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Determination of Aromatase and Some Biochemical Parameters in Breast Cancer Patients in Mosul City, Iraq

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Abstract

The study included 60 patients with breast cancer diagnosed through biopsy, ranging in age from 30 to 73 years, from January 2024 to March 2024 at Ibn-Sina Teaching Hospital and Mosul Oncology and Nuclear Medicine Hospital in Mosul. Determination of the aromatase enzyme and several biochemical parameters, including aromatase, urea, creatinine, and electrolytes Na+, K+, Cl, compared with the 30 control healthy individuals who tested negative for breast cancer. Their age was identical to that of the patients, and they had no history of illness.

Keywords: Aromatase, breast cancer, electrolytes (Na, K, Cl), urea, and creatinine.

Introduction

Mutated cells in the breast tissue become cancerous cells that expand and form tumors, causing breast cancer to begin. Breast cancer is usually discovered in women over the age of 50, individuals who were assigned to either female or male at birth, and it can also be found in younger women and men. The tumor may spread from the breast to other tissues of the body, which is represented by approximately 80% of the cases of this cancer [1-3]. There are more signs and symptoms of this cancer, like shape change with a lump in the breast, liquid discharge from the nipple, rejection of milk, a nipple that has recently inverted, or a red spot of skin. The possibility exists of bloated lymph nodes, bone pain, yellow skin, and breathlessness [4,5].

The growth and development of breast tumors are greatly influenced by estrogens, although postmenopausal women have the highest rate of this disease due to the cessation of ovarian estrogen production. It has become a fact that estrogens are still generated in extra-glandular tissues in postmenopausal women by the aromatase enzyme complex, which converts androstenedione to estrogen [6].

Aromatase, also referred to as estrogen synthetase, is a crucial enzyme involved in a critical step of estrogen production, and the CYP19A1 gene is responsible for encoding it. Catalyzing different processes related to steroid production is done by this monooxygenase, which is part of the cytochrome P450 superfamily [7]. By converting androstenedione into estrogen and testosterone into estradiol, aromatase performs the final steps in androgen-dependent estrogen biosynthesis [8,9]. Numerous tissues contain the aromatase enzyme,

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such as the adipose tissue, skin, brain, placenta, blood vessels, gonads, and bone. In addition, it can be found in uterine fibroids, endometrial tissue, and breast cancer; it is recognized as a vital component in sexual maturation. The levels of aromatase usually rise with age, but they drop after menopause.

Conversely, the enzyme activity diminishes when prolactin is present at a higher level. Other factors, such as obesity and insulin, are responsible for influencing the activity [10]. Estrogens are involved in many body functions, such as regulating reproduction, behavior, and metabolism. Regulating aromatase levels and activity leads to control of estrogen production, which in turn has endocrine, paracrine, and autocrine effects on tissues [11,12]. The expression of aromatase and the production of higher levels of estrogens in breast cancer tissues have been observed; this is a major reason why aromatase has gained a lot of attention in breast cancer treatment. In women following menopause, the aromatase converts androgens peripherally to produce estrogens when the ovaries are no longer functioning [13]. A large number of breast cancer patients are women who have passed through menopause, despite the fact that estrogen production in the ovaries ceases after this stage, and peripheral tissues produce an adequate amount to promote tumor growth. Therefore, targeted therapy for breast cancer can be successful by inhibiting aromatase, which catalyzes the final and rate-limiting step of estrogen synthesis [14,15]. The progression of hormone-receptor-positive breast cancer is influenced by estrogens, which attach to and stimulate the estrogen receptor. Research indicates that estrogen receptor-positive cells are present in around 70% of breast cancer cases [16]. Hormone receptor-positive breast cancer can be controlled by reducing estrogen levels by inhibiting aromatase, which can reduce the chance of recurrence [17,18].

In the current study, aromatase activity was assessed in the blood serum of both breast cancer patients and a healthy control group to explore the influence of the enzyme on breast cancer. To examine their role in this cancer, creatinine and urea levels were introduced as parameters, along with electrolytes (Na+, K+, Cl-). In cancer patients, electrolyte imbalance is a common occurrence due to malignancies or negative effects of antineoplastic drugs, such as vomiting, diarrhea, and renal disorders; it is crucial to evaluate these disorders in patients and understand how they are related to other hematological abnormalities like neutropenia in the care of cancer patients [19].

