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Breast Cancer

Link between Blood Cell-Associated Inflammatory Indices and Chemotherapy-Induced Hyperglycemia in Women Affected with Breast Cancer: Clinical Studies

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Abstract

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Background Development of treatment-induced hyperglycemia/diabetes is a considerable problem in women undergoing chemotherapy for breast cancer. In this study, baseline levels of blood cell-associated inflammatory indices (BCAII) were analyzed to understand their role in the development of treatment-induced hyperglycemia and diabetogenesis.

Materials and Methods This was a retrospective study, and information on women who were normoglycemic and nondiabetic and of women who were diabetic at the beginning of the treatment were collected from files. Demographic, pathology-related details, and complete blood profile were noted. Neutrophil-to-lymphocyte ratio (NLR), derived neutrophil-to-lymphocyte ratio (dNLR), platelet-to-lymphocyte ratio (PLR), and systemic inflammatory index (SII) which indicate BCAII were calculated. Demographic details were subjected to frequency and percentage, while blood parameters were subjected to one-way analysis of variance followed by post hoc Bonferroni's multiple comparison tests. A p-value of <0.05 was considered significant.

Results The results indicated that a significant difference in levels of total count ($p < 0.035$), neutrophil, lymphocyte, and platelets ($p < 0.001$) were observed. Regarding BCAII, when compared with women who were normoglycemic at the end of treatment, NLR, dNLR, PLR, and SII were significantly high for people who were known diabetics at the beginning of treatment ($p < 0.001$). The dNLR ($p = 0.0008$), PLR ($p < 0.001$), and SII ($p < 0.001$) were significant for people who developed secondary hyperglycemia/diabetes, while only dNLR was significant for people who progressed from normal to prediabetes stage ($p = 0.049$)

Keywords

- breast cancer
- secondary hyperglycemia/diabetes

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- treatment-induced hyperglycemia/diabetes
- blood cell-associated inflammatory indices
- neutrophil-to-lymphocyte ratio
- derived neutrophil-to-lymphocyte ratio
- platelet-to-lymphocyte ratio
- systemic inflammatory index

Conclusion To the best of the authors' knowledge, this is the first study that indicates difference in baseline BCAII and development of treatment-induced hyperglycemia/diabetes indicating that underlying low levels of inflammation may contribute to diabetogenesis in women affected with breast cancer.

Introduction

A recent report from the World Health Organization (WHO) suggests that breast cancer is the most common cancer in women and that in the year 2020, there were 2.3 million women diagnosed with breast cancer and 685,000 succumbed to it.[1] From an epidemiological perspective, while breast cancer rates are higher among women in more developed regions, the rates are increasing rapidly in almost all developing countries of the world.[1] Recent reports from India also suggest that when compared with the women in the Western countries, the incidence of breast cancer is on a rise, and the most worrying aspect is that they are being detected in more numbers in the younger age groups.[2]

In accordance with the standard treatment guidelines, depending on the stage and general health of the women, breast cancer is treated with surgery, chemotherapy, and radiotherapy.[3,4] In addition to this, depending on the epidermal growth factor receptor encoded by the *ERBB2* or human epidermal growth factor receptor 2 (*HER2*) gene and on the estrogen receptor (ER) status ER-positive, immunologicals such as trastuzumab (Herceptin) and tamoxifen/letronat may also be used to slow down the growth of cancer.[3,4] However, on the down side, the action of these anticancer agents and supportive pharmacological agents (such as antiemetics, analgesics, steroids) result in various short- and long-term side effects that may at times be severe and affecting the quality of life of the survivor.[5]

One of the important but less studied side effects is the development of secondary hyperglycemia/diabetes in women who have undergone chemotherapy. From a terminological perspective, secondary hyperglycemia/diabetes is when a normoglycemic (nondiabetic) individual develops hyperglycemia/diabetes after treatment with any pharmacologic agent/s.[6,7] With regard to cancer, reports suggest that administration of certain anticancer drugs and the use of dexamethasone, an important steroidal antiemetic agent effective in mitigating chemotherapy-induced nausea and vomiting is proved to cause secondary hyperglycemia/diabetes.[7–18]

