RESEARCH ARTICLE

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Therapeutic Targeting of *PARP* Expression and Glycolysis Rate-Limiting Enzymes in Breast Cancer Patients

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Abstract

Background: Breast cancer is a heterogeneous disease characterized by diverse biochemical, histological, and clinical features. *PARP1* and glycolysis rate-limiting enzymes play critical roles in cancer progression, making them promising therapeutic targets. **Aim:** This study aimed to evaluate the expression levels of *PARP1* and key glycolytic enzymes (HK, PFK, and PK) in breast cancer patients and assess their potential as therapeutic indicators. **Materials and Methods:** A total of 120 participants (60 breast cancer patients and 60 healthy controls) were included in the study. Blood samples were collected to measure *PARP1* expression and the levels of glycolytic enzymes using ELISA. Statistical analyses were performed to compare the two groups. **Results:** *PARP1* expression and glycolytic enzyme levels (HK, PFK, and PK) were significantly higher in breast cancer patients compared to healthy controls ($p < 0.0001$). **Conclusion:** The overexpression of *PARP1* and key glycolytic enzymes indicates their involvement in breast cancer progression and underscores their potential as therapeutic targets and biomarkers.

Keywords: Breast cancer- *PARP1*- glycolysis- hexokinase- phosphofructokinase- pyruvate kinase

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Introduction

Cancer is a disease characterized by the abnormal proliferation of cells that may spread to other areas of the body, often as a result of genetic or epigenetic alterations in somatic cells [1]. Environmental factors, particularly chemical exposures, also contribute significantly to cancer development by inducing gene mutations [2]. In 2020, cancer accounted for 9.9 million deaths (4.4 million women and 5.5 million men) and 19.3 million new cases globally, including 9.2 million female and 10.1 million male cases. Among women, breast cancer (BC) is the second most prevalent malignancy worldwide, with rising incidence rates across all income levels [3].

Breast cancer is a highly heterogeneous disease, exhibiting diverse biological and histological characteristics. These differences lead to varied clinical outcomes and treatment responses. Consequently, BC patients are classified based on clinical and pathological characteristics to predict prognosis and guide therapeutic approaches [4].

Early mammography screening has proven effective in reducing breast cancer mortality [5]. Another reliable diagnostic tool is biopsy, in which breast tissue samples are examined microscopically to detect and classify tumors [6]. The primary goal of cancer therapy is to induce cancer cell death [7]. In this context, the DNA damage response (DDR) plays a pivotal role in both cancer prevention and treatment. Poly(ADP-ribose) polymerase 1 (*PARP1*), a key regulator of DDR, mediates several signal transduction processes [8].

PARP1 is a multifunctional enzyme, particularly involved in DNA repair and transcription. It is frequently overexpressed in cancer cells, with significant increases observed in cancers of the uterus, breast, ovary, lung, and skin [9]. *PARP1* facilitates DNA repair by attaching to damaged DNA regions and using NAD+ to form poly-ADP chains, which recruit DNA repair proteins through single- or double-stranded break pathways [10]. This process, called poly(ADP-ribosyl)ation, is primarily mediated by *PARP1* using NAD+ as a substrate [11]. Immunohistochemical evaluation of *PARP1* levels in BC cells has emerged as a potential biomarker for disease prognosis and therapeutic response. Studies indicate that higher *PARP1* expression is associated with poorer clinical outcomes [3].

PARP inhibitors, discovered several years ago, have shown significant efficacy in treating cancers with BRCA mutations. Recent research has expanded their therapeutic potential in BC, supported by promising preclinical and translational studies [12]. Additionally, advancements in molecular biology and biochemistry have revealed substantial differences in signal transmission and metabolism between cancerous and normal cells, particularly in glucose metabolism [13].

Glycolysis, the process by which glucose is converted

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into pyruvate, is crucial for cancer cell growth and tumor progression. Cancer cells undergo a metabolic shift known as the Warburg effect, favoring anaerobic glycolysis even in oxygen-rich environments [14]. This phenomenon results in elevated ATP and lactic acid production, promoting tumor growth and creating an acidic microenvironment [15].

