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Serum Lactate Dehydrogenase as a potential predictive index of chemotherapy response in breast cancer patients

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Abstract

Background: Monitoring treatment during breast cancer management is crucial. Lactate dehydrogenase (LDH) expression and activity drive cancer progression through metabolic reprogramming.

Objective: The study aimed to profile serum lactate dehydrogenase in breast cancer patients as a chemotherapy response index.

Methods: A total of 65 breast cancer patients and 64 healthy controls were studied. Archival serum samples from the patients before initiation and after the third cycle of chemotherapy and controls were retrieved from -80 ºC freezer. Clinico-pathological data of study participants were retrieved. Total RNA was extracted from the serum using a commercial kit, and lactate dehydrogenase A mRNA was quantified by RT-qPCR. The serum total LDH activity was determined using a chemistry autoanalyser.

Results: The mean age difference between patients (49.55, SD 11.98) and controls (55.67, SD 13.99) years was statistically significant ($p < 0.01$). However, the BMI and waist-to-hip ratio of patients compared to the controls were not statistically significant ($p > 0.05$). Patients with tumour grade 3 (52.3%), HER 2 positive (30.8%) and stage 3 (46.2%) were over-presented. Serum total LDH activity was significantly elevated in the patients at baseline compared to the controls ($p < 0.01$) but not significant when the activity was compared with after the third cycle of chemotherapy ($p > 0.05$). The pattern remained unchanged when serum LDHA mRNA relative fold change was compared ($p > 0.05$). Nevertheless, the fold change ratio difference for mRNA (3.4) was higher than that of enzyme activity (0.24).

Conclusion: Serum total LDH activity and LDHA expression in breast cancer patients were reduced after the third cycle of chemotherapy. However, LHDA mRNA expression could be a better predictive index of chemotherapy response than enzyme activity.

Keywords: Lactate dehydrogenase, chemotherapy response, breast cancer, enzyme activity, mRNA levels

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INTRODUCTION

Breast cancer is the most common cancer and the fifth leading cause of cancer-related deaths globally [1]. Although the incident rate is higher in developed countries compared to developing countries, breast cancer mortality is higher in developing countries [2]. The high cancer-related mortality has been attributed to late presentation to health facilities, and the reasons include low health promotion for early detection, low education, superstition and sociocultural beliefs, and inadequate specialised health facilities [3].

Several medical approaches have been adopted in breast cancer management; however, treatment options largely

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depend on tumour characteristics such as type of cancer, tumour stage, grade, metastasis and biological subtyping of the cancer [4]. The overall health status of the patient, menopause status, and personal preferences are also considered in the choice of management plan [3,4]. The time of initiation of treatment is key in preventing the spread of the cancer cells, and the therapy could be given as an adjuvant or neo-adjuvant to surgery or to palliate the disease, especially in the metastatic stages [5]. Interventions are either local, such as surgery and radiation, or systemic therapies, where drugs are administered to kill cancer cells. The systemic therapy includes hormonal, targeted or biological therapies and chemotherapy [6]. Chemotherapeutic agents are designed to target cancer cell machinery that promotes active cell proliferation. The chemotherapeutic agents are categorised based on the cellular mechanisms. Alkylating agents and platinants, which include cisplatin and inhibitors of topoisomerase such as daunorubicin, doxorubicin, irinotecan, and etoposide induce DNA damage in proliferating cells [7].

Cytotoxic antibiotics function to prevent DNA and RNA synthesis, while antimetabolites such as gemcitabine interfere with intermediary metabolism [8]. Anti-microtubule agents, including paclitaxel and docetaxel, target microtubules and associated proteins to disrupt cell division [9]. Hormonal agents such as tamoxifen or enzalutamide are required to inhibit hormone synthesis or dysregulate the function of hormone receptors [10], while immunotherapy such as trastuzumab targets cancer cells that express a specific antigen or enhance the natural ability of T cells to fight cancer [9]. Despite several therapeutic attempts to suppress cancer cells' survival and proliferation, therapy resistance or tumour relapse remains a challenge. Several factors have been mentioned to underpin tumour resistance to chemotherapy in patients [11], warranting treatment monitoring to assess response. Currently, breast cancer treatment is based on molecular classification of receptor types, including estrogen receptor (ER) and progesterone receptor (PR) positive, human epidermal growth factor receptor 2 (HER2) positive and triple-negative non-receptor breast cancer [12].

