To evaluate the use of sex steroid hormone levels with some biochemical parameters as a serum tumor marker in patients with breast cancer.

Materials and Methods: Two groups of subjects were included, 50 patients with histologically confirmed diagnosis of Breast Cancer (group I) and 40 healthy female (group II) the age range was (35-70) years were collected from Rizgary hospital and Nanakaly hospital, in Erbil city, Iraq. During the period from May 2015 till November 2015. The measured biochemical parameters included: the level of estrogen, progesterone, prolactin, estradiol, testosterone hormones, some immunoglobulins (IgG, IgA and IgM), also ferritin, sodium and calcium ions levels have been measured in the study.

Results: The results demonstrated significantly high values of steroid hormones ($p<0.001$, $p<0.01$, $p<0.002$, $p<0.05$, $p<0.05$ (estrogen, progesterone, prolactin, estradiol, testosterone) and significantly high values in immunoglobulins IgA, IgG, IgM in breast cancer in comparison with control group. There were also high values of sera ferritin, sodium, and calcium in women breast cancer in comparison with control group.

Conclusion: An elevation of serum steroid hormone, immunoglobulins (IgA, IgG, IgM), Na, and Ca levels in cases of carcinoma breast in our study is signifies, and its importance as a marker of the disease. A serial measurement of these steroid hormones and with some biochemical parameters will have a prognostic significance and help treatment decisions.

Key words: Breast cancer, steroid hormone, biochemical parameters and immunological parameters.

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Introduction

The most common malignant disease in females is breast cancer and is the chief cause of cancer related mortality among women worldwide [1]. The tumor markers in breast cancers like: carcinoembryonic antigen (CEA) and CA 15-3 are generally helpful in the follow-up of the patients with metastatic disease in combination with other diagnostic

techniques. This disease is still needs more precise biomarkers which might be helpful in early diagnosis, assessment of severity and for prediction of therapy response. Hormones are widely believed to be important in breast cancer etiology as several studies linked breast cancer to age at menarche, menopause, first pregnancy after age of 30 and postmenopausal obesity. In general, hormonal risk factors are associated with 1.5 to 2.0 relative risk of developing breast cancer [2].

Oestrogen is the most frequently studied hormone in relation to breast cancer because epidemiological data indicate that prolonged oestrogen exposure (late menopause, early menarche, null parity, and delayed pregnancy) increases the risk of breast cancer. The genomic actions of oestrogens are mediated via oestrogen receptors. These receptors are members of a family of nuclear hormone receptors that bind steroids, thyroid hormone, and retinoids [3]. Two oestrogen receptor molecules have been identified: the original oestrogen receptor alpha (ER-α), and the oestrogen receptor beta (ER-β). Evidence linking oral contraceptives to breast carcinoma is controversial. A few studies suggest a very slightly increased incidence in women who use oral contraceptives. Other reports indicate a decreased risk of breast cancer after discontinuation of combined hormone therapy [4]. Determining the association between the hormones in circulating and breast cancer risk may provide an understanding into the etiology of this disease and may help identify women who are at high risk of it [5].

Prolactin is a paradoxical hormone, which has more than 300 actions correlated to quasi-ubiquitous distribution of its receptors, lactation and reproduction. It may increase breast cancer proliferation and inhibit apoptosis [6].

Progesterone has been hypothesized to both elevate and reduce breast cancer risk. Progesterone levels appear to be a modest risk factor for each pre and postmenopausal breast cancer with significant reverse relation among progesterone levels and breast tumors risk [7]. The pathogenesis of the disease is still unknown. While diagnosis is now more effective through mammographic screening, but mortality rates remain almost unchanged. Estrogens, androgens, and progestins, are steroid hormones, which have been implicated in the pathogenesis and progression of breast cancer. Removing of the steroid hormones from the tumor environment included either hypophysectomy or ovariectomy [8]. During the past decade, insights have been gained about the role of the immunological response in the breast cancer disease process, and the possible use of immunological parameters in the prognosis of breast cancer. Serum immunoglobulin levels were found to be related to the disease stage and tumor load in breast cancer patients. The obvious alteration in serum IgG and IgA levels in breast cancer patients reflects a disturbance in cell–mediated immunity and humoral immunity [9].

So this study aim to evaluate the use of sex steroid hormones levels with some biochemical parameters as a serum tumor marker in patients with breast cancer

Materials and Methods

Patients and Study Design

This case-controlled comparative study was carried out in the Rizgary hospital and Nanakaly hospital, in Erbil city, Iraq. During the period from May 2015 till November 2015, ninety females were enrolled for this study. Out of these, 50 were patients of newly diagnosed/ untreated histopathologically proven breast cancer and 40 were healthy as control group at ages ranging from 35-70 years.

