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A STUDY TO ASSESS METABOLIC SYNDROME AS A RISK FOR CARCINOMA BREAST: AN OBSERVATIONAL SYUDY

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ABSTRACT

Aim and objectives: To assess metabolic syndrome as a risk for Carcinoma Breast.

Material and methods: Study was performed in 50 new histologically confirmed breast cancer patients, either pre- or post-menopausal. All patients underwent assessment of anthropometric parameters and laboratory testing.

Results: Metabolic syndrome was present in 64% of the patients, indicating that more than half of the study population was affected. The remaining 36% did not have metabolic syndrome. This distribution shows a higher prevalence of metabolic syndrome among the patients of carcinoma breast. Patients with MS in breast cancer patients had a significantly higher body weight (mean 68.28 kg) compared to those without MS (mean 58.89 kg, $p<0.001$). Similarly, BMI is higher in the MS group (mean 28.52) in breast cancer patients than in the non-MS group (mean 24.03, $p<0.001$). Waist circumference (mean 97.31 cm vs. 85.28 cm, $p<0.001$) and hip circumference (mean 115.13 cm vs. 107.61 cm, $p<0.001$) were also significantly larger in patients with MS in breast cancer patients. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were significantly elevated in patients with MS in breast cancer patients. Fasting plasma glucose levels were significantly higher in the MS group (mean 141.19 mg/dL) in breast cancer patients compared to the non-MS group (mean 96.94 mg/dL, $p<0.001$) in breast cancer patients. Serum triglyceride levels were also elevated in patients with MS (mean 191.66 mg/dL) versus those without MS (mean 136.94 mg/dL, $p<0.001$) in breast cancer patients. Although HDL-C levels were slightly lower in the MS group (mean 47.94 mg/dL) in breast cancer patients compared to the non-MS group (mean 53.83 mg/dL), this difference was not statistically significant ($p=0.15$).

Conclusion: Metabolic syndrome is present in majority (64%) of the total breast carcinoma patients. Our study adds to the understanding of the connection between

metabolic syndrome and risk of breast cancer, hence, confirming the correlation between metabolic syndrome and carcinoma breast patients. Engaging in multiple methods such as diet, physical activity, and managing stress is crucial in managing insulin resistance and obesity and enhancing cancer prognosis.

Keywords: Metabolic syndrome, breast cancer, waist circumferance, lipid profile, blood pressure.

INTRODUCTION:

The metabolic syndrome consists of an array of metabolic abnormalities that includes central obesity, hyperglycemia, hyperinsulinemia, hypertension, hypertriglyceridemia, decreased high density lipoprotein (HDL) and hypercholesterolemia.

The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) criteria. Presence of three or more of the following clinical criteria is essential for the diagnosis of MetS.

1. Waist circumference >88 cm

2. BP ≥130/85 mmHg

3. HDL cholesterol <50 mg/dl

4. Triglyceride level ≥150 mg/dl

5. Fasting plasma glucose ≥100 mg/dl.

MetS potentially increases the chances of developing breast cancer, by disrupting a variety of interconnected hormonal pathways—including those that involve growth factors, insulin, estrogen, and cytokines.

Different molecular pathways may be activated by MetS via alterations in endocrine, metabolic, and immune cells. These modifications subsequently impact the development of breast tumors. Increased levels of circulating estrogen, such as estradiol, increased insulin levels, decreased circulating adiponectin levels, elevated plasma leptin concentration, and increased production of proinflammatory cytokines, including interleukin-6 and TNF-alpha, are examples of pathways that promote breast cancer cell proliferation and inhibit apoptosis.[1,2]

Obesity induces upregulation of signaling pathways associated with tumor cells, namely the oncogenic Ras-MAPK and PI3K-Akt pathways. Moreover, it is well-known

that the mTOR pathway, which is activated by the Akt pathway, promotes the proliferation of tumor cells.

