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Corelation between Lipid Profile and Systemic Oxidative Stress in Breast Cancer – A Prognostic Approach

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Abstract

Introduction: Breast cancer is the leading cancer among women globally. It is associated with dyslipidemia and oxidative stress, which contribute to its pathogenesis. This study aimed to assess lipid profiles and oxidative stress markers (MDA, Total Bilirubin, Uric Acid) to evaluate their prognostic value in breast cancer patients.

Materials & Methods: A case-control study was conducted on 30 breast cancer patients and 30 healthy controls. Lipid profiles (Total Cholesterol, HDL, LDL, Triglycerides) and oxidative stress markers were measured using standard biochemical methods.

Results: Breast cancer patients exhibited significantly higher levels of Total Cholesterol (Stage 1: 200±15.4 mg/dL; Stage 2: 232±24 mg/dL) compared to controls (181.03±13.54 mg/dL), with a **p-value <0.001**. Triglycerides were also elevated (Stage 1: 142±20 mg/dL; Stage 2: 166±28 mg/dL) against controls (110.8±19.32 mg/dL), with **p-value <0.005**. HDL levels were significantly lower in patients (Stage 1: 30±1.8 mg/dL; Stage 2: 28±2.6 mg/dL) versus controls (41.03±5.53 mg/dL), **p-value <0.001**. LDL levels increased in breast cancer patients (Stage 1: 100±10.6 mg/dL; Stage 2: 124±20.2 mg/dL) compared to controls (86±20.43 mg/dL), **p-value <0.001**. MDA levels, indicating oxidative stress, were significantly higher in both Stage 1 (0.7625±0.0836 nmol/mL) and Stage 2 (0.92±0.0371 nmol/mL) compared to controls (0.14±0.056 nmol/mL), **p-value <0.001**.

Conclusion: Dyslipidaemia and oxidative stress markers like MDA are closely associated with breast cancer progression. Monitoring lipid profiles, especially HDL, and MDA levels could be useful as diagnostic and prognostic tools in breast cancer management.

Keywords: Breast cancer, Oxidative stress, Lipid profile, MDA, Prognosis

Introduction

Breast cancer is the most common cancer affecting women globally, with approximately 2.3 million new cases diagnosed in 2020, accounting for around 25% of all cancers in women. The incidence rates show significant variation worldwide, ranging from 27 cases per 100,000 women in regions like Middle Africa and East Asia, to 92 per 100,000 in North America. In low-resource countries, one in 28 women will develop breast cancer during their lifetime, and for every two women diagnosed, one will lose her life to the disease. [1] Prevalence is rising at an alarming rate with lifestyle modernization, altered fertility pattern, and improved socioeconomic status, which imposes an enormous economic burden on health care system. [2] Several etiological factors like age, environmental and genetic factors, endogenous and exogenous endocrine factors have been implicated in the pathogenesis of breast cancer. With this Increasing incidence & prevalence, it is matter of prime concern to keep check on lifestyle modification which may alter the normal Biochemical parameters therefore, there is need of simple biochemical investigations, which can be easily assayed, are less expensive & will guide to decrease the incidence & prevalence of disease and eventually helps to keep check on progression. In view of this, present study was undertaken to assess the clinical utility of certain biochemical investigations -, oxidative stress (OS) Markers (MDA, Total Bilirubin, Uric acid), Lipid Profile – for Prognosis and monitoring in patients of Breast Carcinoma.

Recent research indicates that lipid profiles, including cholesterol, triglycerides, and other lipid-related markers, may have significant relevance in breast cancer. Several studies have found that alterations in lipid metabolism could contribute to the development, progression, and prognosis of breast cancer. One major finding is the association between elevated levels of high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol and an increased risk of breast cancer. These lipids are believed to play a role in tumour growth and metastasis. For example, a study utilizing Mendelian randomization techniques suggested that genetically elevated HDL and LDL levels are associated with a higher risk of developing breast cancer [3] Moreover, research has shown that different breast cancer subtypes exhibit specific lipid profiles. For instance, triple-negative breast cancer (TNBC), known for its aggressive nature, tends to have increased phosphatidylcholines and cholesterol esters, both of which are linked to more aggressive tumour behaviour. [4] Additionally, the serum lipid profile, including total cholesterol and triglycerides, could potentially serve as biomarkers for breast cancer risk, particularly in premenopausal and postmenopausal women.[5]

Dyslipidaemia which is common in Breast cancer, may cause Oxidative stress. Oxidative stress largely contributes to Breast cancer. Breast cancer cells have a higher level of ROS, and DNA damage induced by ROS is closely related to the occurrence and development of breast cancer [6-8].

