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EFFECT OF CANCER TREATMENT MODALITIES ON SERUM LIPIDS AND LIPOPROTEINS AMONG WOMEN WITH CARCINOMA OF THE BREAST

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Abstract : Serum lipids and lipoproteins were studied in 61 breast cancer patients before initiation of therapy and subsequently during and after completion of cancer therapy. Different serum lipid fractions were estimated by enzymatic method. It was observed that mean levels of serum triglycerides, total cholesterol and low density lipoprotein (LDL)-cholesterol among untreated breast cancer patients decreased significantly after treatment. On the contrary, an increasing trend in the levels of high density lipoprotein (HDL)-cholesterol was noticed in patients during the course of treatment. This study reflects the effects of cancer therapy in the alteration of levels of different serum lipid fractions in the patients with breast cancer.

Key words : breast cancer serum lipids therapy

INTRODUCTION

Breast cancer is the most frequent cancer in women worldwide with more than half a million new cases being reported each year (1). Although, it is the commonest cancer in women in the developed countries, currently more than 40% of all breast cancer cases are found in developing countries with the prediction of increase to 50% by the turn of century (2). There is an increasing trend in the incidence of breast cancer throughout the world including India. At present, carcinoma of the breast is the second most common carcinoma amongst Indian females (3). As such, the pathological process of breast cancer is not clearly understood. It is assumed that sex-steroid hormones have a strong role in the pathological process of breast cancer (4), and sex-steroids (including oestrogen) are closely associated with the lipid metabolism (5). Dietary fat, obesity,

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alcohol intake or hormonal preparations, etc. which are considered as risk factors for the development of breast cancer, have also effects on oestrogen as well as on lipid metabolism.

Since Beatson (6), more than hundred years ago, first showed that oophorectomy had a favourable effect on breast cancer, there has been a continuing interest to find out the exact pathological role of oestrogen in the development of breast cancer and interaction with different risk factors. But, the situation is too complex to understand and accurate measurement of biological effects amongst various factors is almost impossible even in the present state of knowledge. Changes in one area of metabolism may affect other areas. However, experimental evidence indicates that dietary fat influences mammary carcinogenesis; although, human epidemiological evidence is inconsistent. Dietary fat is a likely important determinant of postmenopausal breast cancer as part of an intricate and inseparable interaction of lifestyle cancer risk factors (7). Changes not only in the quantity but also in the composition of dietary fat influence lipid metabolism (8). Kuller (9) commented that higher fat intake may heighten the risk of breast cancer directly through increased blood oestrogen levels and/or secondarily through increased obesity. Similarly, after reviewing the literatures published from 1966 to 1998, Wu et al (10) concluded that reduction in dietary fat can result in a lowering of serum oestradiol levels. Further, several investigators (11, 12) suggested that dietary fat plays an important role in the development of obesity. There is some evidence regarding increased peripheral conversion of adrenal androgens into oestrogen (aromatization) in obese women (13). This increased rate of aromatization in peripheral adipose tissues may be responsible for higher risk for breast cancer. On the one hand, increasing obesity has been correlated with a progressive fall in sex hormone binding globulin (SHBG) level (14), which is positively associated with percentage of free oestradiol or percentage of oestradiol not bound to SHBG (15). On the other hand, obesity has been found to be associated with changes in lipoproteins (16).

Alcohol consumption increases breast cancer risk in women (4, 17). Recently, Enger et al (18) observed that alcohol may preferentially increase the risk of oestrogen receptor (ER)-positive/progesterone receptor (PgR)-positive breast cancer in postmenopausal women. Epidemiological evidence indicates that alcohol consumption is associated with elevated plasma levels of HDL-cholesterol in both men and women (19). Also, alcohol intake may increase blood oestrogen levels (4, 20, 21).