Insulin resistance can lead to hyperinsulinemia, where the pancreas produces more insulin to maintain blood glucose levels. High levels of insulin and IGF can promote the proliferation of breast cancer cells and inhibit apoptosis (cell death), thereby facilitating cancer progression.[3] Older females often experience chronic low-grade inflammation, which is a hallmark of metabolic syndrome. Inflammatory cytokines and adipokines (hormones produced by adipose tissue) can create an environment conducive to cancer development and progression. This inflammatory state is more pronounced in individuals with obesity and metabolic syndrome, further increasing breast cancer risk in the elderly.[4]

AIMS AND OBJECTIVES:

To assess metabolic syndrome as a risk for Carcinoma Breast.

MATERIAL AND METHODS:

This cross-sectional prospective study was conducted at the Government Medical College and Hospital, Guru Nanak Dev Hospital (GNDH), Amritsar from December 2022 to April 2024. 50 New Histologically confirmed breast cancer patients, either pre- or post-menopausal. All patients underwent assessment of anthropometric parameters and laboratory testing. Informed consent was obtained after a detailed explanation of the procedure Pregnant or lactating females, Patients with history of drug intake such as steroids, androgens, oral contraceptives, or drugs known to interfere with glucose or lipid metabolism and Patients who had received neoadjuvant chemotherapy at the time of presentation were excluded from the study.

Physical Examination

All patients underwent assessment of anthropometric parameters:

1. **Body Weight:** Measured using an electronic scale to the nearest 0.1 kg, with patients barefoot and wearing light clothing.

2. **Height**: Determined using a portable Seca stadiometer according to World Health Organization norms.

3. **Body Mass Index (BMI)**: Calculated as weight in kilograms divided by height in meters squared. Obesity was defined as a BMI value of 27 kg/m² or higher.

4. **Waist and Hip Circumferences:** Measured to calculate the waist-to-hip ratio

(WHR). Upper body fat distribution was defined as a WHR greater than 0.8.

5. **Blood Pressure (BP):** Measured on the right arm using a sphygmomanometer after a minimum rest period of 5 minutes. The average of three measurements was recorded. Hypertension was defined as systolic BP (SBP) ≥140 mmHg or diastolic BP (DBP) ≥90 mmHg, following the criteria of the Seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.

Laboratory Investigations

A blood sample of approximately 10 ml was taken from each participant after an overnight fast of at least 8 hours. The samples were analyzed for:

1. **Fasting Plasma Glucose**
2. **Serum Triglyceride Level**s
3. **High-Density Lipoprotein (HDL) Levels**
4. **Low-Density Lipoprotein (LDL) Levels**
5. **Serum Cholesterol Levels**

RESULTS:

A. METABOLIC SYNDROME:

Metabolic syndrome was present in 64% of the patients, indicating that more than half of the study population was affected. The remaining 36% did not have metabolic syndrome. This distribution shows a higher prevalence of metabolic syndrome among the patients of carcinoma breast.

B. MENOPAUSAL STATUS AND METABOLIC SYNDROME:

Menopausal status also showed a significant association with metabolic syndrome. Among premenopausal patients, 15.6% had metabolic syndrome, while 50.0% did not. In contrast, 84.4% of menopausal patients had metabolic syndrome, and 50% did not. The chi-square value of 6.75 and p-value of 0.009 indicates a significant association between menopausal status and metabolic syndrome in breast cancer patients.

C. WAIST CIRCUMFERENCE AND METABOLIC SYNDROME:

Waist circumference showed a significant association with metabolic syndrome in breast cancer patients. Among breast cancer patients with normal waist circumference, only 6 (18.8%) had metabolic syndrome, whereas 13 (72.2%) did not. Conversely, among patients with abnormal waist circumference, 26 (81.2%) had metabolic

syndrome, while only 5 (27.8%) did not. The chi-square value of 13.98 and p-value of <0.001 indicates a strong significant association in breast cancer patients.

D. BP AND METABOLIC SYNDROME:

Overall blood pressure, considering both systolic and diastolic measures, was significantly associated with metabolic syndrome in breast cancer patients. Among breast cancer patients with normal blood pressure, 18 (100.0%) did not have metabolic syndrome, whereas 22 patients (68.8%) with elevated blood pressure had metabolic syndrome. The chi-square value of 22.09 and p-value of <0.001 indicates a strong significant association in breast cancer patients.

