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RESEARCH ARTICLE

LIPID PROFILE AND ITS SIGNIFICANCE IN BREAST CANCER

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Abstract

Background: According to WHO, breast cancer is the most common cancer in the women worldwide, so early diagnosis is the best way to reduce its morbidity and mortality. Among various risk factors, the relationship between serum lipid profile and breast cancer is still unclear. Therefore, this study was conducted to evaluate this relationship.

Methodology: Prospective, descriptive observational study with a comparative study design conducted at Fauji Foundation Hospital, Rawalpindi between November 2018 to April 2019.

Results: 140 patients were divided into two groups i.e. cases and controls. Both groups were equally sub divided based on menstrual status. Independent student t-test was applied for comparison between the groups. BMI was significantly higher in the study group as compared to control group ($p=0.002$). Serum TG and LDL levels were higher in breast cancer patients ($p=0.032$ and $p=0.07$ respectively). Cholesterol level was not statistically different in any group ($p>0.05$). Higher HDL levels were seen in pre-menopausal cases ($p=0.004$) but there was no statistical difference when studied across cases and control groups.

Conclusion: As breast cancer is the most common tumor in females, so early diagnosis is the key to reduce its morbidity and mortality. In this study, higher BMI, TG and LDL levels were seen in breast cancer patients as compared to controls. So, it may be concluded that BMI and dyslipidemia have some role in the etiology of breast cancer.

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Introduction:-

Background:

Cancer accounts for about 1 in every 7 deaths worldwide.^[1] According to WHO, breast cancer is the most common cancer in the women worldwide i.e. 25% of all new cancer cases among women. Among them, 53% of cases occur in the economically developing countries.^[2] Asian countries represent 59% of the global population and have the largest burden of breast cancer. Asian patients make 39% of new cases worldwide and this incidence is still dramatically rising. Among the Asian countries, the age standardized incidence rate (ASIR) of breast cancer is the highest in Pakistan.^{[1][3][4]}

Due to this increasing incidence, the pathophysiology of breast cancer has become an area of increasing interest for the pathologists and researchers.^[5] Various factors are thought to be associated with the increased risk of breast

cancer. These include higher consumption of animal fat, obesity, sedentary lifestyle, early menarche, late menopause and increased age at first pregnancy.^{[6][7]} Researchers have recently discovered the association of high levels of circulating lipids with various cancers including colon cancer and breast cancer.^[8] There are several reports of elevated fasting plasma lipid levels in both pre and post-menopausal breast cancer patients.^[9] However, their role in the pathophysiology of breast cancer still remains unclear.^{[10][11]}

Cholesterol is a structural component of the cell membrane and is involved in the key cellular signaling pathways.^{[12][13]} Cells internalize cholesterol from the circulating low density lipoprotein (LDL) through the LDL receptors on the cell surface.^[14] Previous in vitro studies have found that LDL receptor is expressed in greater proportion in human breast cancer cells, so it is hypothesized that targeting this LDL receptor might be an important therapeutic technique in treating breast cancer.^[15] Observational studies have also shown that statins, used in treating dyslipidemia, can reduce breast cancer incidence and recurrence, however more studies are needed to confirm this.^[16] Therefore, association between serum fasting lipid levels and breast cancer has important prognostic as well as therapeutic implications and this relationship should be studied further.

Various studies have been conducted to find out the association of dyslipidemia with breast cancer, however the studies have shown contrasting results.^{[11][15]} Therefore, this study is conducted to find out the relationship between fasting lipid profile and breast cancer and appreciate its significance as a potential risk factor in our population.

Objective:-

1. To compare fasting serum lipid profile between breast cancer patients and controls.
2. To study lipid profile distribution according to menstrual status in cases and control groups.

Operational definition:

Obesity:

Obesity has been defined by the National Institute of Health (NIH) as a body mass index (BMI) of 30 and above. BMI is a measure of body fat based on height (m) and weight (kg) that applies to adult men and women.

BMI

Under-weight	=	
Normal weight	=	
Overweight	=	
Obesity	= BMI of 30 or greater	

Categories:

<18.5
18.5–24.9
25–29.9

Menopause:

Menopause has been defined by National comprehensive cancer network (NCCN) as:

1. Prior bilateral oophorectomy.
2. Age ≥ 60 y.
3. Age < 60 y and amenorrheic for 12 or more months in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression and follicle-stimulating hormone (FSH) and estradiol in the postmenopausal range.
4. If taking tamoxifen or toremifene, and age < 60 y, then FSH and plasma estradiol level in postmenopausal ranges.

Case:

All females with ages 35-74 years reporting to oncology department with biopsy proven breast cancer.