The overexpression of key glycolytic enzymes plays a central role in this metabolic shift. Enzymes such as hexokinase (HK), pyruvate kinase (PK), and phosphofructokinase (PFK) are upregulated in many cancers, making them attractive therapeutic targets [16]. In glycolysis, HK catalyzes the conversion of glucose to glucose-6-phosphate, serving as the first rate-limiting enzyme. Among its isoforms, HKII is particularly significant in rapidly growing tumors, as it supports enhanced glycolysis, thereby providing energy for DNA synthesis [17, 18]. PFK1, a key enzyme in glycolysis, is modulated by cytoplasmic metabolites such as fructose-2,6-bisphosphate, ATP, and ADP [19]. PFKFB3, a bifunctional enzyme, has been associated with lymph node metastases and poor survival outcomes in various malignancies [20]. Pyruvate kinase (PK), the final rate-limiting enzyme in glycolysis, is particularly influenced by the PKM2 isoform, which plays a critical role in cancer cell metabolism and tumor proliferation [21, 22]. The present study aimed to investigate the link between *PARP1* expression and glycolysis rate-limiting enzymes in breast cancer patients.

Materials and Methods

Subjects and Methods

This study involved 120 participants, including breast cancer patients and healthy controls. Data on all participants, such as sex, age, and BMI, were collected. The control group was carefully selected to ensure that none of the participants had any other diseases or disorders. The mean age of the participants ranged from 40 to 59 years. Data collection was conducted between October 2023 and February 2024, and all laboratory analyses were performed at the Baghdad Laboratory/ Al-Qadisiyah.

Blood Sample Collection and Preparation

Blood samples (5 ml) were collected from each participant and divided into two sections:

1. Gene Expression Analysis:

One milliliter (1 ml) of blood was stored in a K2EDTA tube for gene expression analysis.

2. Serum Analysis for Glycolysis Enzymes:

The remaining blood was collected in a gel tube and centrifuged at 3600 rpm for 10–15 minutes to separate the serum. The serum was then aliquoted into Eppendorf tubes and stored at -20°C for later analysis of glycolysis rate-limiting enzymes.

Enzyme Assays

The glycolysis rate-limiting enzymes were measured using a sandwich enzyme-linked immunosorbent assay (ELISA) method, employing the following kits:

- Human Hexokinase (HK) ELISA Kit
- Human Phosphofructokinase (PFK) ELISA Kit
- Human Pyruvate Kinase (PK) ELISA Kit

Statistical Analysis

Data were collected, analyzed, and presented using Microsoft Office Excel 2013 and GraphPad Prism 9.2.0. Categorical data were represented using numerical values, while quantitative data were expressed as mean ± standard error of the mean (SEM). For normally distributed data, an unpaired t-test was performed to compare the mean values between groups. Chi-square analysis was used to examine qualitative data. A P-value of less than 0.05 was considered statistically significant.

Results

Comparison of Demographic Characteristics Between Women With Breast Cancer and Healthy Women

Table 1 presents a comparison of demographic characteristics between women with breast cancer and healthy controls.

The mean age of women with breast cancer did not differ significantly from that of the healthy controls ($p = 0.1208$). Similarly, no significant difference was observed in the mean body mass index (BMI) between the two groups ($p = 0.8695$), as shown in Table 1.

Comparison of Studied Biomarkers Between Women with Breast Cancer and Healthy Women

Measurement of Poly (ADP-ribose) Polymerase Expression

The study findings indicate that women with breast cancer exhibited significantly higher gene expression levels of poly (ADP-ribose) polymerase compared to healthy controls. The increase was statistically significant ($p < 0.0001$), as illustrated in Figure 1.

Measurement of Serum Hexokinase

The study findings suggest that the group of women with breast cancer had higher serum levels of hexokinase (pg/mL). This increase was statistically significant ($p < 0.0001$), as shown in Figure 2.