Bilirubin and Uric Acid is considered marker of oxidative stress. Bilirubin's inhibitory impact on NADPH OXIDASE activity presumably explains much of anti-oxidant activity of heme oxygenase, which cleaves heme to biliverdin, CO and free iron. Oxidative stress causes increase in xanthine oxidase activity and thus increases uric acid levels.

Some of the consequences of carcinoma cell oxidative stress are: Accelerated tumour progression due to RS

mediated inactivation of additional tumour suppressor genes within tumour cells and increasing expression of proto-oncogenes [9-11], activation of growth-promoting signalling pathways due to RS mediated promotion of cell proliferation in vitro [12], increasing blood supply to tumour cells, [13] and consequently increasing risk of metastasis [14]. In addition, oxygen radicals may augment tumour cells migration, increasing the risk of invasion and metastasis [14]. One of the most important oxidative stress markers is Malondialdehyde (MDA), low-molecular-weight aldehydes derived from lipid peroxidation processes, which has been used as a marker of lipid peroxidation [15]. Malondialdehyde can be formed when hydroxyl free radicals such as ROS react with fatty acid components of cell membranes so that a chain reaction is known as fat peroxidation. The fat peroxidation will break the chain of fatty acids into toxic compounds and cause damage to cell membranes. [16]

Aims & Objectives

Aim

1. To assess lipid profile in patients with breast carcinoma and normal healthy subject.
2. To compare the serum MDA, total bilirubin & Uric acid levels in breast cancer patients with healthy controls.

Objective

1. Whether Dyslipidaemia is associated with oxidative stress

Material and Method

- The study was conducted in Central India from August 2023 to December 2023 using a case control study.
- 30 clinically and histopathologically confirmed Breast Carcinoma patients of the age group of 30-70 years served as cases and 30 normal healthy females in same age group served as controls. The parameters were estimated by standard biochemical methods. Biochemical markers- associated with oxidative stress (OS) - (MDA, Total Bilirubin, Uric acid), Lipid Profile were assessed.
- Patients confirmed as having breast cancer through Fine Needle Aspiration Cytology (FNAC) investigation were considered as study populations.
- The sample size was determined by double population proportion formula.
- Socio-demographic and clinical characteristic data were collected using an interviewer-administered questionnaire.

Inclusion Criteria

1. Age of Patients: - 30 - 70 years females.
2. TNM stages of Breast Carcinoma, T- Tumor N-Lymph node M-Metastasis.
3. BMI: 18.5-25
4. Early Breast Cancer= $T_{1-2}\,N_{0-1}\,M_0$/ $T_3\,N_0\,M_0$ - Stage 1

Locally Advanced Breast Cancer = $T_3\,N_1\,M_0$ / $T_4\,N_{1-3}\,M_0$ / $T_{1-4}\,N_{2-3}\,M_0$ – Stage 2

Metastatic Breast Cancer= $T_{1-4}\,N_{1-3}\,M_1$ – Stage 3

Exclusion Criteria

1. History of chronic illness and other malignancies;
2. History of acute inflammation such as common cold;
3. Chronic smoker or alcoholics.
4. Pregnant Females

Sample Collection and Data Analysis

Five milliliters of venous blood were collected using a serum separator test tube and labeled with participant's identification.

- The collected blood was left on the test tube rack at room temperature for 30 minutes to clot and centrifuged by using a BT-2000 universal centrifuge

adjusted at 4400 revolution per minute (RPM) for 5 minutes to separate serum from whole blood.