Oestrogen and progesterone might have a suppressive action on cholesterol and also similar changes could be observed in plasma triglycerides and LDL-cholesterol levels. DeLeon et al (22) demonstrated that hormonal contraceptives, specially the synthetic progestagens, lower the plasma triglycerides levels; while Park (23) reported the alteration in serum lipids due to oral contraceptives with a particular decreasing effect on high-density lipoproteins. Zumoff (24) has suggested that postmenopausal oestrogen administration can produce breast cancer promoting effects in association with

other factors like consumption of alcohol, family history of breast cancer, the presence of susceptible genes (e.g., abnormal BRCA1, BRCA2 or p53) and the prevalence of increased 16-alpha-hydroxylation of oestradiol [oestrogen is metabolised mainly through two major pathways and one of them is 16-alpha-hydroxylase pathway which yields potent oestrogen that may play a positive role for the development of breast cancer (25-27)]. Further, Bissonnette et al (28) observed that oestrogen preparations cause a decrease of plasma cholesterol whereas increase in the levels of triglycerides, oestradiol and oestrone in postmenopausal women.

In the present study, different serum lipid fractions were analysed in patients with breast carcinoma before, during and after cancer therapy in order to find out their changes in relation with the treatment modalities.

METHODS

Patients – 61 patients of histopathologically proven carcinoma of the breast were randomly selected from the Department of Radiotherapy, Maulana Azad Medical College and associated Lok Nayak Hospital, New Delhi. Standard questionnaires (29) related with clinical and epidemiological parameters were used for all patients. The mean age of the patients included for the study was 47.6 ± 11.33 years. Out of total 61 cases, 30 patients were postmenopausal whereas 31 were premenopausal. All postmenopausal patients received endocrine therapy (i.e., tamoxifen) along with radiotherapy or chemotherapy. Blood samples were collected at three different time points. First sample was collected before initiation of radiotherapy and/or any systemic treatment, while second sample was collected after completion of radiotherapy. Similarly third sample, after completion of chemotherapeutic treatment, was collected.

The patients received treatment were as follows: Radiotherapy (RT)-Radical RT 50 Gy over five weeks to chest wall and draining lymphnodes and palliative RT (for bony metastasis) 30 Gy in 10 fractions over 2 weeks to involved area, over 5 Fr/week utilizing telecobalt machine. Chemotherapy (CT) – Cyclophosphamide 500 mg/m^2, Methotrexate 40 mg/m^2 and 5-Flurouracil 600 mg/m^2 (CMF) i.v. on day 1 and day 8, repeated every 21 days x 6 cycles. Endocrine therapy- Tab Tamoxifen 10 mg BD.

Controls – 32 women with minor surgical ailment were selected from the Surgery Department of Maulana Azad Medical College, New Delhi. The mean age of 32 control women was 44.6 ± 11.27 years. Following criteria were maintained during the selection of controls: (i) No benign breast lesions as evident by clinical examination. (ii) No family history of breast cancer. (iii) No hormonal therapy within the period of 3 months before the time of collection of blood. (iv) No hypertension or cardiovascular disease. (v) No obese control or with habit of smoking or chronic alcohol intake.

After overnight fasting, peripheral venous blood samples were collected from cases and control subjects. Serum was separated within 6 hours of collection of blood and was stored at –20°C, until the samples were subjected to analysis. Triglycerides, total cholesterol and HDL-cholesterol were estimated by enzymatic

method. Triglycerides and total cholesterol were measured at 500 nm by standard coupled enzymatic procedures (30, 31). HDL-cholesterol was determined by phosphotungstic acid and magnesium chloride precipitation method. After centrifugation, the supernatant contained HDL-fraction was assayed for HDL-cholesterol using the cholesterol enzymatic method (32). LDL-cholesterol was calculated from the measured concentrations of total cholesterol, HDL-cholesterol and triglycerides, according to the formula of Friedewald et al (33).

Statistical analysis - The Student 't' test was employed to test group means of various lipids measured and their controls. The log transformation was employed to achieve the normality of the data. The group means of the various lipids measured at three different time points, such as, before initiation of therapy, subsequently during and after completion of cancer therapy were compared using repeated measures of analysis of variance. New-men Keuls multiple comparison test was employed to determine the significant difference in the mean values among the various pairs of different durations. If the New-men test statistics (Q) is more than the critical value at 5%, the two groups were considered to be significant. The similar analysis was carried out for premenopausal and postmenopausal women.

