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ORIGINAL ARTICLE

Investigation the Role of Lactate Dehydrogenase, Caspase and the Oxidative Stress Levels in Breast Cancer Patients

Shams Firas Adnan[1*] and Zainab N. Al-Abady[1]

[1]Department of Chemistry, Faculty of Sciences, University of Al-Qadisiyah, Al-Qadisiyah 58002, Iraq

***Corresponding author:**

sci.chem.mas.22.16@qu.edu.iq

Department of Chemistry
Faculty of Sciences
University of Al-Qadisiyah
Al-Qadisiyah 58002, Iraq

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Abstract

Background Breast cancer (BC) is a significant public health issue, characterized by its heterogeneity in clinical presentation, biological behavior, and response to therapy. Elevated levels of lactate dehydrogenase (LDH) and caspase-3, along with oxidative stress markers such as malondialdehyde (MDA) and catalase activity, have been linked to breast cancer progression and prognosis.
Aim This study aims to investigate the relationship between serum levels of LDH, caspase-3, MDA, and catalase activity in breast cancer patients compared to healthy controls, providing insights into potential diagnostic and prognostic biomarkers.
Materials and Methods A total of 120 participants, including breast cancer patients and healthy controls, were recruited. Blood samples were collected, and serum levels of LDH, caspase-3, MDA, and catalase activity were analyzed using enzyme-linked immunosorbent assay (ELISA) and spectrophotometric methods. Data were statistically analyzed using unpaired t-tests and chi-square analysis, with a significance threshold of $p < 0.05$.
Results Breast cancer patients exhibited significantly higher serum levels of LDH, caspase-3, and MDA ($p < 0.0001$) compared to healthy controls. In contrast, catalase activity was significantly lower in the patient group ($p < 0.0001$). These findings highlight the potential role of these biomarkers in breast cancer diagnosis and prognosis.
Conclusion Elevated LDH, caspase-3, and MDA levels, alongside reduced catalase activity, are associated with breast cancer. These biomarkers could serve as valuable tools for early detection and monitoring therapeutic responses in breast cancer patients.

Keywords: Breast cancer; Lactate dehydrogenase; Caspase-3; Oxidative stress; Malondialdehyde; Catalase activity

1 Introduction

Cancer is a disease characterized by aberrant cell proliferation that may spread to other parts of the body, often as a result of somatic cell genetic or epigenetic changes [1]. In 2020, cancer caused 9.9 million deaths (5.5 million men and 4.4 million females) and produced 19.3 million new cases worldwide (10.1 million males and 9.2 million females). Breast cancer (BC) is the second most prevalent malignancy among women globally [2]. Breast cancer (BC) consists of a diverse array of tumors that exhibit significant differences in clinical presentation, morphology, genetic characteristics, biological behavior, and therapeutic response.

Notwithstanding great progress in our comprehension and treatment of breast cancer, it persists as a substantial public health issue and continues to provide considerable problems globally [3]. Early mammography screening has been shown to reduce breast cancer mortality [4]. Biopsy is another important diagnostic procedure that involves analyzing breast tissue samples under a microscope to identify and categorize cancers. Breast cancer diagnosis with this technology is regarded as dependable and precise [5]. In this regard, lactate dehydrogenase (LDH) and caspase-3 are crucial to cancer metabolism and apoptosis. LDH enables the metabolic adjustments of cancer cells to promote rapid proliferation, while caspase-3 is crucial for the execution of apoptosis. Targeting these enzymes presents prospective therapeutic strategies for improving cancer therapy effectiveness and addressing resistance mechanisms in tumors [6, 7]. Researchers have studied the predictive value of plasmatic lactate dehydrogenase (LDH) levels in breast cancer. Multiple studies have linked elevated LDH levels to a negative prognosis, heightened risk of incidence, recurrence, and related death in individuals with breast cancer [6].

Lactate Dehydrogenase (LDH) is an enzyme that catalyzes the conversion of pyruvate to lactate during anaerobic glycolysis and the reverse reaction under aerobic conditions. LDH is essential for cellular energy production, particularly in conditions where oxygen availability is limited [8]. In several cancer cells, LDH is increased as a result of the Warburg effect, whereby glucose is preferentially metabolized to lactate despite the availability of oxygen. This transition to anaerobic metabolism enables cancer cells to swiftly generate energy and sustain their development metabolically, even in low-oxygen environments. The elevated generation of lactate may create an acidic tumor microenvironment, facilitating cancer cell invasion and metastasis [9].

