Article published online: 2025-12-10

Original Article

Effect of Neoadjuvant Chemotherapy on Endothelial Function, Stress Levels, and Oncovascular Risk Factors Among Patients with Locally-Advanced Primary Breast Cancer: A Prospective Analytical Study

Injamam ul Hossain[1] Zachariah Bobby[1] Prasanth Ganesan[2] Sunitha V. C.[3] Kamila Thalapalliyil[1]

[1] Department of Biochemistry, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry, India
[2] Department of Medical Oncology, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry, India
[3] Department of Radiodiagnosis, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry, India

Address for correspondence Zachariah Bobby, PhD, Department of Biochemistry, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry 605006, India (e-mail: zacbobby@yahoo.com).

Ind J Med Paediatr Oncol

Abstract

Introduction Neoadjuvant chemotherapy (NACT) is expected to cause cardiovascular complications among patients with breast cancer (BC). Cytoadipokines (Leptin, adiponectin) and cell adhesion molecules (CAMs) have been associated with BC pathogenesis. Psychological distress has been reported in patients with BC. Cardiovascular disorders and endothelial dysfunction are expected to be higher among BC patients who receive NACT.

Objective To assess the effect of NACT on cardiovascular function, various endovascular factors such as leptin, adiponectin, sICAM, sVCAM, and stress levels in patients with locally-advanced primary BC.

Materials and Methods Forty newly diagnosed patients with BC who had planned for NACT were recruited, and the following assessments were performed before and after NACT. Endothelial function was assessed by brachial artery flow-mediated dilation (baFMD) using color Doppler. Stress level was assessed by questionnaires, PSS (perceived stress scale), PHQ-9 (Patient Health Questionnaire-9), and GAD-7 (generalized anxiety disorder-7). Blood levels of oncovascular risk factors (leptin, adiponectin) and CAMs (sVCAM, sICAM) were assessed by ELISA.

Results There was increased endothelial dysfunction (baFMD: 10.8 [8.3–14.2] and 6.5 [2.9–11.4]; $p < 0.01$), decreased serum leptin levels (30.1 [24.3–40.9] and 20.4 [13.1–30.6]; $p < 0.01$), trends for increased adiponectin/leptin ratio (1.69 [0.95–3.6] and 2.73 [1.72–5.76]; $p = 0.067$) and sICAM (283.1 [231.9–357.0] and 323.5 [261.4–395.8]; $p = 0.063$) levels after NACT. Stress levels (PSS: 7 [5–10] and 9 [7–14]; $p = 0.007$, PHQ-9: 4 [2–5] and 8 [4–11], $p < 0.01$ and GAD-7: 2 [2–4] and 6 [4–9], $p < 0.001$) were found to be increased after the NACT. Dyslipidemia was also observed after chemotherapy.

Conclusion NACT was associated with increased endothelial dysfunction, stress levels, dyslipidaemia, and altered onco-vascular risk factors among the BC patients.

Keywords
- cell adhesion
- cardiovascular diseases
- risk factors
- cytokines
- adipokines
- stress
- psychological
- generalized anxiety disorder

DOI https://doi.org/10.1055/s-0045-1814392.
ISSN 0971-5851.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Introduction

Breast cancer (BC) is the most common cancer among women worldwide.[1] Onco-vascular risk factors are implicated in both cancer and cardiovascular disease pathogenesis.[2–5] Specific factors, such as leptin, adiponectin, and cell adhesion molecules (CAMs) such as sICAM-1 and sVCAM-1, are involved in the pathogenesis of BC.[2] Neoadjuvant chemotherapy (NACT) in BC is administered before surgical treatment of patients with locally advanced malignant tumors and may impact the oncovascular risk factors.[6] NACT affects shared pathways in cancer and cardiovascular disease, increasing long-term CV risk in BC patients. Various studies suggested that chemotherapeutic regimens such as docetaxel, doxorubicin, and cyclophosphamide, etc., cause impaired vascular function through different mechanisms.[7]

Adiponectin is an insulin-sensitizing hormone produced by adipocytes that maintains metabolic homeostasis. Serum adiponectin levels show an inverse relationship with BC development and with the biologically aggressive phenotype of the tumor.[3] In BC, adiponectin manifests pro-apoptotic, anti-proliferative, and anti-migratory effects.[8]

Leptin is an anorexigenic hormone that suppresses appetite through a hypothalamic central feedback mechanism. It is mainly secreted by adipose tissue. In BC, leptin signaling regulates the expression of vascular endothelial growth factor, E-cadherin, survivin, cyclin D1, p53, and other tissue factors. All these molecules are involved in inflammation, angiogenesis, proliferation, invasion, and migration.[4] The adiponectin/leptin ratio is inversely related to the cell survival and tumor proliferation of BC.[9]