Collection of Blood Samples

Fasting blood samples were collected from cancer patients just before mastectomy

[pre level (First stage)] and healthy controls. Venous blood samples (5 ml) were drawn from each patient then serum was separated for the measurement of some biochemical parameters. All chemicals used throughout the whole work were of analytical grade. Progesterone, estrogen, prolactin, estradiol and testosterone kits were purchased from BioCheck, Inc.Foster City, USA.

Biochemical parameter of serum

Estrogen hormone (Est. H) in serum or human plasma (heparin) was analyzed by miniVIDAS analyzer for the quantitative measurement of 17α-estradiol in serum or human plasma (heparin), using Enzyme Linked Fluorescent Assay [10]. Progesterone hormone (Prog. H) in serum or in plasma (heparin or EDTA) was analyzed by mini VIDAS analyzer for the quantitative measurement in serum or in human plasma (heparin or EDTA), using ELFA technique [11]. Prolactin level was measured in stored consecutive serum samples using an immune radiometric assay [12]. Serum estradiol and Testosterone were determined using BioCheck, Inc. Foster City, USA according to [13]. Ferritin concentration in sera was determined using the immunoradiometric assay IRMA Ferritin (INEP, Belgrade-Zemun, Serbia). Radioactivity was measured on a gamma-counter (WIZARD, LKB). The serum immunoglobulin (IgG, IgA, and IgM) levels in both patients and controls were determined by turbidimetry method using an immunoglobulin kit (Chronolab, Switzerland). Serum total protein was determined by Biuret method using kit manufactured by RANDOX (United Kingdom). Serum calcium was determined by colorimetric method using manufactured kit by Biocon (Germany). And finally sodium in serum was determined using flame emission spectrometry.

Statistical analysis

The SPSS software package (Version11.5, SPSS Inc., Chicago, Illinois, USA) was used to analyze the data. The results are expressed as mean ± SD our date were analyzed statistically using paired t-test to compare subjects result for various parameters among different groups tested in the work. The difference is considered significant at $p \leq 0.05$ [14]. Ninety females were enrolled for this study. Out of these, 50 were patients of newly diagnosed/ untreated histopathologically proven breast cancer and 40 were healthy as control group

Results

Out o the ninety females were enrolled for this study, 50 patients with newly diagnosed/ untreated histopathologically proven breast cancer and 40 females were healthy as control group. The results of steroid hormones levels in blood serum of patients women with breast cancer and compared with control are presented in (Figures 1, 2).

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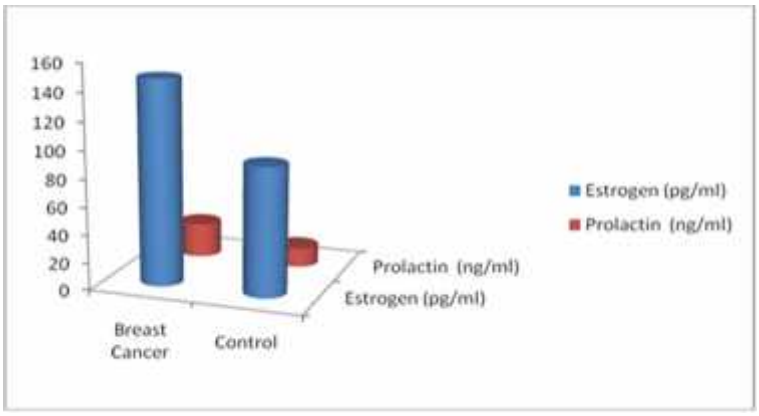

Figure (1): Estrogen and prolactin levels in healthy controls and patients with breast cancer (Values are expressed in mean ± SD).

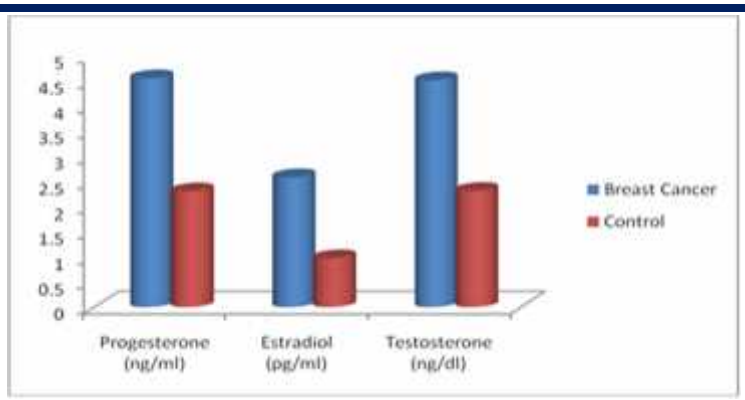

Figure (2): Steroid hormones levels in healthy controls and patients with breast cancer (Values are expressed in mean ± SD)

The results showed significantly high values of steroid hormones levels [p<0.001, p<0.002, p<0.01, p<0.05, p<0.05 (estrogen, prolactin, progesterone, estradiol, testosterone)] and high significantly values (p<0.001, p<0.001, and p<0.05) of sera ferritin, sodium, and calcium ion in women breast cancer in comparison with control group as shown in (Figures 3, 4). There were also high significantly high values in immunoglobulins IgA, and IgG, (p<0.05) as seen in (Figures 4) and there was no significant difference (p > 0.05) in IgM in patients with breast cancer in comparison with control group as shown in (Figure 4. .