Evaluation of treatment effectiveness is critical in breast cancer management, and predictive and prognostic markers identify patients who respond to treatment. Commercially available genomic assays are currently employed to establish possible recurrence and potential benefits of chemotherapy [13]. Search for new prognostic markers is on the increase and may be combined with histopathological evaluation to monitor therapy response. Serum CEA and CA 15 - 3 are promising biomarkers for evaluating therapy response in patients receiving systemic therapy, and new biomarkers such as circulating tumour cells and circulating tumour-derived DNA are being studied [14]. Breast cancer cells adopt metabolic reprogramming and avoid oxidative phosphorylation [15]. Derailed bioenergetic process characterised by low expression of the catalytic subunit of mitochondrial H+-ATP synthase and a drop in the ATPase activity is linked to a decreased oxidative phosphorylation [16]. Conversion of pyruvate to lactate in breast cancer cells is a very promising target for therapy evaluation. Lactate dehydrogenase A (LDHA) is a metabolic isoenzyme responsible for the conversion of pyruvate to lactate in the cytoplasm under anaerobic conditions [17]. The LDHA-mediated metabolic reprogramming promotes cancer cell proliferation and drug resistance by alleviating reactive oxygen species-associated apoptotic effects [18]. Data on LDHA isoenzyme expression and LDH activity as a predictive index for chemotherapy response in breast cancer patients is limited. The current study aimed to compare serum LDHA mRNA level and total LDH activity as potential predictive indices for chemotherapy response in breast cancer patients.

MATERIALS AND METHODS

Study design, participants and samples

A total of 129 archival serum samples kept at -80 ^{o}C were retrieved for this study. The samples were collected from female breast cancer patients (65) visiting the Breast Cancer Suite, Korle-Bu Teaching Hospital, Accra, Ghana. The patients were compared with cancer-free healthy controls (64), recruited from the hospital environs in a longitudinal, case-control study. Breast cancer diagnosis was based on histopathology. Blood samples were taken from each patient before the commencement of chemotherapy as a baseline and after the third cycle of chemotherapy. The treatment plan for patients included intravenous (IV) cyclophosphamide 500 mg/BSA, IV adriamycin 50 mg/BSA, and IV 5-fluorouracil 500 mg/BSA, and the chemotherapeutic drugs were administered at three weekly intervals for six cycles. The control women were recruited from the hospital environs after written consent was obtained. Patients diagnosed with other chronic diseases were excluded from the study. Blood samples from the control group were collected at one-time point. Clinical data, including waist-to-hip ratio (WHR), body mass index (BMI) and pathological data, were retrieved from our previous study data files. Ethical clearance was obtained from the Ethical and Protocol Review Committee of the School of Biomedical and Allied Health Sciences, College of Health Sciences, University of Ghana, with ethics identification No. SBAHS/AA/MLAB/10710648/2021-2022.

Laboratory analyses

Serum total RNA extraction and LDHA mRNA quantification

Free total RNA was extracted from a 100 µL serum sample using a commercial kit (QIAamp Circulating Nucleic Acid Kit, USA) following the manufacturer's protocol. The purity and concentration of the eluted RNA were measured using Nanodrop (Thermo Fisher Scientific, USA). The mRNA expression levels of LADHA and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) genes in the serum samples were analysed by RT-qPCR using Luna Universal One-Step Reaction Mix (BioLabs, New England).

Parameters of the polymerase chain reaction (PCR) were as follows: reverse transcription at 55 ºC for 10 min and initial denaturation at 95°C for 1 min, 45 cycles of 95°C for 10 s and 60 °C for 30 s and final melting curve at 72 ºC for 5 min. The primer sequences for LDHA (forward: 5′-GGATCTCCAACATGGCAG CCTT-3′, reverse: 5-AGACGGCTTTCTCCCTCTTGCT-3′) and GAPDH (forward:5′-GTCTCCTCTGACTTCAAC AGCG-3′ and reverse:5′-ACCACCCTGTTGCTGAGCC AA-3′). Glyceraldehyde-3-phosphate dehydrogenase was used to normalise the data. Each sample was set in duplicate, and the average Ct value was used to calculate the expression fold change.

Serum total LDH activity

Serum LDH activity was measured using Anamol Laboratories PVT Ltd reagents (Kolgaon, India) and by UV kinetic method with Mindray BS 200 chemistry autoanalyser (Shenzhen, China) following standard protocols.

Statistical analysis

IBM SPSS for Windows, Version 24.0. Armonk, NY: IBM Corp. was used for statistical analyses. Categorical data was presented as proportion and continuous data was presented as mean and standard deviation (SD). Student T-test was used to determine the significance of the mean difference between continuous variables of patients and controls. ANOVA was used to compare the LDHA mRNA levels and total LDH activity among the baseline, after the second cycle and controls. The predictive index was determined as a ratio of mRNA or activity in patients to controls. $P < 0.05$ was considered significant for all statistical analyses.