Measurement of Serum Phosphofructokinase

The study findings indicate that women with breast cancer had significantly higher serum levels of

Table 1. Comparison of Demographic Characteristics between Women with Breast Cancer and Healthy Controls

Characteristic	Control n=60	Patient n=60	P Value
Age (year)			
Range	40 - 56	40 - 56	0.1208
Mean ± SEM	47.8 ± 0.643	46.48 ± 0.5444	Ns
Body Mass Index (kg/m^2)			
Range	24.04 - 35.75	24.17 - 36.89	0.8695
Mean ± SEM	29.45 ± 0.4313	29.55 ± 0.4082	Ns

N, number of cases; p, probability value; ns, not significant; SEM, standard Error of Mean

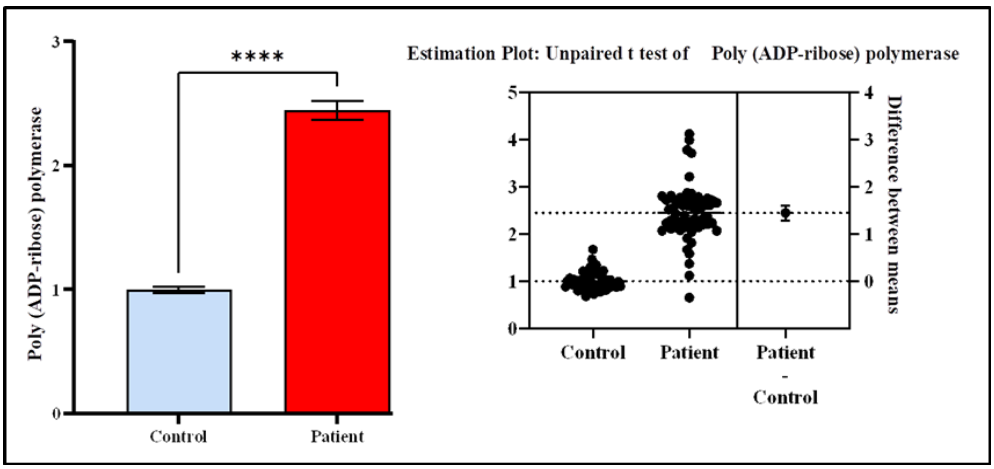

Figure 1. An Analysis of the Mean Levels of Gene Expression Poly (ADP-ribose) Polymerase in Women Diagnosed with Breast Cancer Compared to Those who are in Good Health

Table 2. Correlation Analysis of Biomarkers in Women Diagnosed with Breast Cancer

Characteristic	Correlation	BMI	HK	PFK	PK	Gene expression
Age	Pearson r	0.127	0.048	0.017	-0.136	0.024
	P value	0.335	0.715	0.898	0.3	0.853
BMI	Pearson r	1	-0.13	-0.178	-0.08	-0.119
	P value		0.323	0.174	0.545	0.365
HK	Pearson r		1	-0.059	-0.115	0.147
	P value			0.654	0.383	0.261
PFK	Pearson r			1	0.02	0.031
	P value				0.879	0.816
PK	Pearson r				1	-0.066
	P value					0.614

BMI, Body mass index; HK, Hexokinase; PK, Pyruvate Kinase; PFK, Phosphofructokinase

phosphofructokinase (PFK) (ng/mL) compared to healthy controls. This increase was statistically significant ($p < 0.0001$), as shown in Figure 3.

Measurement of Serum Pyruvate Kinase

The study findings indicate that women with breast cancer had significantly higher blood levels of pyruvate kinase (pg/mL) compared to healthy controls. This increase was statistically significant ($p < 0.0001$), as shown in Figure 4.

Correlation study

Table 2 and Figure 5 present a correlation analysis between several biomarkers and various characteristics (Age, BMI, HK, PFK, PK, and Gene Expression) in women diagnosed with breast cancer.

