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Original Research

Serum lipid profile of breast cancer patients in kashmir

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Abstract

Malignancy of the breast is one of the commonest causes of death in women aged between 40-45 years. The aim of this study was to carry out a comparative study to investigate the effect of lipid profile, oestradiol (EST) and obesity on the risk of a woman developing breast cancer. In this study, 120 women including 60 breast cancer patients (25 to 80 years) were assessed for lipid profile, EST and Body Mass Index (BMI) and 60 controls with similar age range. There was a significant increase in Body Mass Index (BMI) ($p = 0.011$), Total Cholesterol (TC) ($p<0.001$), triglyceride ($p = 0.026$) and low density lipoprotein (LDL-cholesterol) ($p = 0.001$) of the breast cancer patients compared to the controls. With the exception of EST that decreased, the lipid profile generally (TG) increased with age in both subjects and controls with the subjects having a much higher value than the control taken in the study. There was also a significant positive correlation between BMI and TC ($r^2 = 0.022$; $p = 0.002$) and also between BMI and LDL-cholesterol ($r^2 = 0.031$; $p = 0.0003$). Apart from EST and LDL-cholesterol that were increased significantly only in the postmenopausal phase in comparison to the controls, BMI, TC and TG were increased in both pre-menopausal and post menopausal phases with HDL-cholesterol remaining unchanged. This study confirms the association between lipid profile, BMI and increased breast cancer risk.

INTRODUCTION

The breasts are external symbol of beauty and womanhood in women; however cancer of the breast is responsible for the death of millions of women worldwide every year. Malignancy of the breast is one of the commonest causes of death in women aged between 40-45 years [1]. The incidence of this disease is rising in many countries such as Japan and other developing nations and has become a genuine public health problem, with one woman in ten, developing it in her lifetime throughout the world. The incidence of breast cancer increases with age, being uncommon below the age of 32 years; however its behaviour varies from slow to rapid progressive disease despite available treatment. There is a high mortality and poor survival in breast cancer because of partial to low utilization of breast cancer screening measures to detect tumours at a more treatable stage [2].

Breast cancer primarily affects women with occasional incidence in men and female to male ratio of breast cancer prevalence is reported to be 100:1 [1].The aetiology of the disease is unknown, although both low radiation and oncogenic viruses may play a role. A variety of interrelated hormonal, genetic, environmental, and physiological factors exert an influence on the development of this disease [3-4]. Despite the identification of high risk factors, only 35% of breast cancer can explained by known or suspected risk factors, including modifiable behaviours involving diet, overweight, and exercise and alcohol use [4]. Besides, breast cancer incidence, mortality and survival vary widely among woman of different racial or ethnic

background. Diet may also be a factor in the variation of the incidence of breast cancer among women from different racial or ethnic communities [4-5]. There has been much debate regarding the correlation between the intake of total and saturated fat and the risk of breast cancer.

Epidemiological studies have provided evidence on the postulated association between fat intake and breast cancer risk. Migrants from low-to-high-risk countries demonstrate substantial increase in breast cancer risk and corresponding increases in fat consumption [6]. Alteration of oestrogen levels due to changes in gut bacteria by increased fat consumption or obesity with underlying hormonal changes may lead to breast cancer.

Obesity is associated with decreased production of sex hormone-binding globulin, resulting in significant increase in the biological active unbound form of oestradiol [7], which promotes tumour growth in obese women. Increased levels of circulating lipids and lipoproteins have also been associated with breast cancer risk, though published results have been inconsistent [8].

Current statistics estimates the incidence at 5 cases/100,000 women being diagnosed in Kashmir. However breast cancer accounts for the largest number of deaths in United Kingdom and North America of about 34,000 per annum [9]. The aim of this study, therefore, is to find out the effect of lipids and obesity on breast cancer risk in Kashmir. Most of the patients in our study were of high body weight due to varied reasons since few years in this state

MATERIALS AND METHODS

This study was carried out at the Division of Veterinary Biochemistry Faculty of Veterinary Sciences & Animal Husbandry, (F.V.Sc & A.H) Shuhama, Srinagar, Kashmir, 190006 J & K State, in collaboration with Department of Biochemistry Govt. Medical College Srinagar. The study includes 40 premenopausal and 20 postmenopausal breast cancer female patients with 42 premenopausal & 18 postmenopausal normal females as controls of similar age (25-80). However, patients on some drug that interfere with lipid metabolism were excluded from the study. The control group was apparently healthy volunteers who were not taking oral contraceptives or any form of hormonal medication. Women were classified as postmenopausal if they had no menstrual cycles during the preceding three years or if they had undergone a hysterectomy without complete oophorectomy before menopause and were 47 years of age or older.

