Incidence of metabolic syndrome in breast cancer survivors on adjuvant hormonal therapy

Sir,

The increasing incidence of breast cancer in Indian women has been coupled with a significant rise in the population of breast cancer survivors, particularly among women with estrogen receptor-positive tumors.[1] There is growing interest in and concern about the co-morbidities that this clinical population may face related to the adjuvant hormonal treatment received, as studies have shown that the use of aromatase inhibitors (AIs) and selective estrogen receptor modulators (SERMs) in their treatment has raised concerns about agent-specific potential to decrease high-density lipoprotein (HDL) levels and its possible impact on cardiovascular risk.[2] Elevated C-reactive protein (CRP) levels along with the development of metabolic syndrome has also been associated with this group of women.[3] Since there is insufficient data on the occurrence of these events in Indian women, this study attempts to provide a better understanding of the commonality of metabolic syndrome and its relationship with CRP levels in breast cancer survivors, which in turn will support the early diagnosis and management of these metabolic disturbances.

This study was conducted over a period of 6 months, on breast cancer survivors, attending the hospital Tumour Clinic, who either were receiving or had completed 5 years of tamoxifen or letrozole. All women had undergone surgery or had received the full course of radiation or chemotherapy at least 6 months prior to the onset of this study. Patients with significant body weight loss in the 12 months prior to study enrolment, or with history of diabetes, hypertension or obesity before the onset of hormonal therapy, were excluded.

History regarding the demographic details, treatment history and the ongoing therapy (SERMs or AIs) and intake of any other medications was collected, after obtaining an informed written consent from the participants. This was followed by individual assessment of dietary intake and physical activity. To assess the physical activity, the questionnaire designed by the World Health Organization for the surveillance of risk factors of non-communicable diseases was used. A comparison of dietary pattern and physical activity assessment with reference charts in literature rules out the possibility of these parameters solely contributing to the development of metabolic syndrome. Body weight, height and waist circumference were then measured. A fasting blood sample (5 ml) was taken from all the subjects to estimate the lipid, glucose, glycated hemoglobin and CRP levels.

The criteria used to determine the presence of metabolic syndrome in the subjects were those set by the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III).[4] The Chi-square test was used to compare the occurrence of metabolic syndrome between the two groups. Independent Student's "*t*" test was used to compare the continuous data between the two groups. All statistical analyses were carried out at 5% level of significance and $P < 0.05$ was considered as significant.

A total of 28 women were enrolled in the study. Their age ranged between 32 and 70 years, with the median age being 50. Three women were hypertensive, the duration ranging from 2 months to 2 years and one woman had a history of

diabetes mellitus 2 months prior to enrolment in the study. The calories consumed per day by each woman were less than the recommended amount and the median dietary deficit was 50.7%. The physical activity of 71.4% of women came under the high category.

The age at the time of diagnosis ranged from 28 to 68 years (mean 50.8 years). All the women had undergone surgery and chemotherapy as a part of the treatment received for breast cancer. Of the 28 women, 18 were on tamoxifen and 5 on letrozole. The remaining five had completed a course of tamoxifen and had been switched over to letrozole. Four women had completed their course of hormonal therapy. The mean duration of exposure to this hormonal therapy was 3.3 years.

The anthropometric measures demonstrated a mean body weight and BMI of 52.25 kg (±12.58) and 25.29 kg/m^2 (±5.9), respectively. 71.4% of the women fell in overweight and obese category. A diagnosis of metabolic syndrome could be made in 32.14% of the breast cancer survivors using NCEP-ATP III criteria.[4] Tables 1 and 2 show the patterns of individual criteria with elevated blood pressure being the most common criterion present in the affected group.

There were no significant differences across hormone treatment groups (SERMS vs. AIs) for prevalence of metabolic syndrome, although the small sample size limits interpretation of these analyses (*P* value 1.00). When comparing the lipid profiles of the two groups, that is, women with and without metabolic syndrome, it was found that although the HDL levels did not significantly differ between them (*P* value 0.82), the triglyceride levels were significantly higher in women with metabolic syndrome (*P* value 0.02). The mean waist circumference of the affected group was also significantly higher (*P* value 0.0042). Moreover, the BMI of the women with metabolic syndrome was also found to be significantly higher than that of the unaffected women (*P* value 0.0006).