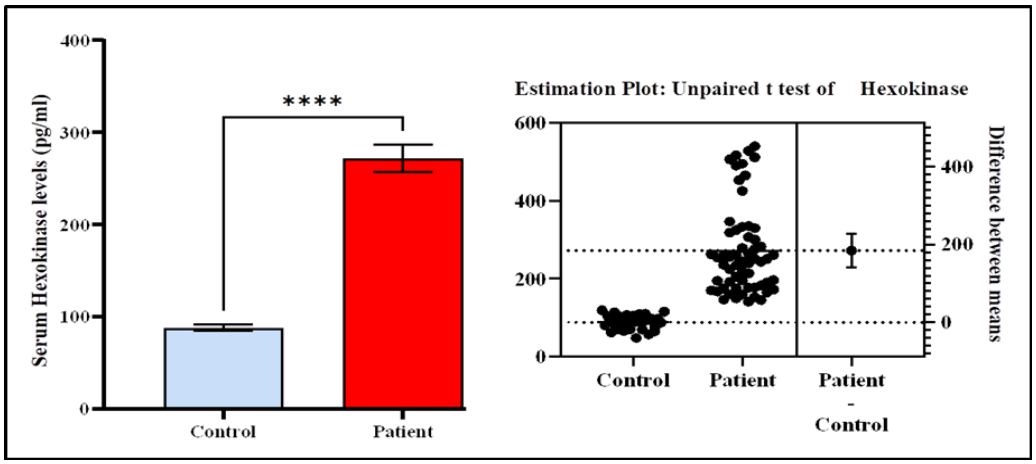

Figure 2. An analysis of the Mean Levels of Serum Hexokinase (pg/mL) in Women Diagnosed with Breast Cancer Compared to those who are in Good Health.

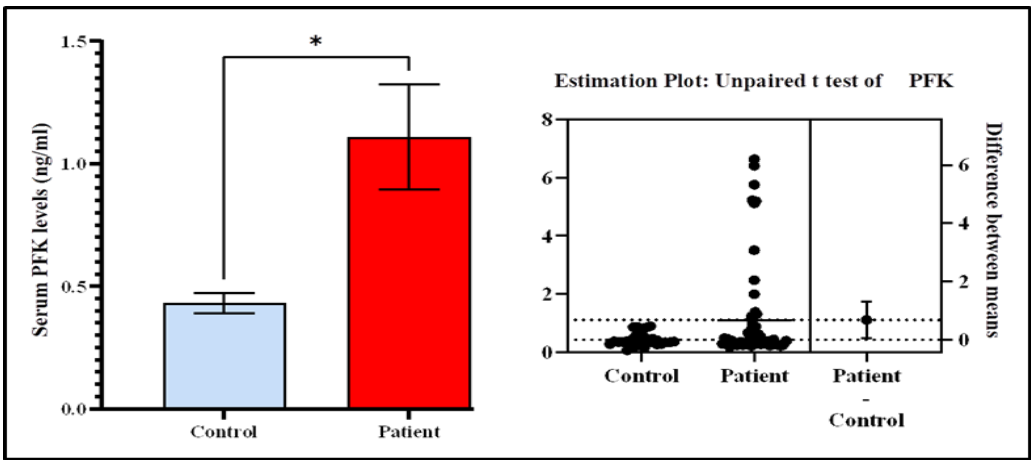

Figure 3. An Analysis of the Mean Levels of Serum Phosphofructokinase (PFK) (ng/mL) in Women Diagnosed with Breast Cancer Compared to Those who are in Good Health.

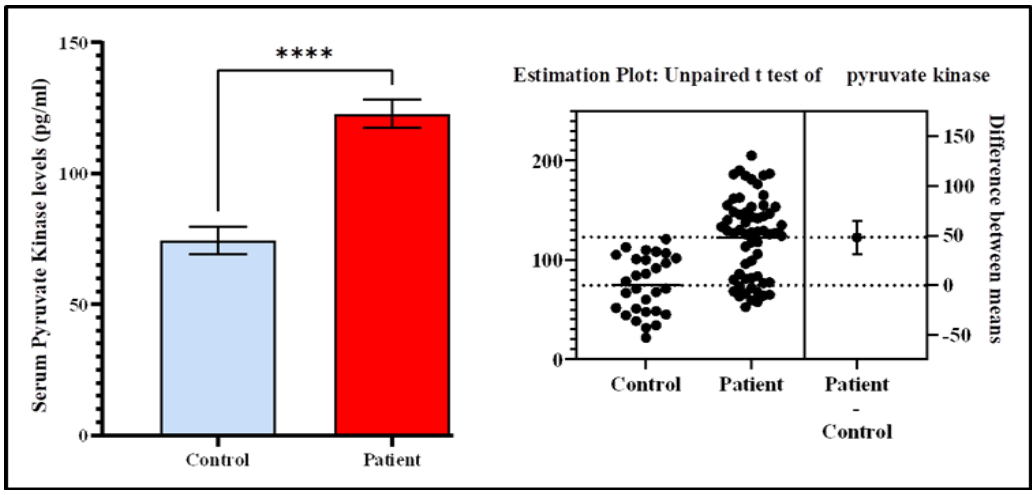

Figure 4. An Analysis of the Mean Levels of Serum Pyruvate Kinase (pg/mL) in Women Diagnosed with Breast Cancer Compared to Those who are in Good Health