The increased expression of Caspase-3 enzyme Caspase-3 expression and activity levels may function as a prognostic indicator in some malignancies. Elevated levels of active caspase-3 correlate with enhanced responses to chemotherapy and higher survival rates. Caspase-3 is often termed the "apoptosis executioner" due to its activation resulting in the disassembly of cellular constituents, such as nuclear fragmentation and chromatin condensation. The control of apoptosis is essential for preserving tissue homeostasis and averting tumorigenesis [10].

Oxidative stress is important to the onset and advancement of breast cancer. This means that there is a difference between the amount of reactive oxygen species (ROS) that an organism makes and how well its antioxidant systems can get rid of them. ROS are very reactive oxygen compounds that come from oxygen [11]. They include free radicals like superoxide anion (O_2^-) and hydroxyl radical (OH^-), as well as non-radicals like hydrogen peroxide (H_2O_2). Under typical circumstances, reactive oxygen species (ROS) participate in cellular signaling and homeostasis. Excessive quantities of reactive oxygen species (ROS) may harm cellular components such as DNA, proteins, and lipids, possibly resulting in carcinogenesis [12].

It is well recognized that cellular lipids are the main target of free radicals, which ultimately produce a range of aldehydes, including "malondialdehyde" (MDA). MDA is often employed as a biomarker of oxidative stress during significant health issues like cancer, etc., since it is a highly cytotoxic and carcinogenic substance. Numerous malignancies have shown a rise in the lipid peroxidation level (MDA) [13], Including our study finding of breast cancer.

Cancer cells often have elevated amounts of reactive oxygen species (ROS) and altered concentrations of antioxidant molecules in comparison to normal cells. The results of our search have decreased of antioxidant Catalase activity levels is a crucial antioxidant enzyme that plays an essential role in protecting cells from oxidative stress by catalyzing the decomposition of hydrogen peroxide (H_2O_2) into water (H_2O) and oxygen (O_2) [14]). Hydrogen peroxide is a by-product of various metabolic processes, and its accumulation can lead to oxidative damage if not efficiently removed. Catalase, therefore, is a critical defense against oxidative stress, which can contribute to the development and progression of diseases, including cancer. and its expression is often diminished in cancer cells [15].

2 Experimental part

2.1 Subjects and methods

This research involved 120 individuals. We selected the sample size using the sample size equation, which included breast cancer patients and healthy controls. Data on all patients during menopause, including sex, age, and BMI, were carefully chosen to make sure that none of the participants had any other diseases or disorders. were collected We carefully selected the control group to ensure that none of the participants had any other diseases or disorders. The mean age of the population ranged from 40 to 59 years, and the data collection took place between October 2023 and February 2024. All laboratory analyses were performed at Baghdad Laboratory/Al-Qadisiyah.

2.2 Blood sample collection and preparation

Blood samples (5 ml) were collected from 120 participants. The samples were divided into two sections:

The blood was collected in a gel tube and centrifuged at 3600 rpm for 10-15 minutes to separate the serum. The serum was then divided and stored in Eppendorf tubes at -20 °C for later analysis of LDH and Caspase-3 Enzymes and The remaining serum was used for biochemical Analysis (MDA levels and Catalase activity (CAT)). The LDH and Caspase-3 enzymes were measured using a sandwich enzyme-linked immunosorbent assay (ELISA) method, employing the following kits:

- Human Lactate Dehydrogenase (LDH) ELISA Kit
- Human Caspase-3 ELISA Kit

The malondialdehyde (MDA) levels [Guide and Shah, 1989] and catalase activity [Aebi, 1974] using spectrophotometric methods.

2.3 Statistical analysis

Data was collected, analyzed, and presented using Microsoft Office Excel 2013 and GraphPad Prism 9.2.0. Numerical values were used to denote categorical data. At the same time, mean and Standard Error of the Mean were utilized to express quantitative data. An unpaired t-test was used to compare the mean values across the several groups for normally distributed data. A chi-square analysis was conducted on the qualitative data. A P-value below 0.05 was considered significant.

3 Results

3.1 Measurement of serum Lactate dehydrogenase

The study findings suggest that the group of women with breast cancer had higher blood levels of lactate dehydrogenase (LDH) (U/L). The values exhibited a significant increase ($p<0.0001$) compared to the healthy women, as seen in Figure 1.

3.2 Measurement of serum Caspase 3

The study findings suggest that the group of women with breast cancer had higher blood levels of caspase 3 (ng/mL). The values exhibited a significant increase ($p<0.0001$) compared to the healthy women, as seen in Figure 2.