Vascular endothelial growth factors (VEGFs), known as CAMs, are expressed on endothelial surfaces. Both ICAM-1 and VCAM-1 play significant roles in the process of BC pathogenesis; sICAM-1 and sVCAM-1 are their soluble forms. The activated endothelial cells can secrete these soluble forms into the bloodstream. The serum concentrations of sVCAM-1 and sICAM-1 are directly related to the pathogenesis of BC and vascular endothelial dysfunction. These VEGFs have pro-angiogenic actions.[10]

A higher rate of depression is seen in BC patients undergoing chemotherapy.[11] The higher levels of pro-inflammatory cytokines released from tissue damage during chemotherapy can promote pain, depression, and fatigue. The chemotherapy causes a decline in estrogen. Estrogen has a role in increasing the brain's sensitivity to serotonin. The decrease in estrogen may also cause depression. Anxiety co-exists with depression in BC and may be increased by chemotherapy.

Brachial artery flow-mediated dilatation (baFMD) can evaluate endothelial function, which can be assessed by noninvasive ultrasonography. Several chronic conditions can affect endothelial function, like hypertension, smoking, hypercholesterolemia, diabetes, and obesity. Mental stress, sleeplessness, and hormonal changes can acutely affect endothelial function. Trastuzumab-mediated endothelial dysfunction was observed in a study conducted by Aamer et al among BC patients.[12] There is only scanty information available about the stress levels and endothelial dysfunction among BC patients who receive NACT.

In the present study, we compared the serum onco-vascular risk factors, stress levels, and vascular endothelial function before and after NACT among a cohort of locally advanced primary BC patients to assess the effect of chemotherapy.

Materials and Methods

Study Design

This prospective analytical study was performed in the Department of Biochemistry in collaboration with the Departments of Medical Oncology and Radio diagnostics of our Institute. The participants of the study were recruited from the outpatient Department of Medical Oncology.

Sample Size

The sample size was calculated based on the most important clinical outcome parameter, baFMD. Lee et al reported a decrease in baFMD after chemotherapy.[13] They reported a decrease in baFMD from11.21 ± 4.45 before chemotherapy to 6.11 ± 2.13 after chemotherapy. The sample size was calculated using www.OpenEpi.com. Based on the above observation, the initial estimate was 17 in the group of study with a 99% CI and a power of 95%. With an expected dropout of 25%, the sample size was corrected to 25. Julia et al reported an increase in generalized anxiety disorder and depression in a group of 32 BC patients receiving chemotherapy.[14] Hence, to adjust for multiple comparisons before and after chemotherapy, we chose a larger sample size of 40. This sample size was found to be sufficient for the other parameters of the study as well.

Inclusion and Exclusion Criteria

Newly diagnosed postmenopausal locally advanced BC (LABC) patients between the age group of 50 to 65 years and having haemoglobin levels >10 g/dL and who were planned for NACT, were recruited from the Department of Medical Oncology of our Institute. Patients having a BMI > 28 kg/m^2 and BMI < 18 kg/m^2, and patients having liver and kidney disease and metastasis were excluded. The age group was restricted to postmenopausal women of 50 to 65 years. Although this reduces the generalizability of the study, it was expected to avoid the influence of female reproductive hormones on the study outcome.

Methods

Patients were explained briefly about the study protocol, and written informed consent was obtained. The standard NACT delivered at our center consisted of three cycles of FEC (five fluorouracil, epirubicin, cyclophosphamide) and four cycles of docetaxel 75 mg per m^2 dose (all cycles were delivered in 3 weekly intervals).[15] Patients who were HER2 positive received neoadjuvant trastuzumab (8 mg per kg in cycle 1 and 6 mg per kg in subsequent cycles) along with the docetaxel cycles (once in 3 weeks). Our objective was to assess the

cumulative effect of NACT on cardiac function and not its immediate acute effects.

Assessment of Stress Levels

The stress levels were assessed by standardized questionnaires such as PSS (perceived stress scale),[16] PHQ-9 (Patient Health Questionnaire-9),[17] and GAD-7 (generalized anxiety disorder-7).[18]

Assessment of Blood Levels of Oncovascular Factors

Serum biomarkers: 5 mL of fasting blood samples were collected from study participants before the first cycle of NACT. The post samples were collected approximately 2 to 3 days after the last chemotherapy to avoid acute drug effect bias. However, the samples were collected within 1 week. The blood samples were taken before and after the seven cycles of NACT (approximately 5–6 months). The blood samples were taken on days when NACT was not administered. The first blood sample was taken on the day before the start of the cycles of chemotherapy, and the second sample was taken on days after the last chemotherapy when the patient came for follow-up. Serum samples were stored at −20°C within 30 minutes of blood collection. Serum adiponectin, sICAM, and sVCAM were estimated using commercial ELISA kits from Ray Biotech, USA. Serum leptin level was estimated using the DBC ELISA kit.