1. Age

A positive correlation was observed with BMI (Pearson r = 0.127); however, this was not statistically significant (P = 0.335). Correlations with other biomarkers (HK, PFK, PK, and Gene Expression) were very weak and not statistically significant.

2. BMI

No statistically significant correlations were found with HK, PFK, PK, or Gene Expression (P values > 0.05).

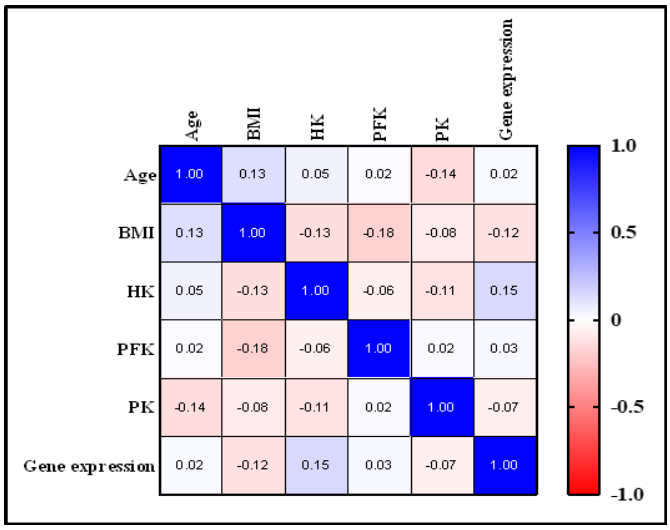

Figure 5. An Illustration of the Pearson r Correlation Analysis of Biomarkers in Women Diagnosed with Breast Cancer.

Pearson r values indicated weak relationships.

3. Hexokinase (HK)

No statistically significant correlations were observed with other biomarkers, including PFK, PK, and Gene Expression.

4. Phosphofructokinase (PFK)

Correlations with other biomarkers, including BMI, HK, and Gene Expression, were weak or not statistically significant.

5. Pyruvate Kinase (PK)

No significant correlation was observed with Gene Expression (Pearson r = -0.066, P = 0.614) or any other variables listed in the table.

Discussion

The average age of women with breast cancer in this study was 46.48 ± 0.5444 years, while the mean age of the control group was 47.8 ± 0.643 years. Statistical analysis showed no significant difference between the two groups (p = 0.1208), indicating that age was not a confounding factor. This suggests that both the control and patient groups were well-matched with respect to age, minimizing the risk of age-related biases. These findings align with other studies that match control groups based on age to avoid confounding effects in breast cancer research [23].

Similarly, the comparison of BMI between the two groups revealed no significant difference. The BMI range for the breast cancer group was 24.17 to 36.89 kg/m², with a mean of 29.55 ± 0.4082 kg/m², while the control group had a BMI range of 24.04 to 35.75 kg/m², with a mean of 29.45 ± 0.4313 kg/m². The p-value of 0.8695 further confirms that there was no statistically significant variation in BMI between the groups. Although an elevated BMI is commonly associated with an increased risk of breast cancer, especially in postmenopausal women, the lack of a significant difference in BMI in this study may suggest that BMI did not play a prominent role in distinguishing breast cancer patients from healthy controls in this specific population [24].