Recently, we have observed that in normoglycemic Indian women undergoing curative treatment for breast cancer, the incidence of development of glucose intolerance was high.[7] Our observations of the study suggested that by the end of the radiation treatment (which is the modality adopted after completion of surgery and chemotherapy), 24.89% were prediabetic, 10.97% were diabetic after being in the prediabetic stage, 8.22% became diabetic without going through a prediabetic stage, and only 55.91% did not develop either per diabetic or diabetic condition.[7] A strong correlation was also observed between the development of secondary hyperglycemia/diabetes and prediabetes with body mass index (BMI) and age.[7]

From a biochemical perspective, accumulating evidence from innumerable clinical observations have conclusively shown that chronic inflammation plays a central role in the development and progression of both diabetes and cancer.[19–22] Reports suggest that when compared with the nondiabetic population, the incidence of gastric, liver, pancreatic, colorectal, urinary tract, breast, and female reproductive cancers is high in type II diabetes, and is accompanied by higher mortality.[23] Mechanistically, hyperglycemia, hyperinsulinemia, insulin resistance, and increased generation of free radicals, oxidative stress, and levels of inflammatory processes are proposed to play a role for the association between increased incidences of cancer in diabetics.[23] In addition to this, some of the diabetes-associated dysregulated cytokines such as tumor necrosis factor-α (TNF-α), interleukin (IL)-6, and leptin that have an essential role in initiation and progression by inducing oxidative stress, inflammation, and participating in process such as epithelial mesenchymal transition, angiogenesis, and metastasis are believed to be the cardinal link between diabetes and cancer.[24]

The quantification of diabetes-associated cytokine dysregulation such as serum concentrations of cytokines such as resistin, IL-6, IL-10, TNF-α, and leptin,[24] although useful as a marker, necessitates spending of additional finances. In the recent past, accumulating evidence indicate that changes in the number of neutrophils, lymphocytes, and platelets in

circulating blood and the blood cell-associated indices, such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic inflammatory index (SII) are recognized to be potential biomarkers of subclinical inflammatory responses that trigger development of both cancer[25,26] and diabetes.[27] In this retrospective chart-based study, an attempt was made to understand the baseline hematological indices in the development of secondary hyperglycemia/diabetes in normoglycemic women who underwent surgery, chemotherapy, and radiation when compared with women who were diabetic at the beginning of the treatment.

Materials and Methods

We retrospectively reviewed the files of women who have had undergone surgical treatment either radical or simplified mastectomy followed by curative chemotherapy treatment that included a combination of drugs such as cyclophosphamide, anthracycline, paclitaxel/docetaxel, carboplatin alone or combined with other drugs and HER2-targeted therapies between January 2016 and January 2020 at Mangalore Institute of Oncology. The inclusion criteria included collection of data only from women, between the ages of 20 and 80 years, who completed the planned treatment of surgery, chemotherapy, and radiotherapy during the study time point. The exclusion criteria included men who were treated for breast cancer and women who discontinued treatment.

Quantification of the blood glucose levels is an important clinical procedure and is always performed before surgery during the fitness evaluation, before commencement of each chemotherapy cycle, before and after the completion of radiotherapy, and at 1 to 3 months intervals after the completion of radiotherapy. The criteria considered to be diabetic were in accordance with the WHO guidelines of 1999[28] which state individuals with fasting plasma glucose $\geq$7.0 mmol/L, a random plasma glucose $\geq$11.1 mmol/L, or a 2-hour plasma glucose $\geq$11.1 mmol/L during an oral glucose tolerance test as diabetic. The standard practice for management of hyperglycemia/diabetes is in accordance with the standard guidelines[29,30] and includes dietary measures and prescription of oral hypoglycemic drugs or insulin depending on the clinical condition and judgment of physicians.