Patient details regarding age, age at menarche, age at first delivery, last day of menses and age at menopause is taken from the each patient during study. Venous blood samples were collected into Vacutainer plain tubes after an overnight fast from the patients. The blood was allowed to clot, centrifuged at 5000 rpm for 20 min within 25 min of sample collection and serum was collected and stored at -80 ^{o}C until assayed. Measurement of body weight was done scientifically to the nearest 0.5 kg. The height was measured with a wall-mounted ruler & was done to the nearest 0.5 cm. BMI was calculated by dividing weight (kg) by height squared (m^2).

Biochemical & ELISA assay

Total cholesterol (TC), triglycerides (TG), high density lipoprotein-cholesterol (HDL-cholesterol) and low density lipoprotein-cholesterol (LDL-cholesterol) were determined by fully automated Biochemical analyser (Hitachi 912) according to the reagent manufacturer's instruction. Serum oestradiol (E2) was determined by sandwich enzyme immunoassay (SIA) according to the reagent manufacturer's instruction.

RESULTS

The breast cancer patients have significantly higher BMI similar to overweight individuals with increased levels of total cholesterol, triglycerides and low density lipoprotein as compared to the control group (Table 1). Fifty five percent of the breast cancer patients had their serum total cholesterol greater or equal to the upper limit of the reference range (200 mg/dl) whilst 20% of the controls had their greater or equal to the upper limit of the reference range.

Comparisons between patients with different age ranges

With advanced age (Table 2), there was higher lipid profile as reflected by increase trend in TC, TG and LDL-cholesterol in the breast cancer patients up to age of 60 years and in the control group of 70 years of age. It has been found in this study, that the breast cancer patients have higher values in all parameters except HDL-cholesterol than the control group at corresponding age group. There is minimal change in the level of HDL-cholesterol as age increased for both breast cancer patients and the control (Table II). Even though, oestradiol level decreases as the age progresses in both the breast cancer patients and the control group, however breast cancer patients have higher level than the control at the corresponding age (Fig. 1). BMI shows little variation with age in both the breast cancer patients and the control group. However, breast cancer patients have slightly higher BMI than their corresponding control at the various age groups (Fig. 2)

Table 1. Characteristics of whole study population

Parameters	Total	Control	Patients
Age (years mean)	45.40±10.30	42.63±13.40	47.11 ±13.59
BMI(Kg/m^2)	25.50±4.70	24.80±4.80	26.30±4.70^{+}
TC (mg/dl)	178.20±49.20	174.40±40.50	202.00±53.60^{++}
TG (mg/dl)	107.70±59.30	99.50±47.20	115.80±68.50^{+}
HDL (mg/dl)	57.10±22.20	56.70±21.20	57.40±33.20
LDL (mg/dl)	108.50±35.32	99.50±33.20	117.60±42.70^{++}
EST (mg/dl)	35.50±37.30	36.80±39.30	34.30±35.50

The data are presented as Mean SD, BMI: Body Mass Index, TC: Total serum cholesterol, TG: Serum triglycerides, HDL: High Density Lipoprotein, LDL: Low Density Lipoprotein, EST: Oestradiol, $^{+}$p<0.05 and $^{++}$p<0.001 when the patients group was compared to the control group.

Table 2. Comparisons of biochemical parameters between breast cancer patients and control group divided into different ranges of age (years).