Regarding the biomarkers examined, our study showed a significant increase in the expression of *PARP1* in women with breast cancer compared to the control group. This aligns with previous research suggesting that *PARP1* may serve as an independent marker for predicting disease outcomes. While some studies suggest that *PARP1* overexpression is associated with a better prognosis, recent evidence indicates that *PARP1* might adversely affect the clinical behavior of breast cancer [3]. *PARP1*, a key member of the poly (ADP-ribose) polymerase family, plays a crucial role in the DNA damage response (DDR) and genomic integrity [25]. It helps recruit DNA repair proteins to strand breaks and promotes chromatin relaxation [26]. Recent studies have shown that *PARP1* upregulation is prevalent in basal-like breast tumors and correlates with poor overall survival and metastasis-free survival [27]. Our findings support the work of Siraj et al. [28] who indicated that *PARP1* overexpression correlates with malignancies, including breast cancer. Additionally, BRCA1-mutated breast cancers exhibit higher *PARP1* levels, contributing to rapid DNA repair and promoting cancer cell proliferation [29, 30]. Consequently, targeting *PARP1* with inhibitors has become a promising strategy for cancer treatment.

Our investigation also identified elevated levels of the glycolysis-related enzyme Hexokinase (HK) in breast cancer tissues (Figure 2). HK is a key enzyme in the glycolytic pathway, and its overexpression has been associated with various cancers, including breast, pancreatic, and stomach cancers [31, 13]. The Warburg effect, which favors glycolysis over oxidative phosphorylation in cancer cells, leads to increased glucose consumption and lactate production, even in the presence of oxygen [32]. HK II, which is bound to the mitochondrial membrane, plays a key role in promoting glycolysis and preventing apoptosis in cancer cells [33]. Immunohistochemical studies by Brown et al. have shown high expression of HK II in untreated primary breast cancers, further supporting its role in tumor metabolism [34]. Thus, targeting HK II could be a viable therapeutic strategy.

In addition to HK, we found increased levels of Phosphofructokinase (PFK), the second rate-limiting enzyme in glycolysis, in breast cancer tissues (Figure 3). PFK catalyzes the conversion of fructose-6-phosphate to fructose-1,6-bisphosphate, facilitating glycolysis. Elevated concentrations of fructose-2,6-bisphosphate, which suppress PFK, can enhance cancer cell proliferation [35, 36]. Oncogenes like Ras and c-Ras have been shown to increase PFK activity in malignant tumors [37]. El-Bacha et al. reported that the actin network in breast cancer cells regulates PFK activity, further underscoring its role in cancer metabolism [38]. Estrogen has also been implicated in glycolysis regulation, with studies showing increased expression of HK, PFK, and Pyruvate Kinase (PK) following estrogen treatment in rat brains [17].

Finally, our study observed elevated levels of the third rate-limiting glycolytic enzyme, Pyruvate Kinase (PK) (Figure 4). Elevated PK activity promotes glucose uptake, lactate production, and suppresses autophagy, contributing to oncogenic growth [39]. Overexpression of the PKM2 isoform is associated with poor prognosis in various cancers, including lung, gastrointestinal, ovarian, and bile duct cancers [40]. In breast cancer, PKM2 expression correlates with tumor size, TNM stage, and lymph node metastasis [41, 42]. Furthermore, a strong positive correlation has been found between glycolytic genes such as HK2, PFKM, and PKM2, and tumor aggressiveness and cell proliferation [17].

The current study also revealed weak and non-significant correlations between BMI, age, HK, PFK, PK, and gene expression, suggesting that these factors may not be strongly interrelated in breast cancer metabolism. While some studies report similar weak associations, others emphasize the potential influence of population characteristics, cancer subtypes, or methodological differences on these correlations. For example, Xie et al. [43] reported weak and non-significant correlations between BMI and HK, PFK, and PK in postmenopausal

women, suggesting that metabolic enzyme activity might not be strongly influenced by BMI and that cancer progression may disrupt standard metabolic processes independently of body weight . Conversely, Mendes et al. [44] found a significant positive correlation between BMI and HK activity in breast cancer patients, possibly due to differences in sample size or cancer stage.

In conclusion, the combined overexpression of *PARP1* and the three rate-limiting glycolytic enzymes (HK, PFK, and PK) could serve as valuable metabolic biomarkers for both diagnosing and predicting the severity of breast cancer. These biomarkers not only provide insights into the metabolic reprogramming associated with breast cancer but also hold potential as therapeutic targets, offering new avenues for more targeted and effective treatment strategies in breast cancer management.

Author Contribution Statement

All authors contributed equally in this study.

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None
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