Endothelial function: brachial artery FMD (baFMD) was performed in the department of radiodiagnosis at baseline and after seven cycles of chemotherapy. The baFMD technique assessed endothelial function using Color Doppler (Esaote MyLab9 eXP, Italy). Before the baFMD assessment, participants rested for a minimum of 15 minutes; then, basal measurement was performed in the distal third of the upper arm using a USG probe with a frequency range of 3 to 7 MHz. After the basal brachial artery diameter (BBAD) measurement, a BP cuff was positioned on the arm 1 cm distal to the antecubital fossa to stimulate forearm ischemia. The BP cuff pressure was raised >50 mm Hg compared with the systolic blood pressure and kept for 5 minutes, and then the BP cuff was deflated. After deflation, the brachial artery diameter was measured at 30-second intervals for 2 minutes. Among the four diameter values (30 seconds, 1 minute, 1 minute 30 seconds, and 2 minutes), peak values were taken as post-occlusion brachial artery diameter (POBAD). baFMD was calculated using this formula, baFMD (%) = (POBAD − BBAD)/BBAD ×100.[12,13,19]

Statistical Analysis

The Kolmogorov–Smirnov test was used to check the normal distribution of the data. A paired *t*-test was used for normally distributed data, and a Wilcoxon signed-rank test was used for nonnormally distributed data. The McNemar test was used for nominal data analysis. p-Value < 0.05 is considered statistically significant. To control for Type I error due to multiple comparisons, we applied the Bonferroni correction. The adjusted significance threshold was calculated by dividing the standard α level (0.05) by the number of comparisons (n). The effect size was calculated using Cohen's d formula.[20]

Table 1 Baseline and treatment characteristics of the patients

Parameters	*n* (%)
Age in years (mean ± SD)	55 ± 5
Menopausal status	
Premenopausal	0 (0)
Postmenopausal	40 (100)
T-stage:	
T2	11 (28)
T3	13 (33)
T4	13 (33)
N-stage	
N1	16 (40)
N2	11 (28)
ER positive	18 (45)
PR positive	14 (35)
HER2 positive	10 (25)
Triple-negative	11 (28)

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor-2; PR, progesterone receptor.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Institute Ethics Committee (JIP/IEC/202/129, dated June 23, 2021). Written consent was obtained from the patients in the study.

Results

Baseline Characteristics

Between August 2021 and May 2022, 40 patients with BC were recruited. The mean age was 55 years (►**Table 1**). The stage was T3 in 33% and T4 in 33% of patients, and 68% had node-positive disease. The proportion of patients with hormone-positive and triple-negative disease was 80 and 28%, respectively.

Effect of NACT on BMI, Lipid Profile, and Fasting Blood Glucose Levels

Among BC patients statistically significant increase in blood pressure, BMI, total cholesterol, triglycerides (TGs), LDL-cholesterol, and non-HDL-cholesterol was observed after the NACT. There was a trend toward an increase in the fasting blood glucose levels, which did not reach statistical significance. (►**Table 2**). However, the overall change in blood pressure range did not reach the clinically significant range of hypertension. The overall change in fasting blood glucose also did not reach the diagnostic range of diabetes mellitus.

Table 2 Comparison of blood pressure, BMI, lipid profile, and fasting blood sugar (FBS) level among breast cancer patients before and after NACT

Parameters	Before chemotherapy; $n = 40$	After chemotherapy; $n = 40$	*p*-Value
Systolic blood pressure (mm Hg)	122.1 ± 8.4	128 ± 10.2	<0.01[a]
Diastolic blood pressure (mmHg)	80.8 ± 3.1	82.4 ± 3.9	0.018[a]
BMI (kg/m^2)	24.8 (21–26.7)	24 (20.4–26.1)	<0.01[a]
FBS (mg/dL)	106 (94–140)	120 (102–163)	0.08
Total cholesterol (mg/dL)	203 ± 46	216 ± 54	0.022[a]
LDL-cholesterol (mg/dL)	133 ± 33	143 ± 36	0.035[a]
TGs (mg/dL)	172 (117–216)	197 (143–261)	0.005[a]
HDL-cholesterol (mg/dL)	36 (30–47)	34 (30–44)	0.467
Non-HDL cholesterol (mg/dL)	164 ± 45	179 ± 50	0.008[a]
VLDL-cholesterol (mg/dL)	34 (23–43)	38 (27–52)	0.021[a]

[a]*p*-Value < 0.05 is considered statistically significant.