Age group (years)	25-30	31-40	41-50	51-60	61-70	71-80
Pa rameters			Patients			
TC (mg/dl)	182.93	198.94	203.89	205.29	196.60	178.25
TG (mg/dl)	95.30	101.60	117.52	139.08	98.95	136.35
HDL (mg/dl)	55.00	56.84	57.39	53.43	64.80	56.50
LDL (mg/dl)	108.43	116.19	116.06	125.40	113.02	115.25
			Controls			
TC (mg/dl)	166.09	172.92	175.47	175.04	204.97	104.90
TG (mg/dl)	78.42	95.91	106.97	109.82	110.35	95.00
HDL (mg/dl)	71.92	54.41	56.13	52.00	60.67	45.04
LDL (mg/dl)	76.03	100.86	105.99	102.00	124.67	37.80

The data are presented as Mean SD, BMI: Body Mass Index, TC: Total serum cholesterol, TG: Serum triglycerides, HDL: High Density Lipoprotein, LDL: Low Density Lipoprotein.

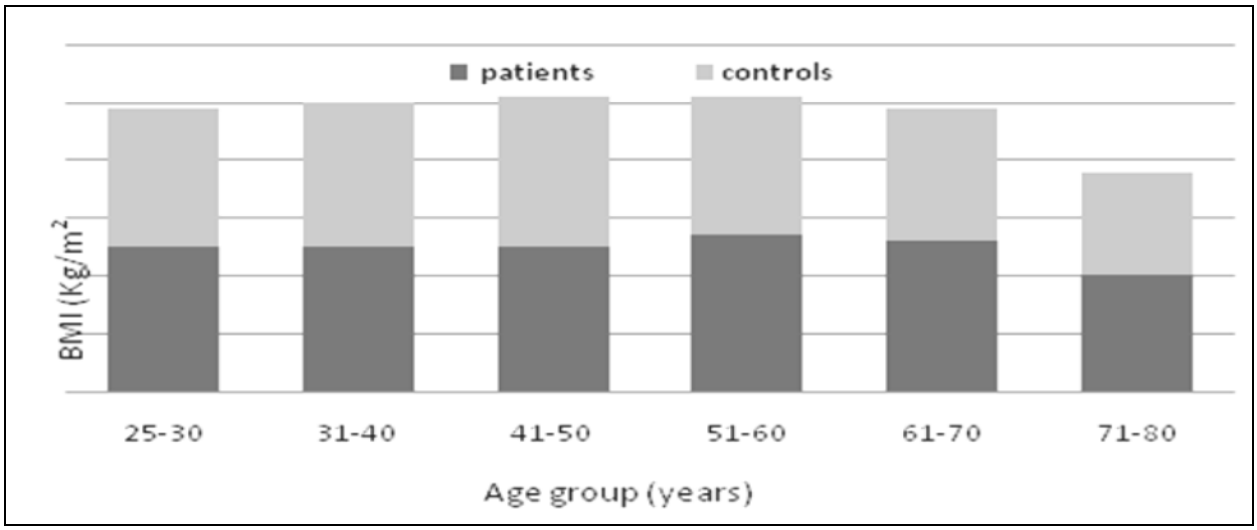

Figure 1.