Control:

All healthy females with ages 35-75 years matched to cases in regards to age, BMI and menstrual status.

Fasting serum lipid profile:

Normal Values according to Fauji Foundation Hospital, Rawalpindi laboratory in mmol/L.

Serum Cholesterol: < 5.2 mmol/L

Serum Triglycerides (TG): < 1.71 mmol/L

Serum Low density lipoprotein (LDL): < 3.4 mmol/L

Serum High density lipoprotein (HDL): > 0.9 mmol/L

Methods:-

It was a prospective, descriptive observational study with a comparative study design. Total duration of study was 6 months from the time of approval i.e. 01-11-2018 till 30-04-2019. We included 140 patients by stratified sampling based on our parent study data and divided them equally into 2 groups i.e. 70 cases and 70 controls. Both of the groups were then equally subdivided into 2 groups based on the menstrual status i.e. 35 pre-menopausal and 35 post-menopausal. Patients who met the following inclusion criteria were included:

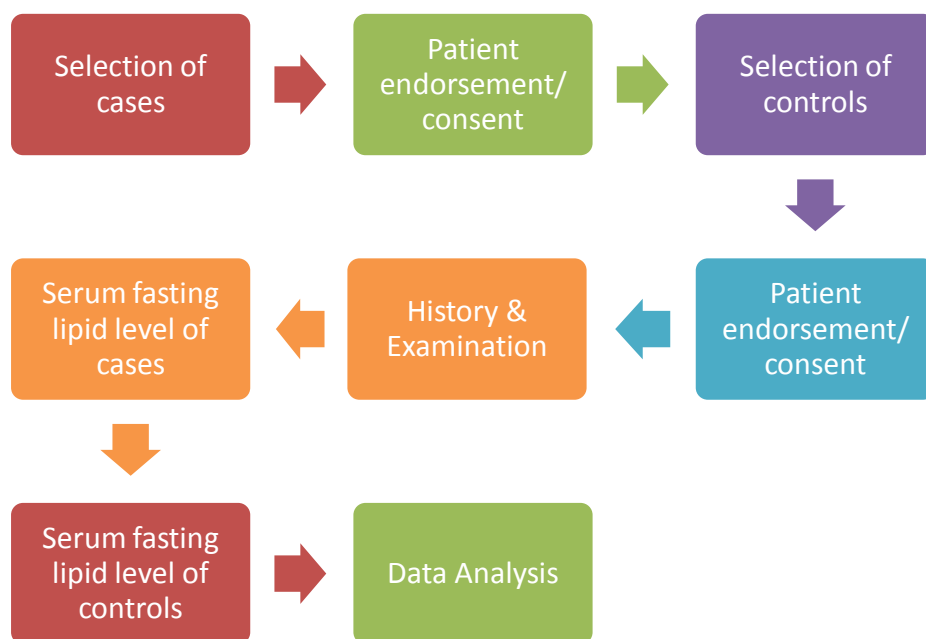
1. All breast cancer patients 25-75 years old diagnosed on biopsy or FNAC who were treatment naïve, were taken as cases.
2. All females 25-75 years old without breast cancer or any other co morbidities were enrolled as controls.
3. All patients with ECOG performance status of 0-1.
4. All patients who agreed after written consent.

Patients with the following features were excluded from the study:

1. Patients with co morbidities (hypertension, diabetes mellitus, hyperlipidemia, renal failure, chronic liver disease etc.).
2. Patients with malignancies other than breast cancer.
3. Patients with BMI >35.
4. Patient on prior chemotherapy, endocrine therapy, or who had recurrent breast cancer.
5. Patients on lipid lowering drugs or anti diabetic medications.

Pregnancy:

Cases were selected from both outpatient and inpatient departments after taking an informed consent and fulfillment of inclusion criteria. Matched controls were selected in a similar manner. Detailed history regarding disease and menstrual status was taken and examination was done. BMI was calculated by measuring height in meter and weight in kg. Then, fasting serum lipid profile samples of both groups were sent before starting any treatment for cases and the data was analyzed afterwards.



Conceptual Framework:

SPSS 23 was used to analyze the data. Variables to be studied included: Age, BMI, menstrual status and fasting serum lipid profiles. Descriptive analysis included means and standard deviations of the continuous variables like age, BMI and fasting serum lipid profile were calculated. In analytical statistics, first of all frequency and percentage was calculated for categorical variable like menstrual status. In the second step, independent student t-test was applied for comparison between cases and control groups. A p-value of <0.05 was considered significant.

Effect modifiers like age, BMI and menstrual status were controlled by stratification among the cases and controls.