Table 3 Comparison of serum leptin, adiponectin, adiponectin/leptin ratio, sVCAM-1, sICAM-1 levels, and baFMD among breast cancer patients before and after chemotherapy

Parameters	Before chemotherapy; $n = 40$	After chemotherapy; $n = 40$	*p*-Value
Leptin (ng/mL)	30.1 (24.3–40.9)	20.4 (13.1–30.6)	<0.01[a]
Adiponectin (μg/mL)	58.4 (43.2–80.0)	54.6 (40.0–85.5)	0.528
Adiponectin/Leptin	1.69 (0.95–3.6)	2.73 (1.72–5.76)	0.067
sICAM-1 (ng/mL)	283.1 (231.9–357.0)	323.5 (261.4–395.8)	0.063
sVCAM-1 (ng/mL)	391.6 (314.8–516.4)	395.5 (316.1–541.7)	0.361
baFMD (%)	10.8 (8.3–14.2)	6.5 (2.9–11.4)	<0.01[a]

Abbreviations: baFMD, brachial artery flow-mediated dilation; sICAM-1, soluble intercellular adhesion molecule-1; sVCAM-1, soluble vascular cell adhesion molecule 1.
[a]*p*-Value < 0.05 is considered statistically significant.

Effect of NACT on Serum Leptin, Adiponectin, sICAM, sVCAM, and baFMD Levels

There was a significant ($p < 0.01$) decrease in the leptin levels and baFMD after chemotherapy among the BC patients. There was a trend toward an increase in the adiponectin/leptin ratio and sICAM levels after chemotherapy among the patients (►**Table 3**; ►**Fig. 1A, B**)

Effect of NACT on Perceived Stress, Depression, and Anxiety among BC Patients

There was a significant increase in perceived stress, depression, and anxiety among BC patients after chemotherapy (►**Table 4**; ►**Fig. 2A–C**).

There was a significant decrease in serum leptin level after NACT with a medium effect size; additionally, there was a significant increase in anxiety and depression after NACT with a larger effect size (►**Table 5**).

Further, there was a significant increment in the frequency of depression and anxiety among the BC patients after chemotherapy (►**Table 6**).

Thirty-five percent of the patients shifted to mild and above depression level, and 53% patients shifted to mild and above anxiety level after NACT.

Correlation Analysis Between Various Parameters Before NACT

There was a significant positive correlation between baFMD, GAD-7, PHQ-9, and CAMs like sICAM-1, sVCAM-1 (►**Table 7**).

Correlation Analysis Between Various Parameters After NACT

There was a significant positive correlation between PSS, PHQ-9, and GAD-7 scores after NACT (►**Table 8**).

Discussion

The potential risk for cardiovascular disorders, endothelial dysfunction, and psychological stress is expected to be higher among the BC patients who received NACT. This could increase the morbidity and mortality of BC patients. This study demonstrates the significant impact of NACT on serum biomarkers and clinical stress assessment in patients with LABC. Along with changes in stress levels and elevation of markers associated with cardiovascular disorders, altered endothelial function was also observed. This is one of the first studies examining several factors contributing to cardiovascular diseases.

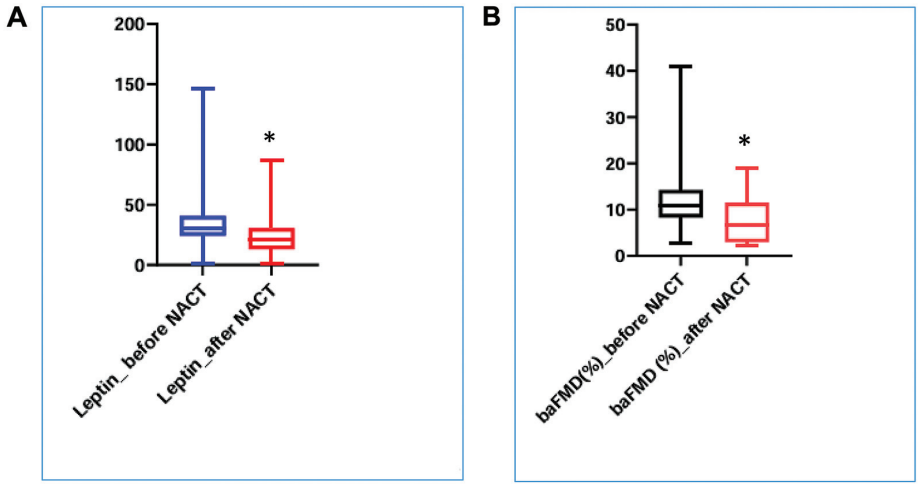

Fig. 1 Effect of NACT on serum leptin levels and baFMD (%). (**A**) On serum leptin levels and (**B**) on baFMD (%). *p-Value < 0.05 is considered statistically significant.

This study observed a significant decrease in serum leptin levels after NACT among the BC patients. There are no previous reports of serum leptin levels in LABC patients undergoing NACT. Tas et al reported decreased serum leptin levels in nonsmall cell lung cancer after chemotherapy.[21] From the available information in the literature, it is impossible to explain the decrease in leptin after chemotherapy. The leptin production is under the strict control of pro-inflammatory cytokine action, especially TNF-α and IL-6, through upregulation of the "ob" gene expression. This may be taken into consideration when providing an explanation.[14] Leptin is considered a cardiovascular risk factor.[22] In cross-sectional studies, increased leptin levels have been reported among BC patients compared with healthy controls.[23] Since leptin is elevated in both cardiovascular diseases and cancer, it may be considered an oncovascular risk factor. The reduced leptin levels observed in the study after NACT may be reducing CV risk.