- Serum total Cholesterol (TC), Triglycerides (TG), High-Density Lipoprotein (HDL-c) and Low-Density Lipoprotein (LDL-c) were analyzed by enzymatic colorimetric method using the XL640 auto analyzer following the manufacturer's instruction and standard operating procedures.
- Similarly, Uric acid, Total Bilirubin, were analyzed using Beckman Coulter AU4500.
- Serum MDA levels was estimated by the Draper and Hadley's double heating method of LPO. In this method Thio-barbituric acid reacts with MDA to form a stable pink colour with maximum absorption at 535 nm.

Results

A total of 60 participants were included in this study. Of them, 30 (50%) were controls, 30 were cases 18 were stage 1 & 12 were stage 2.

Table 1: Lipid Profile with stages of Breast cancer and Control

Investigations Lipid Profile	Stage 1 Mean (SD)	Stage 2 Mean (SD)	Control Mean (SD)	P value Significance
Total Cholesterol	200(15.4)	232(24)	181.03 (13.54)	P=<0.001**
Triglyceride	142(20)	166(28)	110.8 (19.32)	P<0.005**
HDL	30(1.8)	28(2.6)	41.03 (5.53)	P<0.001**
LDL	100(10.6)	124(20.2)	86.0 (20.43)	P<0.001**

This table presents a comparison of lipid profile parameters across three groups: Stage 1 breast cancer patients, Stage 2 breast cancer patients, and a control group. It summarizes the mean values and standard deviations (SD) for Total Cholesterol, Triglycerides, HDL (High-Density Lipoprotein), and LDL (Low-Density Lipoprotein) for each group. The table also provides p-values and significance levels to indicate whether the differences between the groups are statistically significant. Total Cholesterol and LDL levels are significantly higher in both Stage 1 and Stage 2 breast cancer patients compared to the control group, which suggests a potential link between elevated cholesterol levels and breast cancer progression. HDL levels are significantly lower in breast cancer patients, which may indicate that lower HDL could be associated with increased cancer risk or progression. Triglyceride levels are also significantly elevated in breast cancer patients, particularly in Stage 2, compared to the control group.