RESULTS

Clinical parameters of study participants

A total of 129 female participants were recruited for the study: 50.38% (n = 65) were diagnosed as breast cancer patients, and 49.62% (n = 64) as the controls. The mean age (49.55, SD 11.98) of the patients compared to the control group and the age distribution was statistically significant (p = 0.009). The BMI and waist-to-hip ratio of patients and control were statistically insignificant (p > 0.05). About 52% (n = 34) of the diagnosed cancer cases occurred in the right breast, 45% (n = 29) in the left breast and about 3% (n = 2) in both breasts. (Table 1). The majority (60.0 %, n = 39) of the patients presented with grade 3. About 31% (n = 20) of the participants were human epidermal growth factor 2

Table 1. Clinical parameters of study participants

Characteristics	Case (N = 65)	Control (N =64)	95% CI of mean difference	p-value
Age (yrs)	49.55 ± 11.98	55.67 ± 13.99	-10.65 – (--1.58)	0.009*
BMI (kg/m^2)	29.35 ± 6.26	27.88 ± 4.55	-0.44 – (3.37)	0.131
W/H ratio	0.97 ± 0.98	0.85 ± .087	-0.12 – (0.36)	0.334
Affected breast	n (%)		-	-
Left	29 (44.6)		-	-
Right	34 (52.3)		-	-
Both	2 (3.1)		-	-

Table 2. Pathological characteristics of breast cancer patients

Characteristics	Frequency n (%)
Cancer Grade	
Grade 1	5 (7.7)
Grade 2	21 (32.3)
Grade 3	39 (60.0)
Molecular subtype	
Luminal A	1 (1.5)
Luminal B	4 (6.2)
Human Epidermal Growth Factor Receptor (HER 2)	20 (30.8)
Triple negative	18 (27.7)
Unknown	22 (33.8)
Stage of breast cancer	
Stage 1	5 (7.7)
Stage 2	21 (32.3)
Stage 3	30 (46.2)
Stage 4	9 (13.8)

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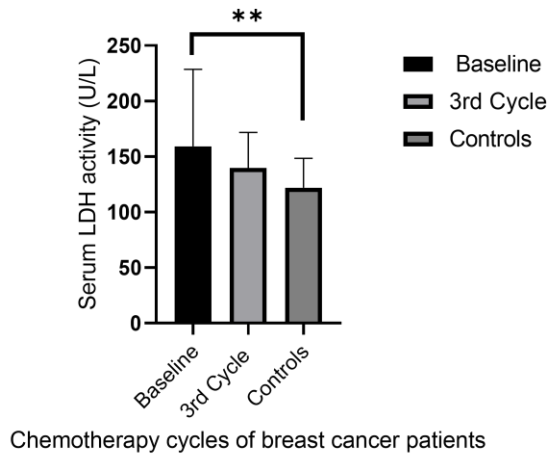

Figure 1. Serum LDH activity in breast cancer patients on chemotherapy. *p < 0.01

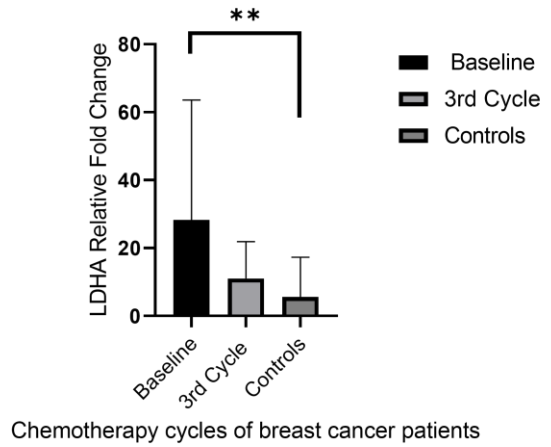

Figure 2. Serum LDHA mRNA expression levels in breast cancer patients on chemotherapy. *p < 0.01

Table 3. Predictive index of serum LDH in chemotherapy response in breast cancer patients

Biomarker	Ratio of mRNA levels and enzyme activity		Change in ratio
	Baseline	3rd Cycle	
LDHA mRNA levels	5.40	2.00	4.2
Total LDH Activity	1.28	1.04	0.24

Ratio was calculated by dividing mean LDH expression fold change or activity in patients by that of the controls.

(HER 2) positive, and 28% (n = 18) showed triple-negative subtypes (Table 2).

Serum total LDH activity

Figure 1 shows the serum LDH activity in breast cancer patients at baseline (chemotherapy-naïve patients) and the third cycle of chemotherapy compared with the apparently healthy controls. The controls showed a statistical significant reduced LDH levels compared to the baseline counterparts ($p < 0.01$). Among the cancer patients, there was a reduced LDH activity at the third cycle of chemotherapy compared to the baseline activity, although the level was not statistically significant ($p > 0.05$).