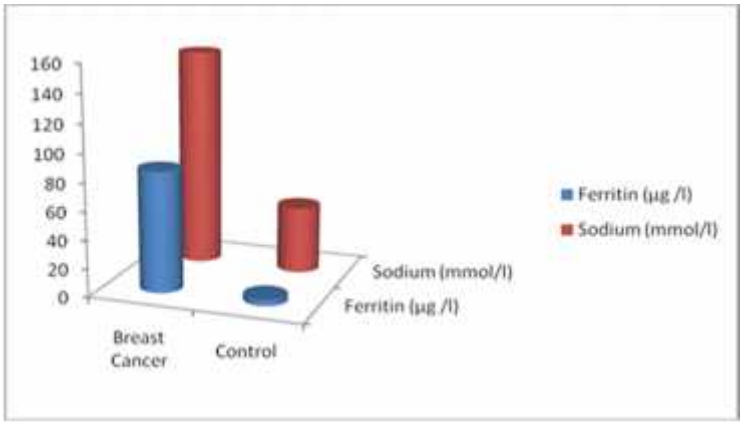

Figure (3): Ferritin, and sodium levels in healthy controls and patients with breast cancer (Values are expressed in mean ± SD)

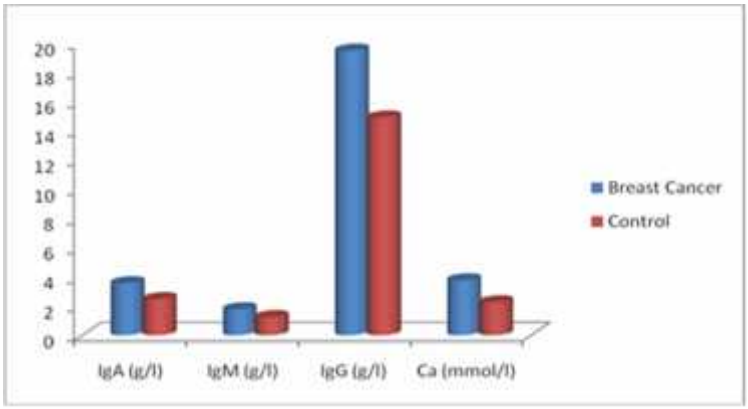

Figure (4): Immunoglobulins and Ca levels in healthy controls and patients with breast cancer (Values are expressed in mean ± SD)

Discussion

The results of steroid hormones concentrations in blood serum of control and patients women with breast cancer. The data indicated significant difference in the mean of estrogen, testosterone, prolactin, estradiol and progesterone that higher than the control. Serum estrogen levels were significantly higher ($p<0.001$) in female with breast cancer when compared with those of the control subjects.

Estrogen cause to tumor by promoting the cells proliferation with existing mutation or perhaps by increasing the opportunity for mutations that manage the growth and differentiation of mammary cells which may play an important role in the development of breast cancer [15]. Another possible mechanism of action may be through the metabolism of estrogen, which may cause oxidative stress and have a role in mammary cancer growth. Estrogen metabolites may utilize DNA mutations from DNA or ROS mutations which may cause to the accumulation of genomic alterations essential for mammary tumorigenesis [16]. The estrogen responding to the cells is depending on whether they have estrogen receptors. Classifying breast cancers into estrogen receptor status e.g. estrogen receptor positive (ER+) or estrogen receptor negative (ER-) and it is done to assist in the selection of appropriate therapies [17]. In general, ER+ breast cancers are more commonly correspond with generative related risk factors with endogenous estrogen exposure, for example number of pregnancies, early menarche, and late age childbearing [18].

Serum estradiol levels increased significantly in female with breast cancer with time. Breast cancer risk is increased by early menarche and by late menopause. This suggests that the high serum concentrations of oestradiol, in premenopausal women cause a greater increase in breast cancer risk per year than the much lower concentrations of progesterone and oestradiol in postmenopausal females. Oestradiol is genotoxic, and it is likely that the high serum concentrations of these hormones in premenopausal women increase breast cancer risk by increasing the mitotic rate of the breast epithelial cells [19]. Bioavailable estradiol or free estradiol is hypothesized to be readily available to the breast tissue and examined to be the most biologically active estrogen fractions and when compared with the total estradiol, a stronger association with one of these fractions and breast cancer risk might be expected [20].