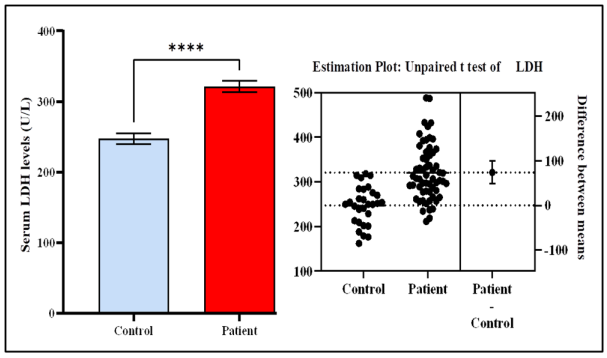

Figure 1: An analysis of the mean levels of serum lactate dehydrogenase (LDH) (U/L) in women diagnosed with breast cancer compared to those who are in good health. The Figures show a highly significant (p-value < 0.0001) difference in patients with breast cancer as compared with control. Data are expressed as means ± SEM. Indicates *significant $P \leq 0.05$.

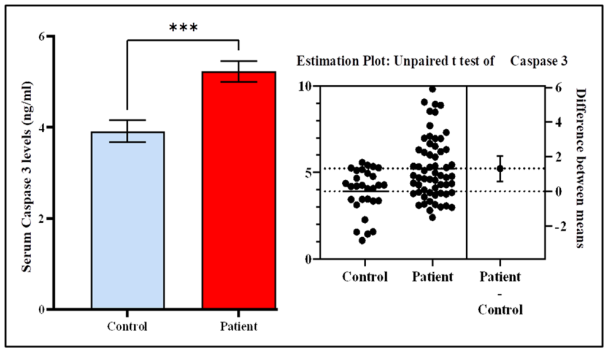

Figure 2: An analysis of the mean levels of serum caspase 3 in women diagnosed with breast cancer compared to those who are in good health. The Figures show a highly significant (p-value < 0.0001)difference in patients with breast cancer as compared with control. Data are expressed as means ± SEM. Indicates *significant $P \leq 0.05$.

3.3 Measurement of serum Malondialdehyde

The study findings suggest that the group of women with breast cancer had higher blood levels of malondialdehyde (MDA) (mM). The values exhibited a significant increase ($p<0.0001$) compared to the healthy women, as seen in Figure 3.

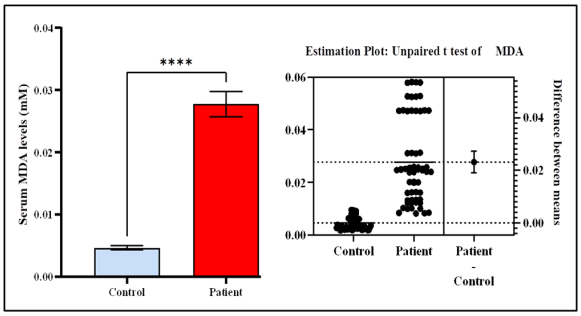

Figure 3: An analysis of the mean levels of serum malondialdehyde (MDA) (mM) in women diagnosed with breast cancer compared to those who are in good health. The Figures show a highly significant (p-value < 0.0001) difference in patients with breast cancer as compared with control. Data are expressed as means ± SEM. Indicates *significant P≤0.05.

3.4 Measurement of Catalase activity

The study findings suggest that the group of women with breast cancer had lower serum levels of catalase activity (U/mL). The values exhibited a significant decrease (p<0.0001) compared to the healthy women, as seen in Figure 4.

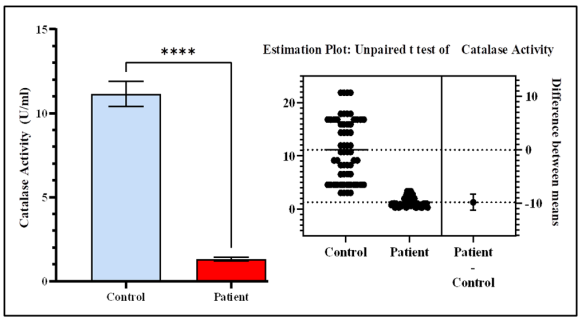

Figure 4: An analysis of the mean levels of serum catalase activity (U/mL) in women diagnosed with breast cancer compared to those who are in good health. The Figures show a highly significant (p-value < 0.0001) difference in patients with breast cancer as compared with control. Data are expressed as means ± SEM. Indicates *significant P≤0.05.

3.5 Correlation study

Table 1 explains the correlation analysis between key biomarkers in women diagnosed with breast cancer. Here's an explanation in detail:

1. LDH (Lactate Dehydrogenase)

   (a) Caspase-3: The Pearson correlation coefficient (r) is -0.096, indicating a very weak negative relationship between LDH and Caspase-3. This means higher LDH levels are slightly associated with lower Caspase-3 levels, but the relationship is not statistically significant (P = 0.467).