Although changes in the adiponectin levels were not found, trends of an increase in the adiponectin/leptin ratio after chemotherapy among the BC patients were observed ($p = 0.067$). According to Gema et al, an Adiponectin/Leptin ratio is considered normal when equal to or higher than 1.0, where adiponectin and leptin levels are expressed in µg/mL and ng/mL, respectively. Moderate-medium increased risk is predicted for a ratio between 0.5 and 1.0, and a severe increase in cardio-metabolic risk is suggested for a ratio below 0.5.[24] Among our patients, the ratio was already more than 1.0 (1.69) before chemotherapy, which increased to 2.73 after the chemotherapy. This observation may be explained as part of the ongoing defense mechanism against the toxicity of NACT. It may also be explained by the effect of chemotherapy in reducing the cancer burden. NACT could have reduced the baseline inflammatory state.

Several studies reported higher levels of CAMs among the BC patients compared with healthy controls.[2,25] CAMs

Table 4 Comparison of PSS, PHQ-9, and GAD-7 scores among breast cancer patients before and after chemotherapy

Questionnaire	Reference range	Before chemotherapy; $n = 40$	After chemotherapy; $n = 40$	p-Value
PSS (score)	0–13: low stress 14–26: moderate stress 27–40: high stress	7 (5–10)	9 (7–14)	0.007[a]
PHQ-9	0–4: minimal depression 5–9: mild depression 10–14: moderate depression 15–19: moderately severe depression 20–27: severe depression	4 (2–5)	8 (4–11)	<0.01[a]
GAD-7	0–4: minimal anxiety 5–9: mild anxiety 10–14: moderate anxiety 15–21: severe anxiety	2 (2–4)	6 (4–9)	<0.01[a]

Abbreviations: GAD-7, generalized anxiety disorder-7; PHQ, Patient Health Questionnaire-9; PSS, perceived stress scale.
[a]p-Value < 0.05 is considered statistically significant.