E. FBS AND METABOLIC SYNDROME:

Fasting blood sugar levels were significantly associated with metabolic syndrome in breast cancer patients. Among patients with normal FBS, 17 (94.4%) did not have metabolic syndrome, whereas 20 patients (62.5%) with elevated FBS had metabolic syndrome. The chi-square value of 15.33 and p-value of <0.001 indicates a strong significant association in breast cancer patients.

F. TG AND METABOLIC SYNDROME:

Triglyceride levels were significantly associated with metabolic syndrome in breast cancer patients. Among patients with normal TG levels, 15 (83.3%) did not have metabolic syndrome, whereas 24 patients (75.0%) with elevated TG had metabolic syndrome. The chi- square value of 15.78 and p-value of <0.001 indicates a strong significant association in breast cancer patients.

G. HDL-C AND METABOLIC SYNDROME:

High-density lipoprotein levels were significantly associated with metabolic syndrome in breast cancer patients. Among patients with normal HDL levels, 12 (66.7%) did not have metabolic syndrome, whereas 23 patients (71.9%) with low HDL had metabolic syndrome. The chi-square value of 7.02 and p-value of <0.001 indicates a significant association in breast cancer patients.

H. ASSOCIATION BETWEEN VARIOUS PARAMETERS AND METABOLIC SYNDROME:

PARAMETERS	Metabolic syndrome		T-	p-value
	absent (n=18)	present (n=32)		

	Mean	SD	Mean	SD	test	
Age (years):	42.94	8.60	56.81	9.64	5.070	<0.0001
Duration of menstrual cycle (days):	4.61	1.14	4.56	1.24	0.14	0.89
Age of menarche:	11.28	1.45	11.69	1.57	-0.91	0.37
Number of menstrual cycles per year	11.06	2.29	10.31	2.95	0.92	0.36
Body weight(kgs)	58.89	7.65	68.28	8.69	-3.82	0.00
Height(cms)	154.00	5.14	153.97	4.78	0.02	0.98
BMI:	24.03	3.17	28.52	3.45	-4.55	0.00
Waist circumference(cms):	85.28	7.94	97.31	9.37	-4.59	0.00
Hip circumference (cms):	107.61	7.18	115.13	7.88	-3.34	0.00
Waist to hip circumference ratio (WHR):	0.79	0.04	0.84	0.05	-4.08	0.00
SBP (mmHg):	116.67	9.77	137.47	16.74	-4.82	0.00
DBP (mmHg):	76.44	4.73	89.03	10.53	-4.79	0.00
Fasting plasma glucose (mg/dL):	96.94	14.78	141.19	45.60	-3.98	0.00
Serum triglyceride levels (mg/dL):	136.94	24.85	191.66	53.97	-4.05	0.00
HDL-C level (mg/dL):	53.83	14.74	47.94	13.26	1.45	0.15
Low-density lipoprotein level (mg/dL):	90.72	14.66	129.19	29.13	-5.23	0.00
Serum cholesterol level (mg/dL):	193.83	28.44	252.81	59.43	-3.95	0.00

- **General Characteristics:**

The average age of patients with metabolic syndrome (MS) in breast cancer patients is 56.81 years compared to 42.94 years for those without MS, whose difference is statistically significant ($p<0.0001$).

- **Anthropometric Measurements**

Patients with MS in breast cancer patients had a significantly higher body weight (mean 68.28 kg) compared to those without MS (mean 58.89 kg, $p<0.001$). Similarly, BMI is higher in the MS group (mean 28.52) in breast cancer patients than in the non-MS group (mean 24.03, $p<0.001$). Waist circumference (mean 97.31 cm vs. 85.28 cm, $p<0.001$) and hip circumference (mean 115.13 cm vs. 107.61 cm, $p<0.001$) were also

significantly larger in patients with MS in breast cancer patients. The waist-to-hip ratio was higher in the MS group (mean 0.84) compared to those without MS (mean 0.79, $p<0.001$).

- **Blood Pressure**

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were significantly elevated in patients with MS in breast cancer patients. The mean SBP in the MS group is 137.47 mmHg compared to 116.67 mmHg in the non-MS group ($p<0.001$). Similarly, the mean DBP was

89.03 mmHg in the MS group and 76.44 mmHg in the non-MS group ($p<0.001$) in breast cancer patients indicating significant association.