Table 2: Oxidative stress biomarkers with stages of Breast cancer and Control

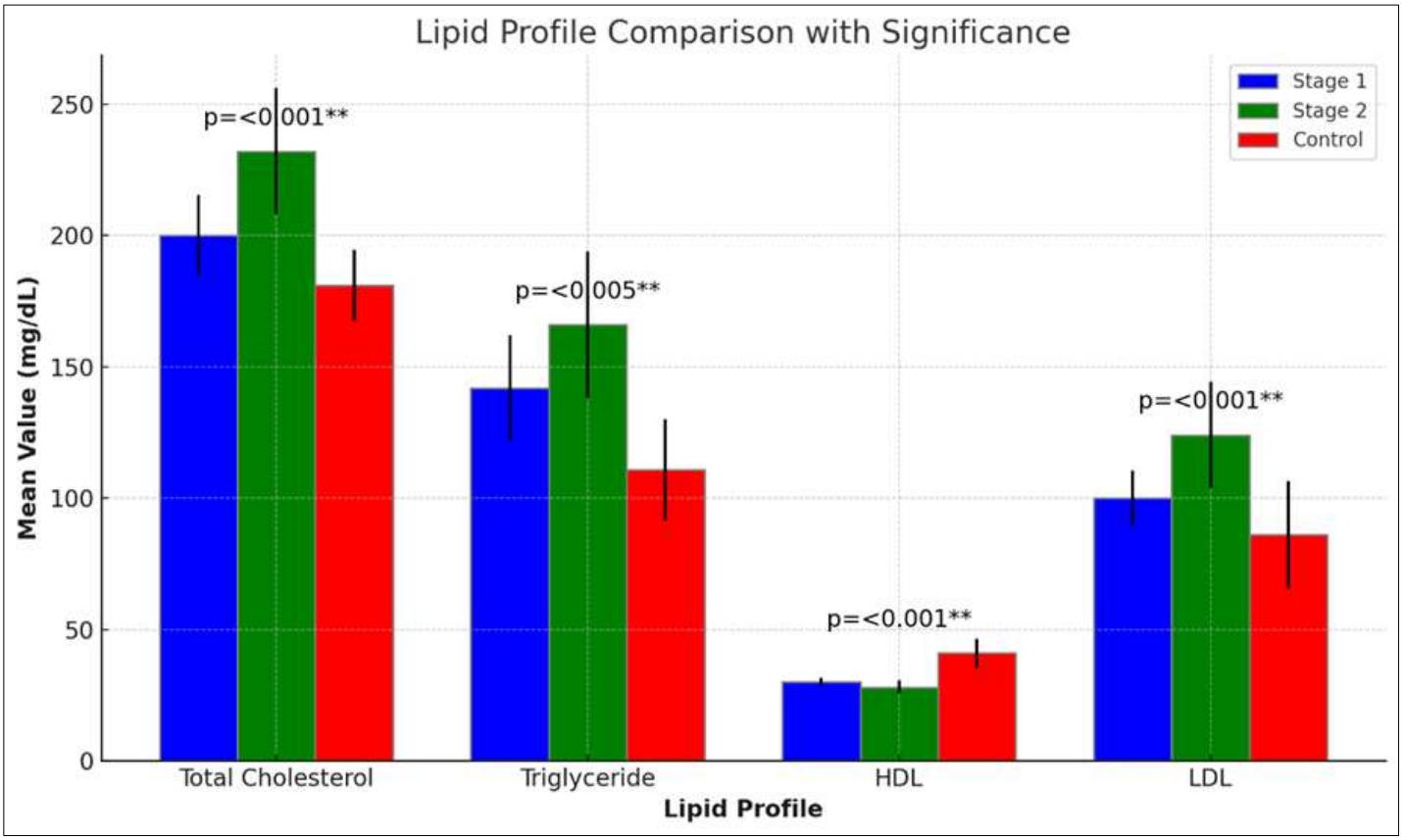
Investigations	Stage 1 Mean (SD)	Stage 2 Mean (SD)	Control Mean (SD)	P-value
Total bilirubin	0.6 (0.14)	0.32 (0.2)	0.4 (0.11)	P = 0.78
Uric acid	4.0 (0.9)	4.1 (0.8)	3.94 (0.82)	P = 0.96
MDA levels	0.7625 (0.0836)	0.92 (0.0371)	0.14 (0.056)	P < 0.001**

This table presents a comparison of Oxidative stress biomarkers (Total bilirubin, UA, and MDA levels) across three groups: Stage 1 breast cancer patients, Stage 2 breast cancer patients, and a control group. The p-values are provided to determine the statistical significance of the differences among these groups. Total Bilirubin (T bil) and Uric Acid (UA) levels do not show significant differences between the groups, (P value > 0.05) implying these markers may not be directly related to the disease stage in breast cancer. MD Levels show (P value < 0.05) a significant increase in both Stage 1 and Stage 2 cancer patients compared to controls, suggesting that oxidative stress plays a crucial role in the pathology of breast cancer.