Two research assistants extracted the data from the medical records provided to them by the medical records department of the hospital. The demographic details such as age at the time of breast cancer diagnosis, domicile, BMI, type of diet, marital status, number of children, previous history of diabetes, hypertension, and menopausal status, and clinical data included histopathological details TNM staging, hormonal receptor status (estrogen, progesterone), and HER2/neu status ascertained by immunohistochemical methods and fluorescence in situ hybridization assay to further validate the HER2-positive status were collected when available in the files.

Data on baseline complete blood counts and when hyperglycemia/secondary hyperglycemia/diabetes developed were entered in Microsoft excel by the research assistants. The NLR, PLR, and SII are as follows: NLR = neutrophil counts/lymphocyte counts, PLR = platelet counts/lymphocyte counts, and SII = platelet counts $\times$ neutrophil counts/lymphocyte counts. In addition to this, the derived NLR (dNLR) was calculated using the formula: dNLR = absolute neutrophil counts/(total white blood corpuscles – absolute neutrophil counts).

Statistical Analysis

Only those data that met the inclusion criteria were entered in to Excel sheet. The data entered in to Microsoft excel was exported to SPSS (IBM version 22, Chicago, Illinois, United States) for analysis. The descriptive data were subjected to frequency and percentage. The baseline CBCs and the blood cell-associated inflammatory indices (BCAII) were subjected to one-way analysis of variance followed by post hoc Bonferroni's multiple comparison tests. All tests of statistical significance were based on a two sided and a p-value of <0.05 was considered significant.

Results

During the study time point from January 2016 to January 2020, a total of 919 cases of cancer that met the inclusion criteria were selected. The demographic details such as age at the time of cancer diagnosis, domicile (village, town, city), BMI, type of diet, marital status, number of children, clinical data on TNM stage, ER, progesterone receptor, and Her2 status, and blood parameters are represented in ►Table 1.

The results suggest that majority of the women were from city (48.1%; 442/919), in their fourth decade of life (32.6%; 300/919), married (902/919; 300/919), normal BMI of 18.5 to 22.9 (48.7%; 448/919), with mixed diet habit (62.8%; 577/919) (►Table 1). Regarding the tumor details in accordance with the TNM classification, majority of the patients were confirmed to have tumor of T2 (52.4%; 482/919); nodal status N1 (33.6%; 309/ 919); and M0 status (79.0%; 726/919) (►Table 1).

With regard to the hormone receptor status, it was observed that majority (44.1%; 328/744) were positive for estrogen and progesterone, while for HER 2 status, majority (64.8%; 468/722) were negative (►Table 1). The results also suggest that 27.7% were triple negative (200/722), while 14.5% (105/722) were triple positive (►Table 1).

Regarding diabetes, of the 919 cases, 213 were diabetics at the beginning when cancer was detected, and surgery treatment was yet to be initiated (►Table 1). Of the 706 normoglycemic women, 19.69% (139/706) developed prediabetes stage, and 23.94% (169/706) developed hyperglycemia/diabetes, while 56.37% (398/706) were normoglycemic at the end of radiation treatment (►Table 1).

Regarding the hematological indices, a significant difference in the levels of total count ($p < 0.035$), neutrophil, lymphocyte, and platelets ($p < 0.001$) were observed, while it was insignificant for hemoglobin across the four groups (►Table 2). Multiple comparison analysis was done considering normal to normal versus the other three groups (normal to prediabetic stage at the end of the radiation

Table 1 Data on the demographic, tumor, and on development of treatment-induced diabetes in the study population