- **Metabolic Parameters**

Fasting plasma glucose levels were significantly higher in the MS group (mean 141.19 mg/dL) in breast cancer patients compared to the non-MS group (mean 96.94 mg/dL, $p<0.001$) in breast cancer patients. Serum triglyceride levels were also elevated in patients with MS (mean 191.66 mg/dL) versus those without MS (mean 136.94 mg/dL, $p<0.001$) in breast cancer patients. Although HDL-C levels were slightly lower in the MS group (mean 47.94 mg/dL) in breast cancer patients compared to the non-MS group (mean 53.83 mg/dL), this difference was not statistically significant ($p=0.15$). However, LDL levels were significantly higher in the MS group (mean 129.19 mg/dL) compared to those without MS (mean 90.72 mg/dL, $p<0.001$) in breast cancer patients. Additionally, serum cholesterol levels were significantly elevated in patients with MS (mean 252.81 mg/dL) in breast cancer patients compared to those without MS (mean 193.83 mg/dL, $p<0.001$).

DISCUSSION:

In order to guarantee the accuracy of the MetS diagnosis and to estimate metabolic syndrome as a risk factor for breast cancer, MetS components was identified in the current study using waist circumference and blood determinations.

The present study included 50 female patients with histologically confirmed carcinoma

breast, admitted in the Department of General Surgery, Government Medical College, Amritsar, to assess the association between metabolic syndrome and Carcinoma Breast. The results of the present study are discussed below.

In present study we observed that Metabolic syndrome was present in 64% of the breast cancer patients, indicating that more than half of the study population is affected. The remaining 36% did not have metabolic syndrome. In the study by Wani et al the prevalence of MetS in cohort of breast cancer patients was 40%.

Several meta-analyses and cohort studies have established a strong association between MetS and a raised risk of breast cancer.[5,6] For example, a meta-analysis involving 195 women conducted by Guo et al[6] found that those with MetS had a 15% more risk of developing cancer breast as compared to those without MetS. MetS increases breast cancer risk in postmenopausal women (adjusted RR = 1.25, 95% CI: 1.12 to 1.39). In contrast, the risk is reduced in premenopausal women with MetS (RR = 0.82, 95% CI: 0.76 to 0.89).

Different molecular pathways may be activated by MetS via alterations in endocrine, metabolic, and immune cells. These modifications subsequently impact the development of breast tumors. Increased levels of circulating estrogen, such as estradiol, increased insulin levels, decreased circulating adiponectin levels, elevated plasma leptin concentration, and increased production of proinflammatory cytokines, including interleukin-6 and TNF-alpha, in metabolic syndrome are examples of pathways that promote cell proliferation resulting in breast cancer.

Among premenopausal patients, 35.7 % had metabolic syndrome, while 64.28% did not. In contrast, 75% of menopausal patients had metabolic syndrome, and 25% did not. The chi-square value of 6.75 and p-value of 0.009 indicates a significant association.

The prevalence of MetS increases significantly with age, especially in postmenopausal women. Studies conducted by Guo et al[6] and berrino et al[7] indicated that women over 50 have a higher prevalence of MetS, which tends to increase the risk of breast cancer. According to Guo et al[6], the hormonal changes accompanying menopause can exacerbate metabolic issues, further increasing breast cancer risk. Postmenopausal weight gain, often linked with MetS, is a significant factor in breast cancer incidence and progression.

The risk of breast cancer is particularly higher in postmenopausal women. Hormonal changes during menopause contribute to an increased likelihood of weight gain and fat distribution changes, primarily leading to central obesity. Central obesity is associated with insulin resistance and chronic inflammation, both of which are critical components

of metabolic syndrome.[8] Inflammatory cytokines and adipokines (hormones produced by adipose tissue) can create an environment conducive to cancer development and progression. This inflammatory state is more pronounced in individuals with obesity and metabolic syndrome, further increasing breast cancer risk in the elderly.[4]

In present study we observed that patients with MetS had a significantly higher body weight, with a mean of 68.28 kg, compared to those without MS, whose mean weight was 58.89 kg ($p<0.001$). Similarly, BMI was higher in the MS group, with a mean of 28.52, versus 24.03 in the non-MS group ($p<0.001$). Waist circumference was also significantly larger in patients with MS, averaging 97.31 cm compared to 85.28 cm in those without MetS ($p<0.001$). Additionally, hip circumference was greater in the MS group, with a mean of 115.13 cm compared to 107.61 cm in the non-MS group ($p<0.001$). The waist- to-hip ratio was higher in the MS group, averaging 0.84, compared to 0.79 in the non-MS group ($p<0.001$).