The mean fasting glucose values of the women with metabolic syndrome were significantly higher when compared to that of the rest of the study population (*P* value 0.01). Both the systolic and diastolic pressures of the group with metabolic syndrome were significantly higher than those of the group which did not have metabolic syndrome (*P* value 0.0006). The mean CRP level in our population was 4.9 mg/dL, significantly above the clinical norm of <1.0 mg/dL.

The incidence of metabolic syndrome in our study is less than the 54.8% found in the study conducted by Thompson *et al*.[1] This can be attributed to the fact that in the latter the study population included women only with BMI greater than 25 kg/m^2. The ICMR task force collaborative study reported the prevalence of metabolic syndrome to be 30% in urban areas of Delhi and 11% in rural Haryana using ATP-3 criteria. The differences in the incidence may be attributed to the socioeconomic difference in study areas and the different criteria that were used for defining metabolic syndrome. Although our study population consisted only of rural women, the value obtained in our study is considerably higher than these trends.

On comparing the two groups, that is, women with and without metabolic syndrome, it was found that those with the syndrome had higher triglyceride levels and though the HDL levels did not differ significantly, they were consistently low in most women (less than 50 mg/dl in 89.3% of the study population). This points to disarray in the lipid profiles, especially in the women with metabolic syndrome.

That the CRP levels are significantly elevated above the reference levels of <1.0 mg/L is of value given the association

Table 1: Distribution of the NCEP-ATP III criteria among breast cancer survivors (*N*=28)

NCEP-ATP III criteria	Mean (SD)	Median	Range
Fasting blood glucose levels (mg/dL)	71.14 (12.62)	67.5	60-105
Blood pressure (mmHg):			
Systolic pressure	124 (14.89)	127	90-160
Diastolic pressure	89 (17.29)	84	68-138
Triglyceride levels (mg/dL)	111.28 (36.71)	111	43-237
HDL levels (mg/dL)	41.96 (7.72)	41	22-66
Waist circumference (cm)	81.21 (11.72)	83	56-107

NCEP-ATP III=National Cholesterol Education Program-Adult Treatment Panel III, SD=Standard deviation, HDL=High-density lipoprotein

Table 2: Percentage of the NCEP-ATP III criteria amongst the breast cancer survivors

NCEP-ATP III criteria	Percentage of study population who fulfill individual criteria (%) (*N*=28)	Percentage of women with metabolic syndrome who fulfill individual criteria (%) (*N*=9)
Fasting blood glucose levels (mg/dL) (>100)	7.1	44.4
Blood pressure (mmHg): (>130/85)	50	100
Systolic pressure		
Diastolic pressure		
Triglyceride levels (mg/dL) (>150)	10.7	44.4
HDL levels (mg/dL) (<50)	89.3	88.6
Waist circumference (cm) (>88)	32.14	66.6

NCEP-ATP III=National Cholesterol Education Program-Adult Treatment Panel III, HDL=High-density lipoprotein

between elevation in CRP levels and risk for CVD among women.[3] This level was similar to the 5.1 mg/dl obtained by Thompson *et al*.[1] The elevated CRP levels may reflect the fact that most of the women in our population had increased body weight and waist circumferences since they are known associated factors.[5] It may also be secondary to the concomitant hormonal therapy, prior cancer treatment, and possibly to an underlying higher baseline inflammatory state in women at risk for breast cancer.[5]

A recent epidemiological analysis from the Health, Eating, Activity and Lifestyle (HEAL) study suggested that tamoxifen use was associated with reduced CRP levels.[6] These findings are limited by the small number of study subjects and the lack of a control group for comparison. However, they support the hypothesis that metabolic syndrome is highly prevalent in overweight breast cancer survivors, suggesting that clinicians should evaluate the entire composite criteria for diagnosing metabolic syndrome routinely when assessing a breast cancer survivor's cardiovascular disease (CVD) risk as CVD is one of the leading causes of non-cancer-related morbidity and mortality in these women. By understanding better and modulating these risk factors, primary care providers can positively impact their long-term outcome using lifestyle interventions such as diet and physical activity interventions and targeting weight control along with improvements in metabolic indicators.

Further, case-controlled studies can be conducted with a larger sample size to establish a definite association between the hormonal therapy and the incidence of metabolic syndrome. Also, whether the type of hormonal therapy, that is, SERMs versus AIs, contributes to increasing the risk of metabolic syndrome can be determined.

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Conflicts of interest
There are no conflicts of interest.

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