   (b) MDA (Malondialdehyde): The correlation coefficient is 0.054, showing a very weak positive relationship, but again, this is not statistically significant (P = 0.680).

   (c) CAT (Catalase activity): The correlation coefficient is -0.200, indicating a weak negative relationship between LDH and CAT, though not statistically significant (P = 0.126).

2. Caspase-3

   (a) MDA: The correlation coefficient is 0.062, which suggests a very weak positive relationship between Caspase-3 and MDA. This relationship is not statistically significant (P = 0.636).

   (b) CAT: The correlation coefficient is 0.027, again showing a very weak positive relationship, with no statistical significance (P = 0.839).

3. MDA

   (a) CAT: The correlation coefficient is 0.123, suggesting a weak positive relationship between MDA and CAT. This is also not statistically significant (P = 0.351).

Table 1: Disparities in blood biomarker measurements between BC patients and the control group.

Characteristic	Correlation	Caspase3	MDA	CAT
LDH	Pearson r	-0.096	0.054	-0.200
	P Value	0.467	0.680	0.126
Caspase3	Pearson r	1	0.062	0.027
	P Value		0.636	0.839
MDA	Pearson r		1	0.123
	P Value			0.351

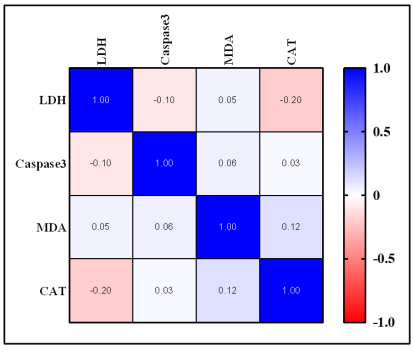

Figure 5: An Illustration of the Pearson r correlation analysis of biomarkers in women diagnosed with BC. The figure None of the correlations between the biomarkers are statistically significant, as all P values exceed the threshold of 0.05. The relationships between these biomarkers are weak, indicating limited direct association in this dataset.

4 Discussion

The current investigation revealed which lactate dehydrogenase (LDH) concentrations in women with breast cancer showed a significant development higher compared to the control group, Figure 1. According to our research, LDH is a valuable independent marker for predicting the development of a disease. Previous studies indicate higher lactate dehydrogenase (LDH) activity is linked to a more advanced stage of disease and has been linked to the development of many cancers, including breast cancer [16]. Elevated blood lactate dehydrogenase (LDH) levels have been linked to increased risks of colon, breast, and gynecological cancers. Studies on metastatic breast tumors have shown a link between poor outcomes, such as recurrence and death, and elevated levels of LDH in the blood [17].

Furthermore, it has been shown that cancer cells may generate energy via anaerobic pathways even when there is an abundance of oxygen. People with cancer often have higher-than-normal levels of serum total LDH and the gene for the isoenzyme LDH-A. Many research have linked these traits to a bad prognosis [18]. The increased LDH level helps these malignant cells meet their metabolic demands and perform anaerobic glycolysis. Patients with breast cancer have particular serum LDH levels that also correspond with clinical TNM staging [19]. However, more recent research indicates that LDH activity may serve as an all-encompassing indicator of cancer prognosis. Serum LDH damages a significant proportion of malignant cells that are continuously developing and whose metabolic process is anaerobic glycolysis because of the elevated lactic acid levels and LDH enzyme activity. Since the anaerobic glycolytic pathway acts differently in tumor cells than in normal cells, this rise in serum LDH levels may cause the tumor cells' excessive lactic acid output [20]. The LDHA isoform is most often seen in malignancies [21]. Since LDHA knockdown may reduce cancer cell proliferation, targeting LDHA might be an effective way to prevent the formation of cancerous tumors [22].Therefore, targeting LDH with inhibitors has emerged as an encouraging approach to cancer treatment. The biological process of apoptosis, also known as normal programmed cell death, eliminates damaged or old cells. Accordingly, apoptotic deregulation is often thought to contribute to tumor development and progression [23]. The executor caspase-3, which is directly activated by caspase-8, -9, and the apoptosome, participates in apoptosis. Normally located in the cytoplasm, it enters the nucleus during apoptosis to interact with its nuclear substrates [24].