Results:-

In this study, lipid analysis was carried out on serum samples of 140 patients i.e. 70 breast cancer patients and 70 control women. Most of the patients were between ages 25-45 years (40.7%) followed by age group 46-55 years (32.9 %). 22.9% patients were between ages 55-65 and only 3.6% patients were between ages 65-75 years. Both the study groups were equally divided into 2 sub-groups based on their menstrual status as shown in table 1. Overall, the mean age of patients was 49.68 ± 9.378 years with a range of 25-67 years. Mean age of cases was 48.94 ± 8.959 whereas mean age of control group was 50.41 ± 9.788 . (Table 2).

As described above, in descriptive analysis, mean and standard deviation was calculated for all continuous variables. (Table 2)

Lipid levels (Total cholesterol, Triglyceride, LDL and HDL) as measured in both groups in premenopausal and post-menopausal women are shown in table 3. As it can be seen that while serum total cholesterol and HDL levels are almost the same among both study groups, levels of serum triglycerides and LDL are higher in both premenopausal and post-menopausal groups in women having breast cancer than their corresponding control groups.

In analytical analysis, independent student t-test was applied for comparison between cases and controls. 1st parameter evaluated was body mass index. It was seen that BMI was significantly higher ($p=0.002$) in the study group as compared to control group (BMI in cases= 26.35 ± 3.978 , BMI in controls= 24.50 ± 2.962). When compared with menstrual status of both study groups, BMI was significantly higher in pre-menopausal cases than controls ($p=0.001$) thus proving that BMI is significantly higher in breast cancer patients.

Present study shows that serum triglyceride levels were higher in breast cancer patients and the t values were highly significant ($p=0.032$). When its distribution was studied across the groups, TG level in premenopausal cases was 2.3 mmol/L and 1.9 mmol/L in pre-menopausal controls, whereas it was 2.6 mmol/L in post-menopausal cases and 2.3 mmol/L in post-menopausal controls. When this difference was translated into p values, it was shown that serum TG levels in pre-menopausal breast cancer patients were significantly elevated than control groups ($p=0.011$).

Serum total cholesterol level was almost the same among both study groups ($p=0.759$). When its distribution was seen across the menstrual groups, it was seen that the cholesterol level was not statistically different in any group ($p>0.05$).

Next parameter assessed was serum LDL level. Mean serum LDL in cases was 2.84 ± 0.611 whereas in controls, serum LDL was 2.56 ± 0.680 and this was statistically significant ($p=0.012$). When seen across menstrual groups, it was seen that LDL levels were significantly higher among post-menopausal breast cancer patients ($p=0.07$).

Last parameter studied in the lipid profile was serum HDL level. Mean serum HDL level in cases was 1.06 ± 0.310 and 1.04 ± 0.258 in controls ($p=0.675$). According to menstrual group distribution, higher HDL levels were seen in pre-menopausal cases as compared to post-menopausal controls ($p=0.004$) but there was no statistical difference when studied across cases and control groups according to their menstrual status.

Comparisons of study parameters across both the groups are mentioned in table 4 and 5.

Table 1:- Age and menstrual status distribution among study groups.

Age groups (years)	Frequency (n)	Percentage (%)
25-35	25	17.8
36-45	32	22.9
46-55	46	32.9
56-65	32	22.9
66-75	5	3.6
Menstrual status	Number of patients (cases) n= 70 (50%)	Number of patients (controls) n= 70 (50%)

Pre-Menopausal	35 (25%)	35 (25%)
Post-Menopausal	35 (25%)	35 (25%)

Table 2:- Descriptive statistics of continuous variables.

Parameters		Total number of patients (n)		Mean $\pm$ Std. Deviation	
Age (years)		140		49.68 $\pm$ 9.378	
Cases	Controls	70	70	48.94 $\pm$ 8.959	50.41 $\pm$ 9.788
Body Mass Index (kg/m²)		140		25.42 $\pm$ 3.617	
Serum Total Cholesterol (mmol/L)		140		4.12 $\pm$ 0.957	
Serum Triglyceride (mmol/L)		140		2.27 $\pm$ 0.987	
Serum LDL level (mmol/L)		140		2.70 $\pm$ 0.659	
Serum HDL level (mmol/L)		140		1.05 $\pm$ 0.284	

Table 3:- Average values of study parameters among groups.