LDHA expression level

Serum LDHA mRNA expression levels in breast cancer patients at baseline and third cycle of chemotherapy compared with controls are shown in Figure 2. LDHA mRNA expression showed statistically significant increased levels in baseline breast cancer patients as compared to the control ($p < 0.05$). LDHA expression levels were seen to be reduced in third-cycle chemotherapy patients as compared to the baseline in breast cancer patients, even though the difference in levels was not statistically significant ($p > 0.05$). Table 3 shows the baseline and third cycle of the chemotherapy response predictive index in patients relative to the control. The difference between baseline and third cycle ratio for LDHA mRNA expression (4.2) is higher than that of the enzyme activity (0.24).

DISCUSSION

The current study reports a comparative analysis of chemotherapy response predictive indices of serum for the first time.

LDHA mRNA levels and total LDH enzyme activity in breast cancer patients

The serum mRNA level of the patients decreased significantly compared to the enzyme activity after the chemotherapy, and the change in the LDHA mRNA level ratio identifies serum LDHA mRNA as a good candidate for predicting chemotherapy response in patients. The current finding supports an earlier study that reported a decreased level of tumour suppressor gene mRNA in serum as a potential predictive biomarker for chemotherapy [19]. A low level of serum LDH in cancer patients after

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chemotherapy was associated with a longer overall survival [20,21]. Similarly, high lactate dehydrogenase mRNA levels and enzyme activity were associated with breast cancer, and the elevated level and increased activity after the first line of chemotherapy correlated with worse disease outcomes [22,23]. Also, the increased activity of LDH was implicated in several cancers, including nasopharyngeal and gastric cancers [24,25], and the activity has been linked to poor cancer prognosis through an accumulation of lactate [23]. LDH reversibly converts pyruvate in the glycolytic pathway to lactate, a pathway considered crucial in driving anaerobic metabolism to support tumour cell growth and survival [23,24]. A study correlated high levels of lactate with cancer metastasis, recurrence, and poor treatment outcome [27]. In similar studies, the degree of breast cancer progression was found to be dependent on lactate concentration, and the concentration was higher in triple-negative breast cancer tissues than in the blood [28,29]. Lactate is described as an oncometabolite since it creates tumour microenvironment acidosis to favour cancer metastasis, angiogenesis, and immunosuppression [30]. Increased acidosis triggers natural killer (NK) cells' inactivation and ineffective apoptosis, causing immune evasion by cancer cells [30].

Both LDH and lactate levels are considered novel targets for accessing cancer cells' survival and proliferation [31]. LDH isoform activity is tissue-specific, and altered expression and activity of the isoforms are indicative of changes in a tissue's metabolic function, especially in pathological conditions [32]. LDH level or activity as a diagnostic, prognostic or predictive biomarker in serum, pleural fluid, urine and tissues of various cancers has been extensively reviewed [32]. However, some reports have indicated that LDH is a non-specific diagnostic marker for cancers and is not routinely used in clinical laboratories [33]. Also, LDH was reported as non-specific for identifying a type of cancer, and an increase in the level or activity of LDH in cancer patients was attributed to necrosis within the tumour and possible haemolysis [33]. The current study did not establish a relationship between serum LDH profile and pathological outcomes and anthropometric measurements of the patients. A greater proportion of the patients presented with grade 3 and stage 3 advanced breast cancers. Further studies in a large study population to relate LDH profile with clinicopathological outcomes and other exposures, including diet and physical activity, will underscore the predictive value of LDH in Ghanaian breast cancer patients.

Conclusion

Serum LDHA mRNA levels and total LDH activity in breast cancer patients were reduced after the third-cycle chemotherapy. Reduction in the mRNA level was highly noticeable compared to the enzyme activity. Further study to establish the relationship between serum LDHA mRNA levels and clinic-pathological will strengthen the predictiveness of serum LDH for monitoring chemotherapy response in the patients.

DECLARATIONS

Ethical consideration

The study protocol was approved by the Ethical and Protocol Review Committee of the College of Health Sciences, University of Ghana. Protocol Identification CHS-Et/M:8-p4.12014-2015. Written informed consent was obtained from all study participants.

Consent to publish

All authors agreed on the content of the final paper.

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None

Competing Interest

The authors declare no conflict of interest for this paper

Author contributions

EAT, BA-B, JN, and OQ conceptualised and designed the work. GKA, NE-BA and PMA conducted the experiments. EAT, DO, and OQ analysed data and interpreted the results. GKA, DO, JN, and SS wrote the manuscript. All authors reviewed the manuscript and approved the submitted version.

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Availability of data

Data is available upon request to the corresponding author

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