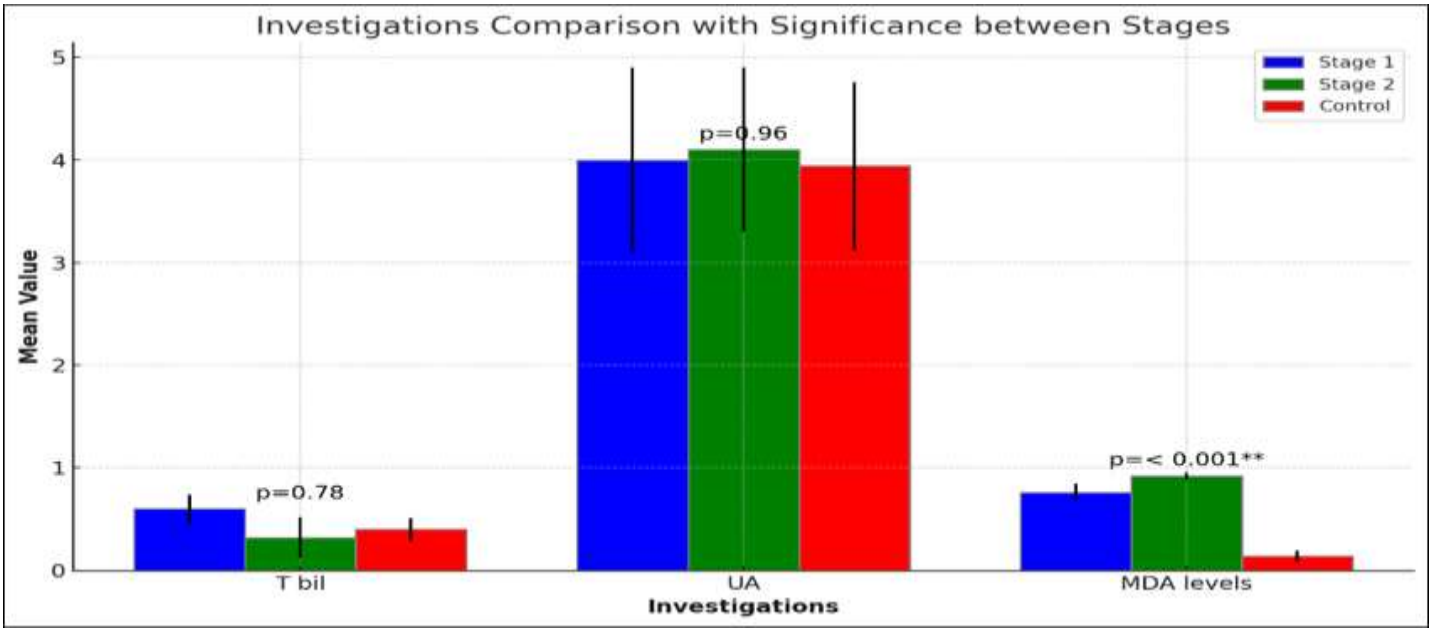
Table no 3: Corelation between lipid parameter & MDA levels with respect to stage of breast cancer and controls.

Lipid Parameter	Correlation	P-value	Significance
Total Cholesterol	0.89	0.3	Not Significant
Triglyceride	0.97	0.16	Not Significant
HDL	-0.99	0.03	Statistically Significant
LDL	0.89	0.31	Not Significant