Parameter	Groups	Count	%
Domicile	Village	138	15.0
	Town	339	36.9
	City	442	48.1
	Total	919	100.0
Age (y)	18–29	21	2.3
	30–39	153	16.6
	40–49	300	32.6
	50–59	235	25.6
	60 and older	210	22.9
	Total	919	100.0
BMI	Underweight < 18.5	291	31.7
	Normal 18.5–22.9	448	48.7
	Preobese 23–24.9	160	17.4
	Obese > 25	20	2.2
	Total	919	100.0
Marital status	Married	902	98.5
	Unmarried	14	1.5
	Total	916	100.0
Children	One	218	23.7
	Two	305	33.2
	Three or more	395	43.0
	Total	918	100.0
Diet	Vegetarian	58	6.3
	Nonvegetarian	284	30.9
	Mixed	577	62.8
	Total	919	100.0
Primary tumor T	T1	21	2.3
	T2	482	52.4
	T3	255	27.7
	T4	161	17.5
	Total	919	100.0
Regional lymph nodes N	N0	261	28.4
	N1	309	33.6
	N2	242	26.3
	N3	107	11.6
	Total	919	100.0
Distant metastasis M	M0	726	79.0
	Mx	183	21.0
	Total	919	100.0
ER/PR status	ER −ve/PR −ve	305	41.0
	ER +ve/PR −ve	33	4.4
	ER −ve/PR +ve	78	10.5
	ER +ve/PR +ve	328	44.1
	Total	744	100.0

(*Continued*)

Table 1 (*Continued*)

Parameter	Groups	Count	%
HER status	HER2 negative	468	64.8
	HER2 positive	254	35.2
	Total	722	100.0
Molecular status	Triple positive	105	14.5
	Mix	417	57.8
	Triple negative	200	27.7
	Total	722	100.0
Glycemic status before and after treatment	Normal to normal	398	43.3
	Normal to prediabetes	139	15.1
	Normal to diabetes	169	18.4
	Diabetes	213	23.2
	Total	919	100.0

Abbreviations: BMI, body mass index; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor.

therapy; normal to diabetes stage at the end of radiation therapy, and known diabetic on detection of cancer) and is represented in ►Table 2.

When compared with group 1, all the indices were altered in people who were known diabetics at the beginning of treatment for total count ($p < 0.01$), neutrophils ($p < 0.001$), lymphocytes ($p < 0.003$), granulocytes ($p < 0.001$), and platelets ($p < 0.001$; ►Table 2). In people who developed prediabetes stage, when compared with group 1, significant changes were seen in neutrophil ($p < 0.003$) and lymphocyte ($p < 0.003$) counts, while for platelets although not significant a trend was seen ($p < 0.064$; ►Table 2). In people who developed secondary hyperglycemia/diabetes, when compared with group 1, significant changes were seen in neutrophil, lymphocyte, granulocytes, and platelets ($p < 0.001$; ►Table 2).

With regard to the BCAII, the results of the study suggest that when compared with group 1, the NLR, dNLR, PLR, and SII were significantly high for people who were known diabetics at the beginning of the treatment (►Table 2). The results also suggest that dNLR ($p < 0.0008$), PLR ($p < 0.001$), and SII ($p < 0.001$) were the only indices significant for people who developed secondary hyperglycemia/diabetes, while only dNLR was significant for people who progressed from normal to prediabetes stage ($p < 0.049$) (►Table 2).

Discussion

The results from the study suggest that majority of the women who developed breast cancers were from the city and in the fourth decade of life (►Table 1). Published reports from India indicate that breast cancer incidence is high in cities and in the age group of 40 to 50 years, and these observations are in agreement to earlier study.[31–33] The other important observation is that nearly 28% of the women were triple negative (►Table 1). Previous studies have shown that the proportion of triple-negative breast cancer ranges from 6.7 to 27.9% in different countries and that the highest incidence is in India possibly due to lifestyle, family history, high mitotic indices, and mutations in the *BRCA1* gene.[34]