SBP&DBP were significantly elevated in patients with MS. The mean SBP in the MS group was 137.47 mmHg, compared to 116.67 mmHg in the non-MetS group ($p<0.001$). Similarly, the mean DBP was 89.03 mmHg in the MetS group, compared to 76.44 mmHg in the non-MetS group ($p<0.001$).

FBS was significantly higher in the MetS group, with a mean of 141.19 mg/dL, compared to 96.94 mg/dL in the non-MetS group ($p<0.001$). Serum triglyceride levels were also elevated in patients with MetS, with a mean of 191.66 mg/dL, versus 136.94 mg/dL in those without MetS ($p<0.001$). Although HDL-C levels were slightly lower in the MetS group, with a mean of 47.94 mg/dL compared to 53.83 mg/dL in the non-MetS group, this difference was not statistically significant ($p=0.15$). However, LDL levels were significantly higher in the MetS group, with a mean of 129.19 mg/dL, compared to 90.72 mg/dL in the non-MetS group ($p<0.001$). Additionally, serum cholesterol levels were significantly elevated in patients with MetS, with a mean of 252.81 mg/dL, compared to 193.83 mg/dL in those without MetS ($p<0.001$). Mohammed et al[9] in their study showed that FBS is statistically higher in breast cancer cases (25.9%) than the control group (8.9%) and in premenopausal women, the risk of breast carcinoma was more than 50% compared to the control group, adjusted odds ratio 2.97, 95% CI, (1.1–8.4).

A study in Mexico studied that women with prediabetes and diabetes had increased risk of breast cancer; the OR for prediabetics being 2.08, 95% CI 1.10–3.96, and for diabetics, 2.85, 95% CI 1.55–5.2638. In a hospital record based descriptive cross sectional study conducted in India, diabetic patients were found to have an increased

risk of presentation at advanced stage and associated poorer outcome for breast cancer in comparison with the non diabetic patients.[10]

Recent studies showed increased association between hyperglycemia and many cancers due to the fact that high glucose levels inhibit apoptosis thereby leading to increased cell viability under hypoxic conditions, thereby facilitating cell survival and malignant progression.

Insulin is the main hormone that stimulates cell proliferation, and it directly promotes the proliferation of breast tissue and tumor cells, thus possibly promoting BC incidence. Besides, insulin promotes tumor cell proliferation by up regulating IGF-1, which increases mitotic activity in tumor cells.

In obese postmenopausal BC patients, adipose tissue is the major source for estrogen synthesis. Estradiol is converted from androgen by aromatization in adipose tissue. Adipocytes secrete IL-6 and TNF-α, which induce aromatization together with prostaglandins. Hence, obesity increases the production of cytokines, leading onto aromatization to increase estradiol. Estradiol decreases adiponectin production and attenuates the antitumor effect of adiponectin.

Hypertension, singly or as a part of metabolic syndrome, has been associated with increased risk of breast cancer.[11] Hypertension and breast carcinoma has common pathophysiologic means, including subclinical inflammation. In our study, hypertension had an adverse effect on breast cancer besides the fact that BP could have been raised in the affected individuals because of the anxiety due to oncology consultation. The result in our study was similar to the study conducted by Khare et al and Wani et al who had same results.