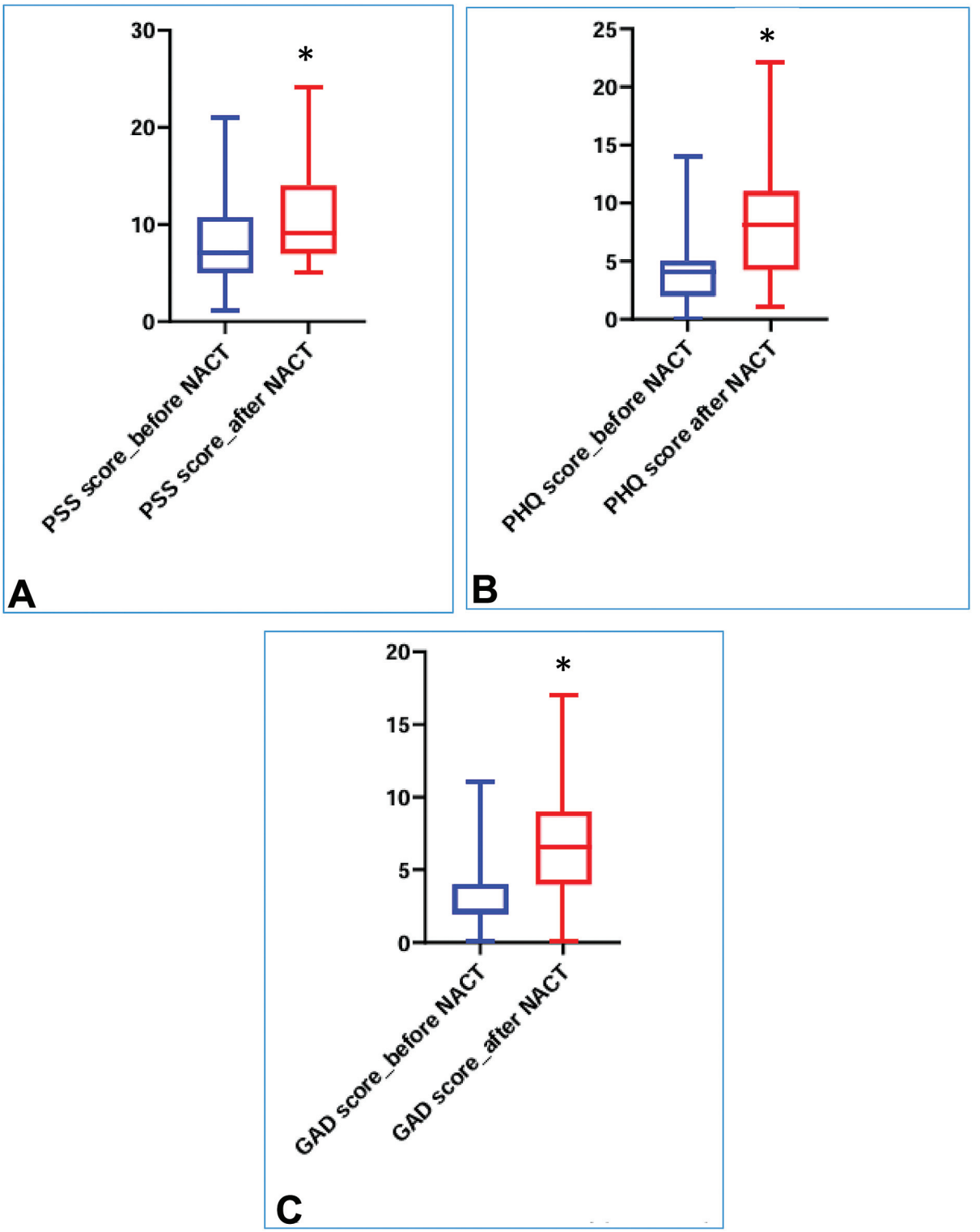

Fig. 2 Effect of NACT on stress parameters. (**A**) Effect of NACT on stress level (PSS score), (**B**) effect of NACT on depression (PHQ-9 score), and (**C**) effect of NACT on anxiety (GAD-7 score). *p-Value < 0.05 is considered statistically significant.

Table 5 Effect size of significant parameters with 95% confidence interval

Parameters	Before chemotherapy; $n = 40$; 95% confidence interval	After chemotherapy; $n = 40$; 95% confidence interval	Effective size (Cohen's *d*)
Leptin (ng/mL)	28.3–46.4	18.2–29.8	0.5
baFMD (%)	9.8–14	6.2–9.3	0.3
PSS (score)	6.8–9.8	9–12.1	0.4
PHQ-9 (score)	3.3–5.2	6.9–10.3	1.0
GAD-7 (score)	2.2–3.6	5.7–8.5	1.16

Abbreviations: GAD-7, generalized anxiety disorder-7; PHQ, Patient Health Questionnaire-9; PSS, perceived stress scale.

Table 6 Effect of NACT on frequency of depression, anxiety, and stress among breast cancer patients

Effect of NACT on the frequency of depression among breast cancer patients			
Group	Minimal depression; PHQ-9 Score (0–4)	Mild and above depression; PHQ-9 score ≥ 5	*p*-Value
Before chemotherapy; $n = 40$	24	16	0.002[a]
After chemotherapy; $n = 40$	10	30	
Effect of NACT on the frequency of anxiety among breast cancer patients			
	Minimal anxiety; GAD-7 score (0–4)	Mild and above anxiety;GAD-7 score ≥ 5	*p*-Value
Before chemotherapy; $n = 40$	33	7	<0.01[a]
After chemotherapy; $n = 40$	12	28	
Effect of NACT on the frequency of stress among breast cancer patients			
	Minimal stress PSS; score 0–13	Mild and above stress; PSS score >13	*p*-Value
Before chemotherapy; $n = 40$	34	6	0.109
After chemotherapy; $n = 40$	28	12	

[a]*p*-Value < 0.05 is considered statistically significant.

Table 7 Correlation analysis between various parameters before NACT

Parameter	Parameter	*r*-Value	*p*-Value
baFMD (%)	GAD-7	0.33	0.038[a]
PHQ-9	GAD-7	0.56	<0.01[a]
sICAM-1	sVCAM-1	0.38	0.015[a]

[a]*p*-Value < 0.05 is considered statistically significant.

Table 8 Correlation analysis between various parameters after NACT

Parameter	Parameter	*r*-Value	*p*-Value
PSS	PHQ-9	0.63	<0.01[a]
PSS	GAD-7	0.67	<0.01[a]
PHQ-9	GAD-7	0.85	<0.01[a]

[a]*p*-Value < 0.05 is considered statistically significant.

promote tumor vascularisation, serving as pro-angiogenic factors. The migration of cancer cells and tumor growth are also promoted by sICAM-1 and sVCAM-1 CAMs.[2] No reports are available on the effect of NACT on the levels of CAMs among BC patients. We found trends of an increase in serum sICAM level ($p = 0.063$) among our BC patients after NACT, with no significant changes in the sVCAM levels. However, Maria et al reported an increase in the levels of serum CAMs among BC patients after cancer treatments in the form of surgery and radiotherapy.[26] This may be explained by the enhanced release of the CAMs from the endothelial surface due to cancer therapy.