Study Group	Menstrual status	Age in years	Body Mass Index (kg/m ²)	Serum Total Cholesterol level (mmol/L)	Serum Triglyceride level (mmol/L)	Serum LDL level (mmol/L)	Serum HDL level (mmol/L)
Cases	Pre-menopausal (n= 35):						
	Mean value	41	25.87	3.9	2.3	2.6	1.1
	Post-menopausal (n= 35):						
	Mean value	56	26.85	4.4	2.6	3.1	1.0
Controls	Pre-menopausal (n= 35):						
	Mean value	42	23.25	3.9	1.9	2.4	1.1
	Post-menopausal (n= 35):						
	Mean value	59	25.75	4.4	2.3	2.7	1.0

Table 4:- Comparison of BMI and Lipid profile according to menstrual status.

Parameters	Cases (n= 70)		Controls (n= 70)	
	Pre-menopausal (n= 35)	Post-menopausal (n= 35)	Pre-menopausal (n= 35)	Post-menopausal (n= 35)
Body mass index (kg/m²)	25.86 $\pm$ 3.755	26.84 $\pm$ 4.187	23.24 $\pm$ 2.685	25.75 $\pm$ 2.715
	*p= 0.000		p= 0.308	
Serum Total Cholesterol (mmol/L)	3.94 $\pm$ 0.806	4.36 $\pm$ 0.855	3.85 $\pm$ 1.085	4.35 $\pm$ 0.985
	*p= 0.039		*p= 0.048	
Serum Triglyceride level (mmol/L)	2.32 $\pm$ 0.926	2.58 $\pm$ 1.319	1.86 $\pm$ 0.483	2.33 $\pm$ 0.933
	p= 0.349		*p= 0.011	
Serum LDL level (mmol/L)	2.62 $\pm$ 0.555	2.68 $\pm$ 0.681	2.43 $\pm$ 0.794	2.80 $\pm$ 0.795
	p= 0.661		p= 0.058	
Serum HDL level (mmol/L)	1.13 $\pm$ 0.269	0.95 $\pm$ 0.217	1.09 $\pm$ 0.350	1.03 $\pm$ 0.264
	*p= 0.004		p= 0.375	

* = p value < 0.05

Table 5:- Comparison of BMI and Lipid profile between groups.

Parameters	Menstrual status	Study group (Mean $\pm$ STD)	Control group (Mean $\pm$ STD)	p value
Body Mass Index	Overall	26.35 $\pm$ 3.978	24.50 $\pm$ 2.962	*0.002

(Kg/m ²)	Pre-menopausal	23.24 ± 2.685	25.86 ± 3.755	*0.001
	Post-menopausal	25.75 ± 2.715	26.84 ± 4.187	0.199
Serum Total Cholesterol (mmol/L)	Overall	4.10 ± 1.059	4.15 ± 0.851	0.759
	Pre-menopausal	3.94 ± 0.806	3.85 ± 1.085	0.690
	Post-menopausal	4.36 ± 0.855	4.35 ± 0.985	0.969
Serum Triglyceride level (mmol/L)	Overall	2.45 ± 1.139	2.09 ± 0.774	*0.032
	Pre-menopausal	2.32 ± 0.926	1.86 ± 0.483	*0.011
	Post-menopausal	2.58 ± 1.319	2.33 ± 0.933	0.361
Serum LDL level (mmol/L)	Overall	2.84 ± 0.611	2.56 ± 0.680	*0.012
	Pre-menopausal	2.62 ± 0.555	2.43 ± 0.794	0.258
	Post-menopausal	3.07 ± 0.587	2.70 ± 0.519	*0.007
Serum HDL level (mmol/L)	Overall	1.06 ± 0.310	1.06 ± 0.310	0.675
	Pre-menopausal	1.13 ± 0.269	1.09 ± 0.350	0.654
	Post-menopausal	0.95 ± 0.217	1.07 ± 0.264	0.203

*= p value < 0.05

Discussion:-

According to WHO, breast cancer is the commonest cancer of women worldwide,^[1] so early diagnosis is the best way to reduce its morbidity and mortality. Various factors are associated with the increased risk including obesity, sedentary lifestyle, early menarche, late menopause and increased age at first pregnancy.^{[6][7]} Among these risk factors, the relationship between serum lipid profile and breast cancer is still unclear.^{[10][11]} Thus, the present study was conducted to evaluate this relationship.

Age is a crucial factor in malignancy and most of the studies show that malignancy presents more in elder population when compared to young ones.^{[17][18]} In our study also, most of the patients were >45 years old (52.9%) as compared to patients <45 years (47.1%). Our result coincides with the results published by Hrituraj Rohariya and colleagues in India in 2017. Their study also showed that 66% patients were > 40 years old.^[19] Another study done in Thailand by Pikul Laisupasin et al. showed similar results.^[20] Both the above mentioned studies were prospective comparative studies similar to our study type.