Low serum HDL cholesterol also has increased risk of breast cancer especially in overweight and obese women. In our study, HDL cholesterol did not affect the risk of breast cancer. Increased plasma triglyceride levels had a positive correlation with histologically documented premenopausal breast cancer. In this study, raised levels of serum triglyceride had significant association with breast cancer risk. The result of the present study was similar with the study conducted by Wani et al.[12]

SUMMARY AND CONCLUSION:

The present study was conducted on 50 female patients with histologically diagnosed breast cancer, admitted in the Department of General Surgery, Guru Nanak Dev Hospital attached to Govt. Medical College, Amritsar, from October 2022 to March 2024 to assess metabolic syndrome as a risk factor for Carcinoma Breast. The results

of the present study are discussed below:

- Metabolic syndrome was present in 64% of the patients.
- Metabolic syndrome in breast cancer patients was significantly associated with menopausal status (p-value 0.009).
- The incidence of metabolic syndrome was significantly associated with higher waist circumference in cancer breast patients (p-value <0.001).
- Overall blood pressure, considering both systolic and diastolic measures, is significantly associated with metabolic syndrome in breast cancer patients (p-value <0.001).
- The difference between fasting blood sugar was significantly associated with metabolic syndrome in breast cancer patients (p-value <0.001).
- There was significant association between serum triglyceride levels and metabolic syndrome in breast cancer patients (p- value <0.001).
- Mean HDL levels were not significantly different between those with or without metabolic syndrome (p-value 0.15).

CONCLUSION:

Metabolic syndrome is present in majority (64%) of the total breast carcinoma patients. Our study adds to the understanding of the connection between metabolic syndrome and risk of breast cancer, hence, confirming the correlation between metabolic syndrome and carcinoma breast patients. Engaging in multiple methods such as diet, physical activity, and managing stress is crucial in managing insulin resistance and obesity and enhancing cancer prognosis.

REFERENCES:

1. Healy LA, Ryan AM, Carroll P, Ennis D, Crowley V, Boyle T, Kennedy MJ, Connolly E, Reynolds JV. Metabolic syndrome, central obesity and insulin resistance are associated with adverse pathological features in postmenopausal breast cancer. Clin Oncol (R Coll Radiol). 2010;22(4):281-8.

2. Goldberg JE, Schwertfeger KL. Proinflammatory cytokines in breast cancer: mechanisms of action and potential targets for therapeutics. Curr Drug Targets. 2010;11(9):1133-46.

3. Zeng X, Yee D. Insulin-Like Growth Factors and Breast Cancer Therapy. In: Madame

Curie Bioscience Database [Internet]. Austin (TX): Landes Bioscience; 2000-2013. Available from: https://www.ncbi.nlm.nih.gov/books/NBK6394/

4. Kawai T, Autieri MV, Scalia R. Adipose tissue inflammation and metabolic dysfunction in obesity. Am J Physiol Cell Physiol. 2021;320(3):C375-C391.

5. Zhao P, Xia N, Zhang H, Deng T. The Metabolic Syndrome Is a Risk Factor for Breast Cancer: A Systematic Review and Meta-Analysis. Obes Facts. 2020;13(4):384-96.

6. Guo M, Liu T, Li P, Wang T, Zeng C, Yang M, Li G, Han J, Wu W, Zhang R. Association Between Metabolic Syndrome and Breast Cancer Risk: An Updated Meta-Analysis of Follow-Up Studies. Front Oncol. 2019;9:1290.

7. Berrino F, Villarini A, Traina A, Bonanni B, Panico S, Mano MP, et al. Metabolic syndrome and breast cancer prognosis. Breast Cancer Res Treat. 2014;147:159-65.

8. Picon-Ruiz M, Morata-Tarifa C, Valle-Goffin JJ, Friedman ER, Slingerland JM. Obesity and adverse breast cancer risk and outcome: Mechanistic insights and strategies for intervention. CA Cancer J Clin. 201;67(5):378-97.

9. Mohammed AM, Hamed HB, Noaman MK, Alieldin N. Metabolic syndrome and breast cancer risk. J Egypt Natl Canc Inst. 2023;35(1):42.

10. Kamal S, Madhumitha SS. Impact of diabetes mellitus on breast cancer outcome. J Med Pharm Allied Sci. 2021;10(4): -3144-7

11. Franceschi S, la Vecchia C, Negri E, Parazzini F, Boyle P. Breast cancer risk and history of selected medical conditions linked with female hormones. Eur J Cancer. 1990;26(7):781-5.

12. Furberg AS, Veierød MB, Wilsgaard T, Bernstein L, Thune I. Serum high-density lipoprotein cholesterol, metabolic profile, and breast cancer risk. J Natl Cancer Inst. 2004;96(15):1152–60.