Regarding development of secondary hyperglycemia/diabetes, of the 706 normoglycemic women, 19.69% developed prediabetes stage, while 23.94% developed hyperglycemia/diabetes before the completion of radiotherapy. Previous studies have shown that 9.7[35] to 13%[36] elderly women developed secondary hyperglycemia/diabetes. When compared with previous observations, the number of women developing secondary hyperglycemia/diabetes is very high in our study, and this may be due to genetic factors. To support this, studies have shown that metabolic syndrome and prediabetes contribute to racial disparities in breast cancer mortality in black women[37] and insulin resistance disproportionately affects more in black women than the white women.[38]

Scientific studies in the recent past have clearly shown that the baseline BCAII have a predictive role in indicating low-grade chronic inflammation that is associated with important chronic diseases such as diabetes, cardiovascular diseases, and cancer.[39] Novel prognostic inflammatory markers of cancer survival and cardiovascular disease are NLR, PLR, and SII.[39] In the recent past, white blood cell-based inflammatory indices, the NLR and PLR, calculated, respectively, from the peripheral neutrophil and lymphocyte counts, platelet and lymphocyte counts, and SII that is an integrated peripheral lymphocyte, neutrophil, and platelet counts into one indicator are useful.[39]

In this study with respect to the BCAII, the results suggest that when compared with normoglycemic people who did not develop prediabetes or diabetes, a significant increase in all the four inflammatory indices NLR, dNLR, PLR, and SII were seen in the women affected with diabetes at the beginning of the treatment (►Table 2). On the contrary, in normoglycemic women who developed diabetes significantly increased levels for dNLR, PLR, and SII was observed (►Table 2). In women who were prediabetic at the end of

Table 2 The data on standard hematological and the various baseline blood cell-associated inflammatory indices in the study groups

Parameters	Groups	*N*	Median	Mean ± SD deviation	Bonferroni's multiple comparison	ANOVA *p*-value
Hb	Normal to normal	398	11.70	11.72 ± 1.66		0.189
	Normal to prediabetes	139	11.70	11.63 ± 1.58		
	Normal to diabetes	169	12.10	11.98 ± 1.45		
	Diabetes at the beginning	213	12.00	11.84 ± 1.62		
Total count	Normal to normal	398	7,210	7,479.42 ± 2,984.65		0.035
	Normal to prediabetes	139	7,110	7,389.21 ± 2,531.5		
	Normal to diabetes	169	7,800	8,247.24 ± 6,822.51		
	Diabetes at the beginning	213	7,750	8,558.95 ± 8,343.94	0.01	
Neutrophil	Normal to normal	398	62.50	61.31 ± 10.34		0.0001
	Normal to prediabetes	139	65.00	64.71 ± 9.21	0.003	
	Normal to diabetes	169	66.00	65.02 ± 9.3	0.0001	
	Diabetes at the beginning	213	68.00	67.8 ± 9.79	0.0001	
Lymphocytes	Normal to normal	398	29.00	30.04 ± 9.9		0.0001
	Normal to prediabetes	139	26.00	26.94 ± 7.95	0.003	
	Normal to diabetes	169	27.00	27.53 ± 8.03	0.02	
	Diabetes at the beginning	213	24.00	25.18 ± 8.9	0.003	
Granulocytes	Normal to normal	398	8.00	8.56 ± 3.86		0.0001
	Normal to prediabetes	139	8.00	8.48 ± 3.91		
	Normal to diabetes	169	6.00	7.31 ± 3.75	0.002	
	Diabetes at the beginning	213	6.00	6.91 ± 3.36	0.0001	
Platelets	Normal to normal	398	217,000	204,689.08 ± 136,210.59		0.0001
	Normal to prediabetes	139	144,000	169,581.62 ± 142,600.62	0.064	
	Normal to diabetes	169	317,000	327,851.6 ± 149,058.24	0.0001	
	Diabetes at the beginning	213	296,000	291,622.07 ± 134,506.67	0.0001	
NLR	Normal to normal	398	2.16	2.41 ± 1.3		0.0001
	Normal to prediabetes	139	2.54	2.74 ± 1.27		
	Normal to diabetes	169	2.48	2.71 ± 1.36		
	Diabetes at the beginning	213	2.84	3.31 ± 2.07	0.0001	
dNLR	Normal to normal	398	1.67	1.78 ± 0.79		0.0001
	Normal to prediabetes	139	1.86	2.04 ± 0.85	0.049	
	Normal to diabetes	169	1.94	2.08 ± 0.9	0.008	
	Diabetes at the beginning	213	2.13	2.48 ± 1.43	0.0001	
PLR	Normal to normal	398	6,700.70	7,612.95 ± 6,293.19		0.0001
	Normal to prediabetes	139	6,000.00	7,086.84 ± 6,879.83		
	Normal to diabetes	169	11,565.22	13,084.5 ± 7,902.18	0.0001	
	Diabetes at the beginning	213	10,958.33	13,355.56 ± 8,841.71	0.0001	
SII	Normal to normal	398	366,477.91	489,314.88 ± 46,2571.94		0.0001
	Normal to prediabetes	139	367,714.29	485,084.18 ± 519,150.13		
	Normal to diabetes	169	734,766.67	882,089.37 ± 618,370.78	0.0001	
	Diabetes at the beginning	213	748,548.39	951,473.63 ± 733,485.64	0.0001	