Obesity is a well-known risk factor for breast cancer irrespective of race or country.^{[21][22]} In the present study, when BMI values were compared between control and study groups, BMI of study group was significantly higher than the control group (p= 0.002). When studied according to menstrual status, BMI of Post-menopausal cases was significantly higher than pre-menopausal cases (p= 0.000). The increased risk in postmenopausal women is explained possibly due to increased level of circulating Estradiol by the conversion of androgens to estrone in the adipose tissue.^[21] These results are similar to the study conducted by H M K Akalanka and colleagues in Sri Lanka in 2019.^[23] They prospectively studied 230 pts (155 cases, 75 controls) in a span of 2 years and saw that higher BMI was associated with breast cancer patients as compared to controls. Another similar comparative study of 200 patients (100 cases, 100 controls) conducted in India also showed similar results.^[6] Similar results reproduced in our study of lesser duration and smaller number of patients further strengthens this association.

Lipid profile and its association with breast cancer was the mainstay of our study. The results showed positive association of TG level in breast cancer patients (p=0.032). On comparison between premenopausal and postmenopausal groups among cases and controls (Table 5), significantly elevated TG levels were found in pre-menopausal breast cancer patients (p= 0.011). Similar results were found in studies conducted by Vipan Kumar and colleagues in India in 2015 and Uzma Raza and colleagues in Pakistan in 2018.^{[6][10]} Both studies were prospective studies containing larger number of patients and were conducted over a period of 2 and 5 years respectively.

The association of total cholesterol level with breast cancer was insignificant (p= 0.759). On comparison between study groups according to menstrual status, the difference is also insignificant (p= >0.05). However, serum cholesterol was significantly elevated among post-menopausal breast cancer patients as compared to pre-menopausal breast cancer patients (p=0.039). These results were similar to a study conducted in Thailand by Pikul Laisupasin et al. in 2013. It was a comparative prospective study of 400 samples and showed no association of cholesterol with breast cancer.^[20] Another retrospective study conducted in China by Xing Li et al. on 1084 breast cancer patients showed similar results.^[24] These results are in support of recent evidence that instead of cholesterol,

the cholesterol metabolite 27-hydroxycholesterol induces the proliferation of estrogen receptor-positive breast cancer cells and facilitates metastasis. Thus, serum cholesterol level is usually not associated with breast cancer risk.^[25]

When serum LDL level was studied, it was seen that elevated levels were positively associated with breast cancer patients ($p=0.012$). According to menstrual status, elevated levels were seen in post-menopausal breast cancer patients as compared to controls ($p=0.007$). Almost all of the studies in literature review showed positive association of elevated LDL levels in breast cancer patients. First study was carried out by Hrituraj Rohariya in India over a period of 1 year. It was a prospective comparative study similar to our study.^[8] Another study was carried out in 2 years in Portugal by Catarina Rodrigues dos Santos and colleagues. It was a prospective study of 244 breast cancer patients and serum lipid profile was studied in these patients which showed positive association of LDL and TG with breast cancer.^[5] These studies strengthen our results as our study is carried out in a limited time.

Last parameter to be studied was serum HDL level. Our study failed to show any association of HDL level with breast cancer and there was no difference among menstrual groups ($p > 0.05$). However, when breast cancer patients were studied according to menstrual status, it was seen that serum HDL level was significantly associated with lower levels in post-menopausal patients ($p=0.004$) as it has a protective role in body and lower levels correlate with increased incidence of malignancy. Similar results were reproduced by two studies. One study was carried out in India in 2017 and the other study was conducted in Pakistan in 2018. Both studies were prospective comparative studies and they also failed to show the association of HDL with breast cancer.^{[8][10]}

All these results suggest that serum lipid profile can be considered as a potential risk factor of breast cancer and correcting dyslipidemia with drugs may assist in therapeutic management of this disease. A cohort study longitudinally following up women, started prior to any ailment, is required to ascertain these findings with confidence. Study constraints include single institution and a short duration study. Furthermore, the association of serum lipids with breast cancer characteristics and survival should also be studied.

Conclusion:-

Breast cancer is the most common tumor in females worldwide, so early diagnosis is the best way to reduce its morbidity and mortality. In this study, higher BMI, TG and LDL levels were seen in breast cancer patients. So, it may be concluded that BMI and serum lipid profile have some role in the etiology of breast cancer but survival studies and association with cancer characteristics are needed to establish their role as a risk factors for breast cancer.

Abbreviations:

BMI: Body mass index

TG: Triglyceride

LDL: Low density lipoprotein

HDL: High density lipoprotein

ASIR: Age standardized incidence rate

NCCN: National comprehensive cancer network

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