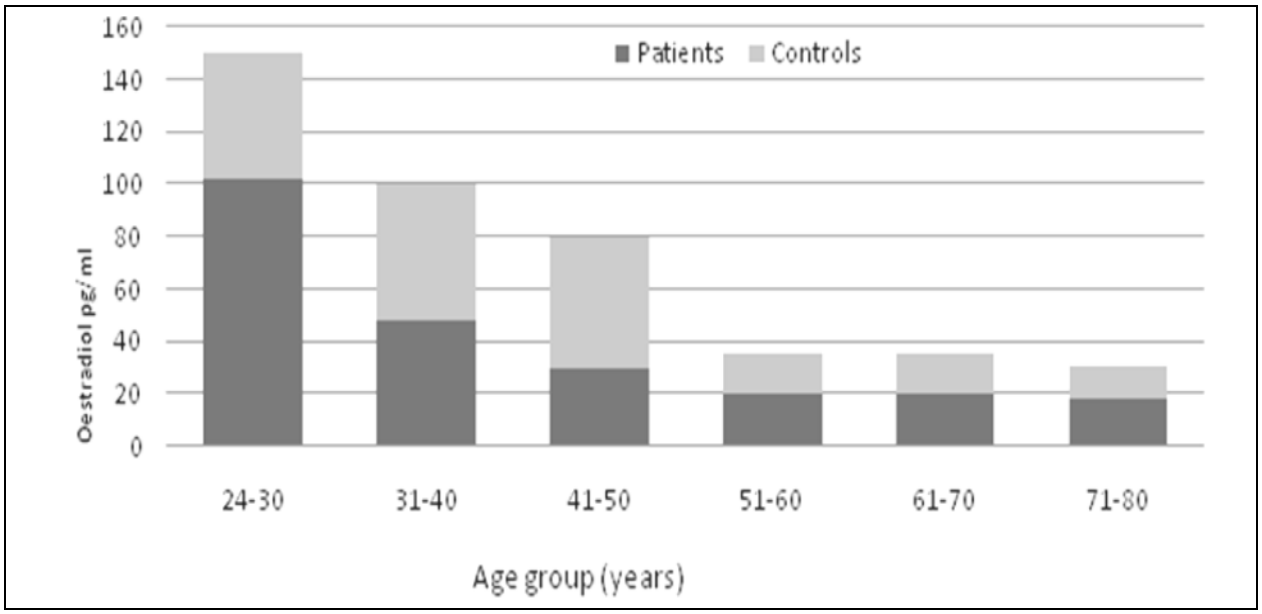

Figure 2.

Table 4. Comparison of pre and post menopausal lipid values to the controls.

Parameters	Pre Mc	Pos Mc	Pre Mp	Pos Mp
BMI (Kg/m^2)	24.90±4.300	24.80±5.200	26.50±4.500	26.30±4.900
TC (mg/dl)	172.52±34.00	17.91±41.26	201.00±64.70^{++}	202.21±44.02
TG (mg/dl)	92.01±37.01	101.91±31.44	102.65±51.14^{+}	124.91±78.21
HDL (mg/dl)	58.43±21.41	54.40±18.81	55.51±19.62	58.92±25.72
LDL (mg/dl)	95.20±32.20	104.70±33.70	116.44±49.37	117.51±37.31
EST (pg/ml)	50.00±34.44	14.50±4.110	50.89±42.90	20.90±12.01

The data are presented as Mean SD, BMI: Body Mass Index, TC: Total serum cholesterol, TG: Serum triglycerides, HDL: High Density Lipoprotein, LDL: Low Density Lipoprotein, EST: Oestradiol, PRE.MC: PRE-menopausal control, PRE.MP: Pre-menopausal patients, POS.MC: Post-menopausal control, POP.MP: post-menopausal patients, $^{+}$p<0.05 and $^{++}$p<0.001 when pre-menopausal compared to control, $^{+}$p<0.05 and $^{++}$p<0.001 when postmenopausal compared to control.

Associations between age, BMI, EST and biochemical parameters:

There was a significant positive correlation between age and TG; age and LDL-cholesterol and significant but negative correlation between age and oestradiol in this study. BMI also showed a significant but positive correlation with TC and LDL-cholesterol (Table 3).

Comparison of pre- and post-menopausal lipid values to the control:

From Table 4, the breast cancer patients have significantly higher BMI, TC and LDL-cholesterol than the control group during both pre- and post-menopausal stage. The results demonstrated a 15% increase in total serum cholesterol levels of premenopausal patients compared to the control women. However, oestradiol and TG are only significantly raised during the postmenopausal stage and not the premenopausal stage.

DISCUSSION

In this study 120 women comprising 60 breast cancer patients and 60 controls were assessed to find out the relationship between Body Mass Index (BMI), lipids and oestradiol and breast cancer risk. The mean age at diagnosis of breast cancer patients selected at random was 48.0 years (Table 1). Majority of the women with breast cancer were found to be within the age group 30-50 (70%), with 65% of this number not aware that they had breast cancer.