ThEre was a significant increase in serum progesterone concentration in breast cancer females compared to the control group. Similar results have been reported by other investigators [21]. These results demonstrated that the increase in ovarian secretion of progesterone hormone might lead to breast cancer in many women. The fact that progesterone does not down-regulate progesterone-receptors in the breast might contribute to its adverse effects. Progesterone has been hypothesized to the both reducing and elevation breast cancer risk. Progesterone levels appear to be a deprecating risk influence for both pre and postmenopausal breast cancer with significant inverse association among progesterone levels and breast tumors risk [22]. A comparison between studied groups regarding the mean serum prolactin levels showed significant differences between breast cancer patients and healthy controls in which higher serum prolactin levels were detected among patients than among healthy controls in this study. This result suggests that, there is a relation between prolactin level and breast cancer. This difference points towards the specificity of prolactin for breast cancer which leads to utilize it as diagnostic and prognostic in this

disease. This finding is in accordance with other results published before [23].

The evidence suggests that prolactin is an important factor in the growth and regulation of normal and malignant cancer cells. The result of present study showed significantly increased levels of prolactin in breast cancer patients compared with healthy control. Large prospective studies have reported a positive association between prolactin levels and breast cancer risk [24]. Prolactin has a role in carcinogenic processes of the breast, possibly due to its stimulatory influence on the immune system and may be by the proliferative and anti-apoptotic effects [25].

A significant increase in serum testosterone in breast cancer women compared to the control groups. Higher levels of testosterone are related to stress associated with breast cancer. Ferritin levels in the sera from healthy individuals and patients with breast cancer. The levels of ferritin were found to be significantly higher ($p<0.001$) in breast cancer patients as compared to controls. This increase may be due to elevated expression of a tumor derived protein which contribute with iron metabolism or contribute to non-specific influence of malignancy on reticulo-endothelial iron metabolism [26]. Rise in serum ferritin levels may be due to elevated iron requirement by malignant cells for growth and for modulation of transferrin receptor [27]. In addition to elevated synthesis by malignant cells, other causes of raised serum levels include presence of hepatic necrosis, and inflammation due to metastasis and decreased hepatic clearance of ferritin [28]. All these factors might have been responsible for higher ferritin levels in advanced stage as compared to early breast cancer.

The level of calcium ion in the serum of breast cancer women found to be significantly high, when compared with control group. Low level of ascorbate in blood should result in increased ionized Ca levels, as Ca complexes with ascorbate [29]. Changing in humoral regulation of calcium resulting from production of parathyroid hormone related protein (PTH-rp) has also been implicated in tumor related with hypercalcemia [30]. Plasma concentration of PTH-rp is rarely elevated in healthy individuals, but elevated levels are detectable in about 80% of hypercalcemia patients with solid tumors. Parathyroid hormone interacts with parathyroid hormone receptors on cell membranes, activating adenyl cyclase, which stumilate the cyclic AMP production and increases intracellular calcium [31]. These actions are responsible for elevating bone demineralization and elevating serum calcium concentrations [32].

A significant increase ($p<0.001$) in sodium ion concentration of blood serum in breast cancer women when compared with control group. The patients with different types of cancer are usually presented with prolonged vomiting due to increase in the intractional pressure which is in agreement with. The vomiting will lead to dehydration and hypernatremia (increased serum sodium ions concentration) results from excess loss of water relative to sodium ion loss, decreased water intake or retention or increased sodium and fluoride ions intake due to an excessive intravenous infusion [33]. These symptoms are commonly attributed either to the cancer treatment or to cancer itself [34].

The serum IgG level for breast cancer patients were significantly higher when compared with control group. Also serum IgA in patients with breast cancer were significantly higher than for the control group. On the other hand, the results also showed that there was no significant difference in serum immunoglobulin IgM. The present study confirmed the finding of most authors [35, 36]. According to which

the IgA levels in breast cancer patients are higher than in controls and that the levels of IgA increases with the advancement in disease stages. Also the patients IgA levels were higher than those of the controls at all disease stages, with a strong positive correlation with the disease stage. A significantly higher IgA level was for patients who developed recurrence than patients who did not. Since the breast cancer cell line proved to secrete their own IgA [36], it is unclear whether this high IgA level and its relation to disease stages are a result of immune system fighting tumor cells or this elevation reflects the load and activity of the malignant cells through host immune modulation or secretion of IgA by their own cells. Any how this gives serum IgA a novel role in breast cancer patients' prognosis [37].

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