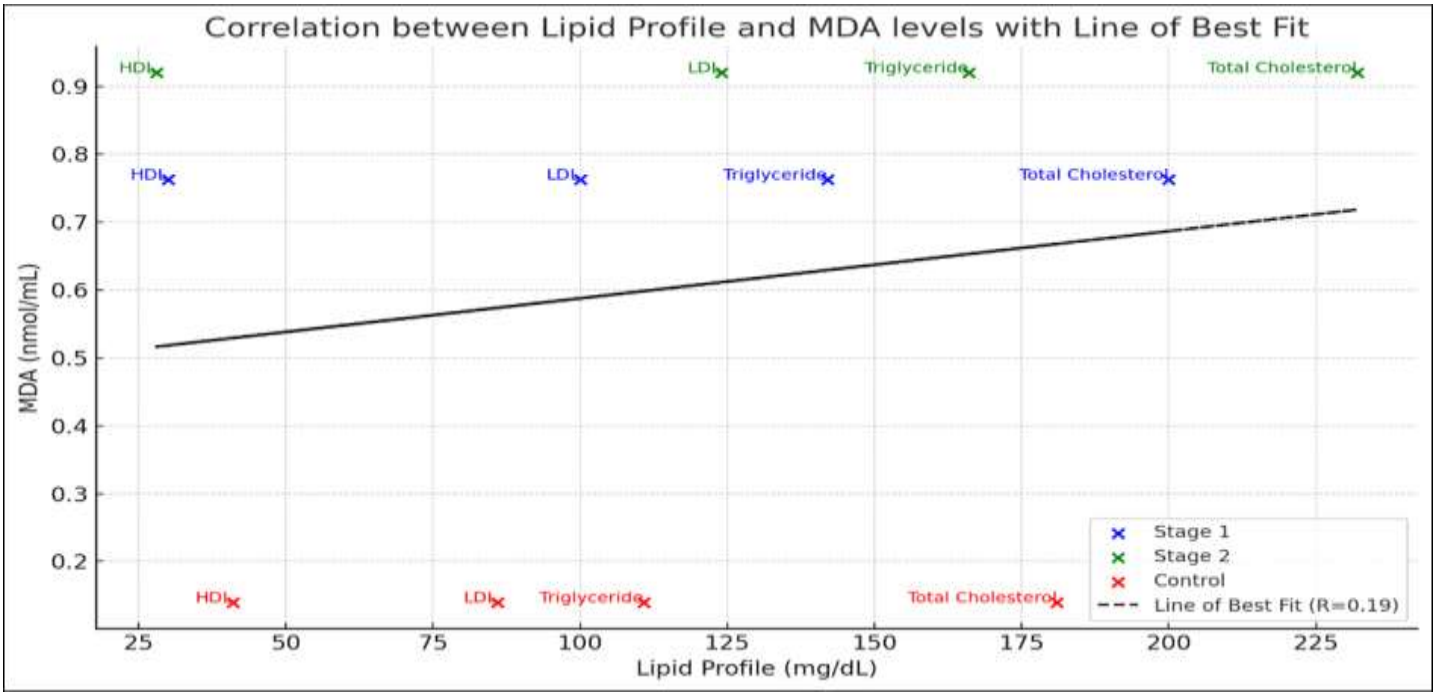
Graph 1: Lipid Profile comparison with stages of Breast cancer and control group



Graph 2: Oxidative stress biomarkers comparison with stages of Breast cancer and control group