Abbreviations: ANOVA, analysis of variance; dNLR, derived neutrophil-to-lymphocyte ratio; Hb, hemoglobin; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic inflammatory index; SD, standard deviation.

the treatment, a trend was observed only for dNLR (►Table 2). Seminal studies in the past have shown that the inflammatory markers NLR and PLR were significantly increased in people affected with diabetes mellitus.[27] In addition to this, reports also suggest that the BCAII are also important in predicting lower extremity vascular lesions,[40] peripheral arterial disease, osteomyelitis, and the need for amputation in diabetic foot infection.[41]

Conclusion

The results of the study suggest that the baseline BCAII are indicative to the development of secondary hyperglycemia/diabetes in women who have undergone chemotherapy for cancer of the breast. The most important aspect that needs to be considered is that calculating these indices are inexpensive as these values are obtained from the blood parameters estimated in the laboratory and does not incur additional costs or resources. As far as the authors are aware of, this is the first study that establishes the importance of baseline inflammatory indices in the development of secondary hyperglycemia/diabetes. Studies are planned to understand the incidence of metabolic syndromes and incidence of cancer metastasis/recurrence in patients who have developed hyperglycemia during treatment period and compare it with cancer patients who were diabetics at the time of diagnosis as well as with who were normoglycemics throughout. The outcome of all these studies will bridge the gaps in the existing lacunae and will be of benefit in patient care. However, the noncompliance in regular follow-up care in the study area is the biggest deterrent for our endeavors and efforts are on in these directions to understand the long-term clinical outcome.

The biggest drawback of the current study is that this was a retrospective chart-based study and from a single-center catering to a population where the incidence of type II diabetes is high. Retrospective studies need to be carried out in different population and areas to have a concrete understanding the link between BCAII and chemotherapy-induced hyperglycemia in women affected with breast cancer. In addition to this, prospective studies are needed to ascertain the role of psychological factors (such as anxiety), physical aspects (such as obesity), and family history of diabetes, and lifestyle pattern needs to be understood in the development of treatment-induced secondary hyperglycemia and diabetes in patients. In this regard, our observation that secondary hyperglycemia/diabetes was more in women with higher BMI[7] suggests that obesity may have a pivotal role and needs to be investigated in detail by considering a range of factors associated in the diabetes-associated cytokine dysregulation such as serum concentrations of cytokines.

Conflict of Interest

None declared.

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