Materials and Methods

This study included 60 patients with breast cancer diagnosed through biopsy, ranging in age from 30 to 73 years. Blood samples were collected from January 2024 to March 2024 from patients receiving treatment at Ibn-Sina Teaching Hospital and Mosul Oncology and Nuclear Medicine Hospital in Mosul, where the oncologist determines the clinical diagnosis for each case. The control group comprised 30 healthy individuals who tested negative for breast cancer. Their age was identical to that of the patients, and they had no history of illness. A venous blood sample with a volume of 10 milliliters was taken from every patient. The clotting process was conducted at room temperature for 10-20 minutes, and the serum was separated by centrifuging at 3000 xg for 10 minutes. After dividing it into three portions, the serum was kept at -20°C until further examination.

The determination of serum human aromatase was conducted using an ELISA kit in accordance with the manufacturer's guidelines (Bioassay Laboratory Technology, Cat. No. E3348Hu, China). The concentration of urea in serum was measured using a kinetic method using a urea kit provided by Biolabo, a company based in France. According to Jaffe's description, the creatinine assay was carried out dependent on the reaction of creatinine with sodium picrate. The reaction of creatinine with alkaline picrate forms an orange complex [20]. The levels of electrolytes (Na, K, Cl) were measured

using a ready-made kit by FUJIFILM, provided by the Japanese company DRI-CHEM NX500iv, model CODE 2450, manufactured in February 2023 with COT number 132803.

Statistical analysis

The SPSS 26 statistical package (SPSS Software, SPSS Inc., Chicago, Illinois, USA) was utilized for the analysis of the data. To determine significant differences between groups, a t-test was utilized. If the p-value was less than 0.05, it was considered statistically significant, and if it was higher, it was not. The analysis of data for multiple variable comparisons is done using one-way analysis of variance (ANOVA). The results are expressed as the mean ± standard deviation (SD).

Results

As illustrated in Table 1, the outcomes reveal a substantial rise in the levels of aromatase in the blood serum of breast cancer patients compared to the control group; meanwhile, the patients exhibited a significant decrease in sodium and chloride levels, while potassium and urea levels remained unchanged. Breast cancer patients aged 30-45 have a higher level of aromatase compared to those who are older, as shown in **Table 2.** The concentration of aromatase increased significantly in the three selected groups based on the duration time, while the electrolytes (K, Cl, Na) decreased significantly, as shown in **Table 3.**

Table (1): Levels of some parameters measured in the blood serum of patients with Breast cancer and their comparison to the control group

Measured Parameters	Control group		Breast cancer patients		(P) value
	mean	SD	mean	SD	
Age (years)	44.32	8.38	48.52	11.08	0.113
Na (mmol/L)	151.56	20.57	124.92	12.63	0.0001*
K (mmol/L)	4.32	0.81	3.92	0.69	0.092
Cl (mmol/L)	106.81	17.77	89.09	11.52	0.0001***
Urea (mg/dl)	32.69	10.62	31.37	9.26	0.661
Creatinine (mg/dl)	0.83	0.24	0.97	0.22	0.041*
Aromatase (ng/mL)	1.665	0.315	2.291	0.437	0.048*

Table (2): Levels of some parameters measured in the blood serum of breast cancer patients (group 30-45 years) and their comparison with the patients of breast cancer (group 46 years and over)

Measured Parameters	Patients with breast cancer, group 30-45 years		Patients with breast cancer group 46 years and over		(P) value
	mean	SD	Mean	SD	
Age (years)	39.87	4.95	48.12	2.02	0.0001***
Na (mmol/L)	128.25	12.62	122.68	10.86	0.48
K (mmol/L)	3.91	0.62	3.88	0.52	0.598
Cl (mmol/L)	91.87	10.50	87.18	9.30	0.44
Urea (mg/dl)	28.47	6.26	31.44	7.09	0.34
Creatinine (mg/dl)	0.816	0.21	0.919	0.32	0.245
Aromatase (ng/mL)	2.42	0.72	2.09	0.62	0.043*

Table (3): Comparison between control and patients depending on the duration time.

Biochemical Parameters	Stages (mean ± SD)				(P) value
	control	0-1 years	2-5 years	6 and over years	
Na (mmol/L)	151.56 ± 30.57	124.93 ± 13.89	128.09 ± 10.53	128.11 ± 8.17	0.009***
K (mmol/L)	4.32 ± 0.81	4.00 ± 0.66927	3.92 ± 0.38	3.633 ± 0.61	0.040*
Cl (mmol/L)	106.81 ± 17.77	89.70 ± 11.74	92.09 ± 8.37	88.22 ± 5.60	0.002***
Urea (mg/dl)	32.69 ± 10.62	33.57 ± 9.80	37.39 ± 18.92	42.02 ± 10.97	0.162
Creatinine (mg/dl)	0.97 ± 0.22	0.99 ± 0.245	1.11 ± 0.37	1.23 ± 0.152	0.070
Aromatase (ng/mL)	1.66 ± 0.315	2.39 ± 1.34	2.33 ± 0.81	2.76 ± 0.95	0.045*