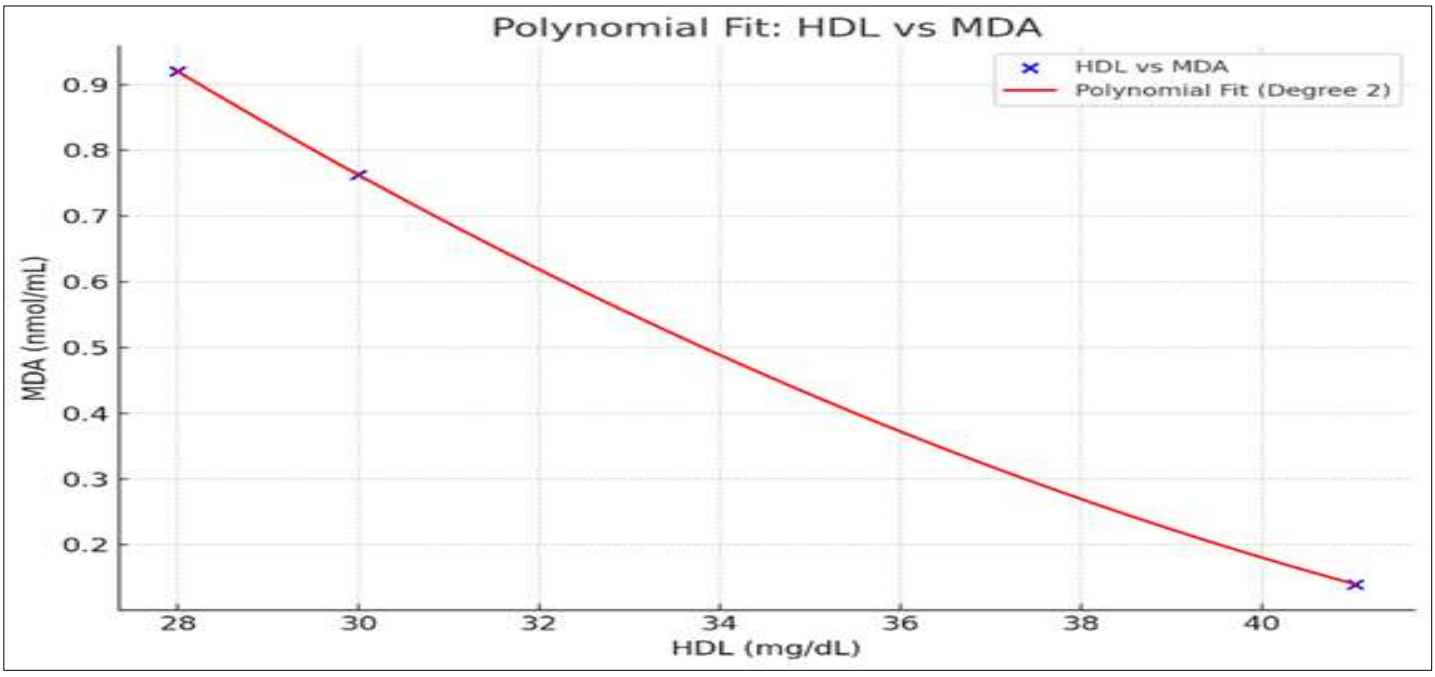


Graph 3: Co-relation graph between lipid profile & MDA with respect to stage 1, stage 2 and control groups.



The plot includes a line of best fit that represents the relationship between the lipid profile (Total Cholesterol, Triglycerides, HDL, LDL) and MDA levels. The RRR-value of 0.19 indicates a weak positive correlation between these parameters, suggesting that while there is some association between lipid profile and MDA levels, it is not a strong one.

Graph 4: Polynomial regression curve of HDL versus MDA



The polynomial regression fit (degree 2) for the relationship between **HDL** and **MDA** levels. The red curve represents the polynomial fit, showing how the relationship between HDL and MDA is captured by a quadratic model. This suggests that the relationship is not perfectly linear; the decrease in MDA with increasing HDL levels follows a slight curve, becoming less steep as HDL increases. The curve shows that MDA levels drop more rapidly when HDL levels are lower (e.g., from 28 to 34 mg/dL). As HDL levels rise further, the rate of decrease in MDA slows down, indicating a diminishing effect as HDL increases.

Data analysis: Data was entered into Microsoft Excel spreadsheet. Tables and Graphs were prepared using Microsoft word and excel software. Continuous variables were presented as Mean ± SD and Median & Range for non-normalised data. Categorical variables were expressed in frequency and percentages. Demographic variables were be compared between 2 groups by performing chi2 test. Statistical analysis was done using Pearson correlation for each lipid parameter with MDA levels. P<0.05 was considered as statistical significance. Statistical software SPSS was used for data analysis.

Discussion

Lipids are water-insoluble molecules that are important in maintaining the structural and functional integrity of membranes, cellular signalling, cell transformation, cancer progression and metastasis. [17] Changes in concentration of serum lipids in patients with breast cancer will result in an increased production of tumour necrosis factor-alpha (TNF-α) and inhibition of adipose lipoprotein lipase activity by insulin, [18] these changes will impair the catabolism of very low-density lipoprotein cholesterol (VLDL-c) which is influenced by dietary fat intake, alcohol consumption, body weight, pregnancy, endogenous hormones, smoking and physical inactivity. [19] we found Total Cholesterol, VLDL and TG levels were significantly higher irrespective of stage of cancer, our finding goes hand in hand with **gentinet kumie et al**. Proliferating cells such as cancer cells have increased requirement of cholesterol and facilitate lipid