In this study, an increase in the level of Caspase3 enzyme, Figure 2 According to Xuan et al. (2017), breast cancer patients with higher caspase-3 expression levels had a much worse chance of surviving [25]. According to the previous studies, show that higher levels of caspase-3 expression are linked to lower overall survival rates. This is especially true for types of breast cancer that show positive results for HER-2 and the progestogen receptor (PR) [24]. Elevated caspase-3 activity has been linked to resistance to chemotherapy and radiation treatment. In some instances, the activation of caspase-3 in surviving tumor cells may result in repopulation and metastasis post-treatment, hence complicating breast cancer care [26]. The tumor microenvironment may affect caspase-3 expression. Inflammation and immune cell infiltration may influence caspase-3 levels, affecting tumor behavior and patient outcomes. Increased caspase-3 expression has been associated with alterations in the tumor microenvironment that promote tumor growth [27].

Consequently, caspase-3 may be an important factor in breast cancer development and progression, and it may also be a useful prognostic parameter.

Our study also found elevated levels of Malondialdehyde (MDA), Figure 3, excessive oxidative stress prevents drug-induced apoptosis, which lessens the effectiveness of chemotherapy medications in killing cancer cells, Lipid peroxidation is more likely to occur when polyunsaturated lipids are attacked by free radicals [13]. MDA is one of the most common lipid peroxidation aldehydes. Along with raising MDA levels, a sign of the growth of cancer cells, it may also react with proteins and DNA to cause gene mutations that will lead to the production of cancer cells. In patients with breast cancer, elevated MDA is linked to a lack of antioxidant defenses and increased Reactive Oxygen Species (ROS) generation. Chemical, biological, and physical carcinogenic agents may cause excessive ROS generation [28].

In other studies , MDA levels were higher in breast cancer patients than controls without statistical significant difference, Because lipid peroxidation may produce toxic and reactive metabolites, a number of studies have shown that it may have a role in the promotion of tumors, Evaluation of MDA in tissues and plasma has been widely used in recent years to a variety of malignancies, including breast cancer [29]. Our study's finding of much higher oxidative stress in breast cancer patients compared to the control group inform efforts to improve breast cancer prevention and treatment.

Finally, our study observed a decrease in catalase activities (CAT) (Figure 4). Research has shown that when comparing breast cancer cells to normal breast tissues, catalase expression is often lower in the former. This decrease might be a factor in the increased reactive oxygen species (ROS) levels, such as H_2O_2. This results in elevated oxidative stress, which would encourage a more aggressive phenotype [15]. Ruqayah et al. in 2020 found that women with BC had lower levels

of CAT activity and glutathione concentration. They concluded that these biochemical changes could serve as biomarkers for monitoring the patients' response to treatment during follow-up and for the early detection of recurrent disease [30]. Various transcription factors are known to influence the transcription of the catalase gene. Research indicates that retinoic acid receptor alpha (RARα) functions as a catalase activity repressor of breast cancer cells through chromatin remodeling, suggesting that modulating these pathways may represent a viable treatment optioning [31]. Research has shown that catalase activity is much lower in breast cancer cells (MCF-7 cells included) than in healthy cells. The cells' increased resistance to chemotherapy may be the cause of this decrease [32].

By investigating the mechanisms behind decreased catalase levels, researchers can develop targeted therapies that restore its function, potentially improving patient outcomes. This approach could lead to more effective strategies for managing oxidative stress in breast cancer patients.

The lack of significant correlation in this study may be due to factors such as patient cohort, sample size, or clinical stage variability. This highlights the complex, possibly indirect relationship between LDH and apoptotic markers. While oxidative stress and metabolic dysregulation are key features of cancer, the weak correlation suggests that factors like tumor microenvironment acidity or hypoxia may influence the relationship. The observed trend may indicate metabolic stress in breast cancer cells, with a shift to anaerobic metabolism potentially inhibiting antioxidant defenses. Further research with larger datasets is needed to confirm these findings, and the interaction between apoptosis and oxidative stress may be influenced by additional factors such as tumor grade, treatment status, or genetic factors.

5 Conclusion

The increased levels of (LDH, caspase-3) enzymes, and MDA levels, along with the decrease in CAT activity levels may serve as valuable metabolic biomarkers for diagnosing and predicting breast cancer severity. These markers also hold potential as therapeutic targets in breast cancer management.

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Conflict of Interest: No conflicts of interest exist between the authors and the publication of this work.
Ethical consideration: This research is part of an approved student thesis under the supervision of the Faculty of Sciences, University of Al-Qadisiyah, Iraq, and it received the approval of the Department of Chemistry, Faculty of Sciences, University of Al-Qadisiyah, Iraq.
Authors' Contribution: The authors contributed to the study as follows: Shams Firas Adnan: Data analysis and interpretation, data collection, and experimental implementation. Zainab N. Al-Abady: Conceptualization, experimental design, and manuscript drafting. All authors read and approved the final manuscript.

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