Discussion

In this study, several suggestions must be taken into account to explain the significant increase in aromatase activity followed by higher estrogen synthesis. The aromatase gene expression is elevated in certain breast cancers, which results in more estrogen production in the cancerous and surrounding tissues. Some cancerous tumors may have higher aromatase enzyme activity compared to normal tissues. The ovaries produce lower estrogen levels in postmenopausal women, in the aromatase can counteract this deficiency by creating estrogen in muscle and adipose tissue, which leads to a rise in local estrogen concentration in the breast region. Certain environmental factors and chemicals can cause a rise in estrogen levels by stimulating aromatase activity or gene expression [21, 22]. The breast cancer group aged 30-45 had a statistically significant increase in aromatase levels in comparison to the breast cancer group aged 46 and older, as shown in **Table 2**. Hormone receptor-positive breast cancer mainly relies on estrogen produced by the ovaries. Treatments like tamoxifen are used to prevent the influence of estrogen on cancerous cells. After menopause, the inhibitors of aromatase, like letrozole, exemestane, and anastrozole, become essential when aromatase takes over as the main supplier of estrogen in the body. These medications work by reducing estrogen production from fat and other tissues, helping to slow cancer growth [23, 24].

In regard to decreased sodium levels in the patients, the release of antidiuretic hormone (ADH) is abnormal in certain cancers, such as breast cancer, which results in the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). This heightened hormone level causes the kidneys to reabsorb more water, which in turn dilutes sodium levels in the bloodstream. Low sodium levels in the patients may result from the disruption of the body fluid and electrolyte balance by certain chemotherapy drugs and other treatments for breast cancer. Patients with breast cancer may experience nausea and vomiting due to the illness itself or as a side effect of treatments, leading to a loss of fluids and essential salts, such as sodium. Nutritional deficiencies or inability to eat enough can affect sodium levels in the body of some cancer patients [25]. The disease itself or its associated treatments can cause high chloride levels in breast cancer patients. Increasing chloride levels in the blood can occur when treating dehydration by administering intravenous fluids with high chloride content. Cancer and its treatments can disrupt the body's ion balance, including chloride levels. Metabolic changes can cause an increase in chloride levels to compensate for the decrease in bicarbonate.

On the other hand, the regulation of salts and fluids in the body can be affected by cancer or its treatments, leading to kidney problems in which their function may be influenced by altered levels of the selected parameters. When bicarbonate levels drop due to specific conditions, the kidneys may increase chloride levels to help maintain overall ion equilibrium [26]. Various chemotherapy drugs and medications for breast cancer can also impact kidney function, reducing their ability to filter waste like creatinine and causing its levels to rise in the bloodstream. Cancer can sometimes block the urinary tract, such as the ureter, which hinders proper urine drainage from the kidneys and can result in elevated levels of creatinine. The presence of malnutrition and weight loss in cancer patients can have an impact on creatinine levels [27].

The findings revealed a significant elevation in aromatase levels when comparing the control group with different patient groups, in accordance with the duration of the disease, with levels rising as the duration of the disease lengthens. Breast cancer patients with prolonged disease duration, such as six years compared to one year, may experience elevated aromatase levels due to several factors. The progression, as the disease advances, tumor growth or genetic alterations may lead cancer cells to produce more aromatase enzymes. This increase

enhances the ability of tumors to convert androgens into estrogens, supporting the growth of estrogen-dependent cancer cells. The area around the tumor, including supporting cells and nearby tissues, may evolve to enhance aromatase activity. Fat and fibroblast cells surrounding the tumor can gradually increase aromatase generation, further supporting tumor growth. Aromatase production can be stimulated by chronic inflammation caused by long-term tumor presence. By increasing aromatase activity, this inflammation creates a local environment that enhances estrogen production. Over time, cancer cells can accumulate more genetic mutations, which could increase aromatase production; also, changes can occur in the balance of hormones in the body, which may further stimulate the production of aromatase in various tissues [28,29].

Conclusion

Elevated aromatase levels were consistently observed in breast cancer patients compared to the healthy control group, indicating its involvement in enhanced local estrogen production that may support tumor growth. Younger patients (30–45 years) exhibited higher aromatase levels than older patients, suggesting age-related hormonal influences.

Electrolyte imbalances, especially decreased sodium and chloride levels, were evident in patients, likely due to cancer-related complications or treatment side effects.

These findings emphasize the clinical relevance of monitoring aromatase and biochemical parameters in breast cancer patients to better understand disease dynamics and guide personalized treatment strategies**.**

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