biosynthesis and metabolism that will finally leads to increased serum cholesterol level in patients with breast cancer. [20,21] Increased level of total cholesterol (TC) and triglyceride (TG) stimulates cell proliferation and induce fibrosarcoma or will lead to the decreased level of sex hormone-binding globulin, which is likely to increase breast cancer risk. Average level of LDL and TG were increased as the stage of the disease progresses. WE Also found significant decrease in level of HDL as compared to control. Serum HDL decreases as the stage of disease progresses. The reason for decreased mean serum HDL-c concentration on malignant breast cancer can be due to abundant expression of scavenger receptor class B type I in human breast tissue which serves as an HDL receptor and mediate its cholesterol uptake. [22] The reason for high serum TC in women with malignant breast tumour can be due to high cholesterol metabolites, 27-hydroxycholesterol, that function as estrogenic and increase proliferation of estrogenic receptor-positive breast cancer cells. [23] obesity as a common risk for breast cancer and dyslipidaemia.[24-26] This could be due to adiposity-related secretion of estrogenic, increases in circulating insulin and insulin-like growth factors, local production of adipokines and leptin that could stimulate the breast cell growth.[27] In addition, obesity decreases the production of sex hormone-binding globulin which in turn results for an increased biologically active unbound form of estrone and oestradiol which promotes cell growth and metastatic potential in breast tumour.

The role of oxidative stress, and lipid peroxidation in initiation and progression of carcinogenesis had been documented by **himetoglu et all.** Changes in lipid and lip levels may create oxidative stress by lipid peroxidation. The ability of HDL to inhibit lipid peroxidation of LDL and biological membranes is widely studied as a protective mechanism against development of chronic diseases [28-32]

We have seen total bilirubin and uric acid as an endogenous marker of oxidative stress, no significant difference was found in patients and control irrespective of stage of disease.

Tumour growth and progression are closely linked to the oxidant–antioxidant balance in cancer patients. [33] Previous studies by **Zaridze et al**. and **Saintot et al.** indicated that plasma levels of malondialdehyde (MDA) were lower in breast cancer patients compared to healthy individuals, (34,35), contrast to our findings. The significant elevation in MDA levels among breast cancer patients reflects increased oxidative stress, which is commonly associated with tumour progression, DNA damage, and cellular transformation in cancer. Our findings are consistent with the results of previous studies. For instance**, Gawel et al. (2004)** demonstrated that MDA levels were significantly elevated in breast cancer patients, suggesting increased oxidative damage in these individuals. [36] Several studies have explored the relationship between HDL (High-Density Lipoprotein) and MDA (Malondialdehyde) in breast cancer, particularly focusing on oxidative stress and lipid metabolism. In breast cancer patients, the antioxidant function of HDL is compromised, leading to increased oxidative stress, which is often measured by markers like MDA. Gabriele **Mazzuferi et al.** had similar findings with elevated MDA levels, along with decreased HDL levels, in breast cancer patients, suggesting a strong inverse relationship between HDL and MDA in the context of breast cancer. [37]. **Pandrangi et al.** have also established a significant association with low HDL & Higher levels of MDA, a marker of

oxidative stress, both associated with more aggressive cancer behaviour. [38]

Conclusion

The Overall prevalence of dyslipidaemia was high on breast cancer patients. The mean value of components of lipid levels was higher in breast cancer patients than in controls. There was significantly lower mean serum HDL-c level among breast cancer and the controls. There was significantly high serum Tri-glyceride in breast cancer than control. This indicates that HDL-c and LDL-c have a potential to be used as a marker of diagnostic and prognostic potential. Therefore, breast cancer patients should monitor their lipid levels to reduce comorbidities and adverse breast cancer outcomes. The strong inverse relationship between HDL and MDA suggests that higher HDL levels may help reduce oxidative stress, as reflected by lower MDA levels. This relationship could be significant in understanding the protective role of HDL in conditions like breast cancer, where oxidative stress is known to play a role in disease progression. **Limitations**

The relatively small sample size may limit the generalizability of the findings to broader populations. The study was conducted in a single centre, which may not reflect the diversity of breast cancer cases globally. Absence of follow-up data limits the understanding of how lipid profile changes affect long-term outcomes in breast cancer patients.

Abbreviations

Sr. No	Serial Number
HDL	High density LIPOPROTEINS
LDL	Low density lipoproteins
VLDL	very low-density lipoproteins
UA	Uric Acid
MDA	Malon- di- aldehyde
TG	Tri-glyceride
T. BIL	Total Bilirubin
BC	Breast Cancer
TNF-α	tumour necrosis factor-alpha
OS	Oxidative stress

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