It has also been hypothesized that the adult weight gain or increased BMI is a strong predictor of postmenopausal breast cancer risk [10]. Several other case-control and prospective studies have also reported that elevated total serum cholesterol is associated with increased breast cancer risk [11]. The higher BMI in the breast cancer patients as compared to the control and the significantly raised BMI level in the breast cancer patients during the pre- and post-menopausal period, indicates a strong association between increased BMI and breast cancer risk. This observation is in agreement with the findings of previous studies [12]. Although, very weak or no association has also been reported by [13].The significantly increased level of TC in the breast cancer patients compared to the controls and its significant positive correlation with BMI in these patients, indicates that, there is an association between TC, BMI and breast cancer risk. This study has also demonstrated a 16% increase in total serum cholesterol levels of the premenopausal patients compared to the control group which is in agreement with a 15% increase in total serum cholesterol levels for premenopausal patients reported by other studies by [14,15]. This study also demonstrated a significant difference between total serum cholesterol levels of postmenopausal cases and the controls. This is in contrast with the non-significant change in total serum cholesterol of postmenopausal case reported [16,17].The association between total serum cholesterol levels and breast cancer risk still seems to be controversial and published results are inconsistent. However a major link has been established between cell growth and cholesterol biosynthesis. If cholesterol synthesis is inhibited and no exogenous cholesterol is available, cell growth will be blocked [18,19]. Cholesterol inhibition, either by decreasing cholesterol availability (lowering of plasma cholesterol) or by decreasing intracellular cholesterol synthesis could inhibit tumor cell growth and possibly prevent carcinogenesis [18].

It has been reported in this study that the serum triglyceride in postmenopausal cancer patients were higher than the control. The percentage increase of triglyceride levels (22%) in this study is consistent with an earlier report of 22% [10], but much lower than the percentage increase of triglyceride levels (31%) reported some were else [10]. On the other hand, there was no significant change in serum triglyceride levels between the premenopausal patients and controls. Though elevated serum triglyceride levels in premenopausal breast cancer patients have been reported [20]. No significant difference was observed in HDL-cholesterol levels between the breast cancer patients and controls in this study; however LDL-cholesterol levels increased between the patients and the controls. The increase in LDL-cholesterol levels of premenopausal patients was (22%) and that of postmenopausal patients was (12%) when compared with the controls. The elevated serum LDL-cholesterol, which is more susceptible to oxidation, may result in high lipid peroxidation in breast cancer patients. This may be cause of oxidative stress leading to cellular and molecular damage thereby resulting in cell proliferation and malignant conversions. Several studies have investigated the role of diet especially dietary fat, in the etiology of breast carcinoma, but its significance has remained controversial [21,22]. Although, the relationship between diet and serum lipid levels is complex, diets containing a large amount of saturated fats may lead to higher lipid levels, particularly cholesterol [14]. Elevated lipid levels precede the development of obesity and breast cancer and thus, may have an etiological or predictive significance [21].

Obesity is not only associated with decreased production of sex hormone binding globulin [7] which results in a significant increase in biologically active unbound form of oestradiol, but also results in the increased production of oestrone, which is produced by aromatization of androstenedione in peripheral adipose tissue. It therefore leads to an overall increase in the active levels of circulating oestrone and oestradiol which may promote the growth and metastatic potential of breast tumor in larger women.

In this study, no significant change was observed in oestradiol levels between the premenopausal cases and the controls. During the postmenopausal phase however, this study demonstrated a significant increase in the level of oestradiol compared to the controls. There was a 50% increase in oestradiol which is much higher than the 30% reported else were [23], earlier data with regard to total oestrogens also suggest increased levels of oestrogen in breast cancer patients [24,25]. It has been hypothesized that the risk of breast cancer is essentially determined by the intensity and duration of exposure of breast epithelium to menopausal oestrogen [26].

Oestrogen, like all other steroid hormones is able to cross cell membranes and bind in a specific manner to their receptors to form a specific hormone-receptor complexes. These complexes bind to specific DNA sites in oestrogen dependent tissues called Hormone Responsive Elements and cause increased transcription of various genes. The end result is increased cell growth, proliferation and protein synthesis and enzyme synthesis [27], with concurrent carcinogenesis.

The findings of this study confirm the detrimental effect of increased BMI or obesity on breast cancer risk. Obesity leads to overall increase in the active levels of circulating oestrone and oestradiol, which may promote the growth and metastatic potential of breast

tumors in obese women. The results also indicate an increased risk of breast cancer with increasing serum oestradiol levels especially during the postmenopausal stage. The mean age (48.0 years) of onset of breast cancer from this study is earlier than in other populations.

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