Elevated serum concentrations of CAMs, sVCAM-1, and sICAM-1 were found in patients with coronary artery

disease.[10] sVCAM-1 is a biomarker that predicts the occurrence, development, and preservation of cardiovascular disease.[26] Since these molecules are found to be elevated in both cardiovascular diseases and cancer, they may be addressed as oncovascular risk factors, a term yet to be coined in the literature. The pathological basis for the increase in these risk factors in cancer and coronary artery diseases is far from clear and needs to be further investigated.

Compared with a baFMD value of 40 in healthy Indians,[3] there was a significant reduction in the levels of baFMD among our BC patients (10.8). This further decreased to 6.5 after the chemotherapy, indicating further deterioration of endothelial function. The only previous study conducted by Lee et al in this regard reports increased endothelial dysfunction in BC patients who received anthracycline-based chemotherapy.[19] Longer-term follow-up studies have indicated that patients who receive chemotherapy may have adverse cardiovascular outcomes later in life. Impaired baFMD may be an early indicator of this problem.

Perceived stress levels, depression, and anxiety may increase among BC patients during chemotherapy due to the release of pro-inflammatory cytokines from tissue damage. Depression is also caused by the decrease in estrogen during chemotherapy. In this study, a significant increase in psychological stress, anxiety, and depression was observed among the BC patients after NACT. A significant portion of patients progressed from minimal to mild and above depression and from minimal anxiety to mild and above anxiety. The only other study in this regard by Reece et al reported high stress and anxiety levels in BC patients after chemotherapy.[21] The inflammation can also promote cardiovascular risk and endothelial dysfunction. Therefore, all three areas of our study, cardiovascular risk, endothelial dysfunction, as well as perceived stress, depression, and anxiety, may be interconnected. However, no correlations were observed between oncovascular risk factors and stress parameters, probably due to the effect of chemotherapy. However, baFMD (%) correlated with GAD-7.

None of the study's patients had any disease progression during chemotherapy. Therefore, the biochemical, radiological, and psychological changes observed could be attributed to the effects of chemotherapy.

Strengths and Limitations

This was a comprehensive study that assessed the effect of NACT on psychological distress, endothelial function, and onco-vascular risk factors among patients with BC. One of the limitations of the study is the smaller sample size.

Future and Generalizability of Research

The same study may be performed in multiple centers to confirm the result and the generalizability of the findings.

Conclusion

NACT of patients with locally advanced primary BC was associated with increased endothelial dysfunction, perceived stress, depression, and anxiety, as well as resulting in changes in onco-vascular risk factors and dyslipidaemia. Future studies may include follow-up of these patients to understand the recovery or persistence of these comorbidities after chemotherapy. This study was of an exploratory nature, and there is a need for larger, multicenter, long-term follow-up.

Data Availability Statement

The authors hereby state the availability of the data in the manuscript.

Authors' Contributions

I.H.: Experimental studies, data acquisition, data analysis, statistical analysis, and manuscript preparation. Z.B.: Concept, design, definition of intellectual content, literature search, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing, and manuscript review. P.G. and S.V.C.: Concept, design, data acquisition, and manuscript review. K.T.: Statistical analyses and manuscript review. The manuscript has been read and approved by all the authors, the requirements for authorship have been met, and each author believes that the manuscript represents honest work and that the information is not provided in another form.

Patient's Consent

Informed consent for publication was obtained from the participants.

Funding

The study was performed with financial support through an intramural grant from our institute (JIP/Res/Intramural/phs-2/2021–22 dated August 17, 2021).

Conflict of Interest

None declared.

Acknowledgment

The authors' institute's (Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry) financial support as intramural funds is gratefully acknowledged.

References

1 Shah R, Rosso K, Nathanson SD. Pathogenesis, prevention, diagnosis and treatment of breast cancer. World J Clin Oncol 2014;5 (03):283–298

2 Thielemann A, Baszczuk A, Kopczyński Z, Nowak A, Grodecka-Gazdecka S. The clinical usefulness of assessing the concentration of cell adhesion molecules sVCAM-1 and sICAM-1 in the serum of women with primary breast cancer. Contemp Oncol (Pozn) 2014; 18(04):252–259

3 Miyoshi Y, Funahashi T, Kihara S, et al. Association of serum adiponectin levels with breast cancer risk. Clin Cancer Res 2003;9 (15):5699–5704