RESULTS

Table I shows the mean and standard deviation (S. D.) of various serum lipid fractions studied, i.e., triglycerides, total cholesterol, HDL-cholesterol and LDL-cholesterol. It was observed that the mean levels of triglycerides (189.3 ± 67.77 mg/dl), total cholesterol (206.8 ± 76.14 mg/dl) and LDL-cholesterol (134.6 ± 65.69 mg/dl) among

TABLE I : Mean, S.D. and statistical significance of different serum lipid fractions in control women and breast cancer patients before, during and after treatment.

Study group	*Triglycerides (mg/dl)*	*Total cholesterol (mg/dl)*	*HDL-cholesterol (mg/dl)*	*LDL-cholesterol (mg/dl)*
Breast cancer patients before treatment (n=61)	189.3±67.77$^{\alpha\beta\gamma}$	206.8±76.14$^{\alpha\beta\gamma}$	35.1±14.68$^{\alpha}$	134.6±65.69$^{\alpha\beta\gamma}$
Breast cancer patinets during treatment (n=61)	171.6±85.34$^{\alpha}$	191.0±72.95$^{\gamma}$	37.1±24.79$^{\alpha}$	119.4±64.82
Breast cancer patinets after treatment (n=61)	158.0±66.71$^{\alpha}$	178.0±65.77	38.2±19.59$^{\alpha}$	110.4±53.37
Normal control women (n=32)	105.5±38.56	167.6±32.71	47.3±14.20	96.8±33.00

$\alpha P<0.01$ (in comparison with normal controls);
$\beta P<0.001$ (in comparison with levels of during treatment);
$\gamma P<0.001$ (in comparison with levels of after treatment),

patients with breast cancer before treatment were found to be higher as compared to control women (105.5 ± 38.56 mg/dl, 167.6 ± 32.71 mg/dl and 96.8 ± 33.0 mg/dl respectively). The differences in mean values of these serum lipid fractions between breast cancer patients and control women were found to be statistically significant. However, the mean level of HDL-cholesterol (35.1 ± 14.68 mg/dl) among breast cancer patients was significantly lower than the control women (47.3 ± 14.20 mg/dl).

There was an overall decreasing trend in the levels of different lipid fractions among patients with breast carcinoma during the course of treatment, except the levels of serum HDL-cholesterol which revealed an increasing trend. It is an interesting observation that the levels of total cholesterol and LDL-cholesterol levels during cancer therapy of the patients reached to the normal levels as of the control subjects.

However, the mean triglycerides level among untreated breast cancinoma patients (189.3 ± 67.77 mg/dl) decreased significantly ($P<0.01$) after the completion of treatment (158.0 ± 66.71 mg/dl) (Table I). Similarly, the levels of total cholesterol and LDL-cholesterol also revealed a significant decrease at the end of the treatment

TABLE II : Mean, S.D. of different serum lipid fractions in pre- and postmenopausal breast cancer patients before, during and after treatment.

Study group	Triglycerides (mg/dl)	Total cholesterol (mg/dl)	HDL-cholesterol (mg/dl)	LDL-cholesterol (mg/dl)
Breast cancer premenopausal patients before treatment (n=31)	185.5±63.52$^{\delta}$	206.9±70.86$^{\delta}$	32.7±12.40	137.3±66.85$^{\delta}$
Breast cancer postmenopausal patients before treatment (n=30)	193.2±72.98$^{\varepsilon}$	206.8±82.47$^{\varepsilon\zeta}$	37.5±16.58	131.9±65.49$^{\varepsilon\zeta}$
Breast cancer premenopausal patients during treatment (n=31)	168.8±79.28	199.4±81.55$^{\delta}$	39.0±31.73	126.6±75.38
Breast cancer postmenopausal patients during treatment (n=30)	174.5±92.47	182.3±63.08	35.2±14.91	112.0±51.98
Breast cancer premenopausal patients after treatment (n=31)	153.3±63.01	174.5±66.34	36.1±14.41	112.0±60.30
Breast cancer postmenopausal patients after treatment (n=30)	162.9±71.08	181.6±66.01	40.3±23.87	108.7±46.12

$\delta P<0.05$ (in comparison with levels of after treatment in premenopausal cases);
$\varepsilon P<0.05$ (in comparison with levels of during treatment in postmenopausal cases);
$\zeta P<0.05$ (in comparison with levels of after treatment in postmenopausal cases).