4 Sánchez-Jiménez F, Pérez-Pérez A, de la Cruz-Merino L, Sánchez-Margalet V. Obesity and breast cancer: role of leptin. Front Oncol 2019;9:596
5 Tas F, Duranyildiz D, Argon A, et al. Serum levels of leptin and proinflammatory cytokines in advanced-stage non-small cell lung cancer. Med Oncol 2005;22(04):353–358
6 Kong Y, Dong Q, Ji H, et al. The effect of the leptin and leptin receptor expression on the efficacy of NACT in breast cancer. Med Sci Monit 2019;25:3005–3013
7 Szczepaniak P, Siedlinski M, Hodorowicz-Zaniewska D, et al; The Journal of Clinical Investigation. Breast cancer chemotherapy induces vascular dysfunction and hypertension through a NOX4-dependent mechanism. J Clin Invest 2022;132(13):e149117
8 Christodoulatos GS, Spyrou N, Kadillari J, Psallida S, Dalamaga M. The role of adipokines in breast cancer: current evidence and perspectives. Curr Obes Rep 2019;8(04):413–433
9 Grossmann ME, Cleary MP. The balance between leptin and adiponectin in the control of carcinogenesis - focus on mammary tumorigenesis. Biochimie 2012;94(10):2164–2171
10 Hulok A, Sciborski K, Marczak J, Bańkowski T, Poręba R, Negrusz-Kawecka M. Soluble cell adhesion molecules - does estimating sVCAM-1 and sICAM-1 concentration provide additional information about cardiovascular risk in patients with coronary artery disease? Adv Clin Exp Med 2014;23(05):735–741
11 Alagizy HA, Soltan MR, Soliman SS, Hegazy NN, Gohar SF. Anxiety, depression and perceived stress among breast cancer patients: single institute experience. Middle East Current Psychiatry. 2020;27:29
12 Sandoo A, Kitas GD, Carmichael AR. Endothelial dysfunction as a determinant of trastuzumab-mediated cardiotoxicity in patients with breast cancer. Anticancer Res 2014;34(03):1147–1151
13 Lee K, Kang I, Mack WJ, et al. Effects of high-intensity interval training on vascular endothelial function and vascular wall thickness in breast cancer patients receiving anthracycline-based chemotherapy: a randomized pilot study. Breast Cancer Res Treat 2019;177(02):477–485
14 Reece JC, Chan Y-F, Herbert J, Gralow J, Fann JR. Course of depression, mental health service utilization and treatment preferences in women receiving chemotherapy for breast cancer. Gen Hosp Psychiatry 2013;35(04):376–381
15 Dhanraj KM, Dubashi B, Gollapalli S, Kayal S, Cyriac SL. Comparison of efficacy of neoadjuvant chemotherapy FEC 100 and Docetaxel 75 versus AC and docetaxel in locally advanced breast cancer: a randomized clinical study. Med Oncol 2015;32(12):261
16 Percieved stress scale.pdf [Internet]. [cited 2021 Mar 27]. Accessed December 1, 2025 at: https://das.nh.gov/wellness/docs/percieved%20stress%20scale.pd
17 Patient-Health-Questionnaire.pdf [Internet]. [cited 2021 Mar 27]. Accessed December 1, 2025 at: https://www.ncor.org.uk/wp-content/uploads/2012/12/patient-health-questionnaire.pdf
18 GAD7 Anxiety Test Questionnaire [Internet]. [cited 2021 Mar 11]. Accessed December 1, 2025 at: https://patient.into/doctor/generalised-anxiety-disorder-assessment-gad-7
19 Meirelles CdeM, Leite SP, Montenegro CA, Gomes PS. Reliability of brachial artery flow-mediated dilatation measurement using ultrasound. Arq Bras Cardiol 2007;89(03):160–167, 176–183
20 Lakens D. Calculating and reporting effect sizes to facilitate cumulative science: a practical primer for t-tests and ANOVAs. Front Psychol 2013;4:863
21 Thijssen DHJ, Bruno RM, van Mil ACCM, et al. Expert consensus and evidence-based recommendations for the assessment of flow-mediated dilation in humans. Eur Heart J 2019;40(30):2534–2547
22 Alemán MR, Santolaria F, Batista N, et al. Leptin role in advanced lung cancer. A mediator of the acute phase response or a marker of the status of nutrition? Cytokine 2002;19(01):21–26
23 Koh KK, Park SM, Quon MJ. Leptin and cardiovascular disease: response to therapeutic interventions. Circulation 2008;117(25):3238–3249
24 Adel MA, Hala A, Kamel A, Hassanien MFR, Assiri. Resistin, Visfatin, Adiponectin, and Leptin: Risk of Breast Cancer in Pre- and Postmenopausal Saudi Females and Their Possible Diagnostic and Predictive Implications as Novel Biomarkers. Hindawi Publishing Corporation Disease Markers.; 2015
25 Frühbeck G, Catalán V, Rodríguez A, Gómez-Ambrosi J. Adiponectin-leptin ratio: a promising index to estimate adipose tissue dysfunction. Relation with obesity-associated cardiometabolic risk. Adipocyte 2018;7(01):57–62
26 Regidor PA, Callies R, Regidor M, Schindler AE. Expression of the cell adhesion molecules ICAM-1 and VCAM-1 in the cytosol of breast cancer tissue, benign breast tissue and corresponding sera. Eur J Gynaecol Oncol 1998;19(04):377–383