(178.0 ± 65.77 mg/dl and 110.4 ± 53.37 mg/dl respectively). Further, no serum lipid fractions, except total cholesterol, significantly altered during the last phase of the treatment (i.e., levels during treatment versus after completion of treatment).

Table II shows mean values and S. D. of various serum lipid fractions and subsequent changes in their levels at different points of therapy amongst premenopausal and postmenopausal groups of breast cancer patients. In premonopausal women with breast cancer, except serum HDL-cholesterol, all parameters showed significantly lower levels after the completion of cancer therapy as compared to levels before initiation of treatment. Further, no serum lipid fractions of premenopausal cases altered significantly in the first phase (before vs. during) of the treatment; as well as in the last phase (during vs. after) of the treatment except total cholesterol which became 174.5±66.34 mg/dl from its during treatment level, i.e., 199.4±81.55 mg/dl.

Table II also shows significant decrease in the levels of total cholesterol and LDL-cholesterol after completion of treatment as compared to their levels before initiation of treatment among postmenopausal breast cancer patients. Serum triglycerides, total cholesterol and LDL-cholesterol levels of postmenopausal patients changed significantly in the first phase of treatment (before vs. during); while, no change in any serum lipid fraction was observed in the last phase (during vs. after) of treatment. Interestingly, like premenopausal patients, postmenopausal cases also did not show any statistically significant alteration in HDL-cholesterol levels throughout their cancer therapy.

DISCUSSION

The present study has highlighted the alterations in serum lipid fractions in patients with breast carcinoma before, during and after cancer therapy. The data of our study has revealed a higher levels of triglycerides, total cholesterol and LDL-cholesterol among breast cancer patients (before treatment) as compared to control women, which is in confirmation with the finding of Kumar et al (34) and Bahadur et al (35). Further, lower levels of HDL-cholesterol as observed in this study has also been reported by Knapp et al (36) and Hoyer and Engholm (37).

A decreasing trend in the levels of triglycerides, total cholesterol and LDL-cholesterol among women with breast cancer during the course of therapy as revealed through this study supports the findings as reported by Subramaniam et al (38). In addition to this, significant increase in the levels of HDL-cholesterol in these patients as noticed in the present study further supports the findings on the status of HDL-cholesterol as observed by Subramaniam and colleagues (38). Alexopoulos et al (39) found that untreated breast cancer patients were associated with hypercholesterolemia and total serum cholesterol, HDL-cholesterol and LDL-cholesterol levels decreased after the completion of chemotherapy. Similar findings were also demonstrated by Bahadur et al (35). Several workers (40–44) have also reported that tamoxifen reduces serum cholesterol and LDL-cholesterol levels in breast cancer patients; but the effect of tamoxifen on HDL-cholesterol varied with the individual patients (42, 43).

Like overall status of HDL-cholesterol levels during therapy, its levels did not change significantly both in premenopausal as well as in postmenopausal groups. Further, statistically significant alterations have been observed in serum triglycerides, total cholesterol and LDL-cholesterol levels. Amongst the various serum lipid fractions studied, total cholesterol levels could be considered as a most sensitive parameter than other lipids and lipoproteins, which clearly reflects the effect of cancer therapy.

There may be some underlying metabolic disturbances or hormonal factors responsible for the alterations of serum lipids. Alternatively the elevated lipid levels in untreated breast cancer patients might be related with dietary factors. Further, the changes during treatment, perhaps, are the result of dietary influence due to psychological stress associated with cancer-therapy. However, the data of our study is based on a limited number of cases and controls; therefore, the study needs to be expanded in order to demonstrate the effects of different treatment modalities on circulating lipid fractions in breast cancer patients.

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