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Original Article

Usefulness of Indian Diabetes Risk Score in Predicting Treatment-Induced Hyperglycemia in Women Undergoing Adjuvant Chemotherapy for Breast Cancer

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Abstract


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In the curative treatment of cancer with adjuvant chemotherapy, antineoplastic drugs, along with glucocorticoids, can induce hyperglycemia. The objective of this study was to assess the utility of the Indian Diabetes Risk Score (IDRS) in predicting treatment-induced hyperglycemia in women who were nondiabetic and normoglycemic at the start of chemotherapy. This prospective study was conducted with nondiabetic women who required adjuvant chemotherapy. Participants voluntarily completed the IDRS, providing information on age, waist circumference, family history of diabetes, and physical activity. Chemotherapy-induced hyperglycemia was defined as fasting blood glucose levels $\geq$100 mg/dL or random blood glucose levels $\geq$140 mg/dL during treatment. Data were categorized into women who developed hyperglycemia and those who remained normoglycemic during treatment and were analyzed using Fisher's exact test. A significance level of $p < 0.05$ was applied. Receiver operating characteristic (ROC) curves were constructed to validate the IDRS for predicting hyperglycemia. A total of 208 women met the inclusion criteria and participated in the study. The results revealed that 38.93% (81/208) developed hyperglycemia by the end of chemotherapy, as observed during their first follow-up after treatment. Fisher's exact test demonstrated a significant difference in the total IDRS score and its domains, including family history, physical activity, and waist circumference ($p = 0.017$–< 0.001), but not age. ROC analysis indicated that an IDRS score above 60 increased the likelihood of developing hyperglycemia, with a sensitivity of 81.3%, specificity of 54.7%, and an area under the curve of 0.727. These findings suggest that the IDRS is a sensitive tool for predicting adjuvant chemotherapy-induced hyperglycemia in breast cancer patients without diabetes. To the best of the authors' knowledge, this is the first

Keywords

- Breast Cancer
- adjuvant chemotherapy
- hyperglycemia
- Indian Diabetes Risk Score
- diabetes

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study to evaluate the utility of the IDRS in predicting treatment-induced hyperglycemia in women undergoing adjuvant chemotherapy for breast cancer. Ongoing efforts are focused on understanding the underlying mechanisms and strategies for mitigation.

Introduction

Globally, breast cancer is a prevalent malignancy, and recent reports published by GLOBOCAN 2018 estimated that it accounts for 11.6% of all cancers in females.[1] It is the leading form of cancer in women and is the fifth most common cause of cancer-related death worldwide.[1] The incidence of breast cancer is also on the rise in India, and quantitatively, although lower than the numbers in the developed countries like United Kingdom (25.8 vs. 95 per 100,000), the mortality is almost similar (12.7 vs. 17.1 per 100,000).[2] Several reports indicate a disparity in the incidence of breast cancer in women between developed and underdeveloped countries, and when compared with developed regions, the numbers are high in the underprivileged and developing countries.[2–5]

Conventionally, in the clinical setup, breast cancer is treated with surgery, chemotherapy, and radiotherapy, and this is based on the stage of the disease and the general health of the woman.[6] However, when compared with other cancers, the pathogenesis of breast cancer is unique. This quality is attributed to the breast cancer stem cells that have the potential to spread to multiple distant organs, principally the bone, lung, liver, and brain, through a unique systematic process termed today as "*metastasis organotropism*."[7–9] Additionally, breast cancer is today considered to be a very heterogeneous disease, and the status of estrogen receptor (ER), progesterone receptor (PR), and the expression and amplification of the human epidermal growth factor receptor type 2 (HER2) are clinically important markers in ascertaining the prognosis and to plan the appropriate treatment modality.[9]

Based on the status of these markers, clinically, breast cancer is today categorized as hormone receptor (HR) positive (HR +; ER +, PR +/−, and HER2 −), HER2 positive (HER2 +) and triple negative (TN; ER −, PR− and HER2 −) and treatment with cytotoxic agents, immunological such as trastuzumab (Herceptin) and antiestrogens are accordingly planned and initiated.[9,10] Of the therapeutic agents, the use of cytotoxic drugs causes severe untoward side effects and to prevent/mitigate it, adjunct pharmacological agents such as antiemetics, analgesics, steroids (glucocorticosteroids), laxatives, antihistamines, and hematopoietic progenitors need to be judiciously administered at the right time and in right dose and sequence.[11]

Clinically, glucocorticosteroids possess anti-inflammatory effects and are used to treat a range of acute and chronic ailments. Steroids are an important constituent in cancer chemotherapy and have been the mainstay for more than 30 years in mitigating treatment-induced nausea and vomiting.[11] However, on the downside, use of steroids is associated with severe side effects and includes adverse effects on cardiovascular health, development of osteoporosis, diabetes, and increased chances of opportunistic infections, thereby negating the beneficial pharmacological effects.[12] Of these, the development of steroid-induced hyperglycemia and diabetes is a major limiting factor, and reports suggest that women who were nondiabetic at the start of the cancer chemotherapy develop treatment-induced hyperglycemia and diabetes, and this affects their treatment outcome, quality of life, and survival.[13–20]

Reports suggest that increasing the therapeutic dose and extent of the therapy, ethnicity, age, and body mass index (BMI) may enhance the risk of developing steroid-induced hyperglycemia and diabetes.[21–26] From a biochemical viewpoint, steroids have a significant effect on glucose metabolism in multiple ways. The most important is that they inhibit glucose uptake in muscle and adipose tissue, and suppression of the hypothalamic-pituitary-adrenal axis causes postprandial hyperglycemia.[27–30] Steroids stimulate the receptor and postreceptor activities of the β cell in the pancreas, trigger gluconeogenesis in the liver, and also mobilization amino acids from extrahepatic tissues.[27–30] Of these, studies with laboratory rats have affirmed that the increased insulin resistance in the skeletal muscle is the major reason for the observed hyperglycemic effect.[29,30]

India is also known to have a higher incidence of type II diabetes mellitus (T2DM). Reports suggest that in the year 2019, there were nearly 77 million people afflicted in the total number, contributed to almost 8.9% of the population.[31] From a clinical perspective, hyperglycemia and diabetes enhance the chances of developing complications that further aggravate the cancer disease burden and increase morbidity.[32] As per the reports based on population-based studies and clinical trials, compared with cancer patients who do not have diabetes, people affected with diabetes and cancer have a poor prognosis, higher chances of recurrence, and cancer-related deaths.[33] Additionally, the quality of life in people affected with diabetes and cancer is poor and necessitates regular medical observation, thereby affecting the individual and the family's financial resources.[34]

Clinically, hyperglycemia during chemotherapy has an important role. Seminal studies by Villarreal-Garza et al (2012) with women undergoing palliative chemotherapy for their metastatic or recurrent breast cancer have shown that there was no difference between diabetic and nondiabetic patients.[35] However, a distinction was seen between nondiabetic patients and diabetic patients who developed hyperglycemia during the treatment. Women who had proper metabolic control had an improved overall survival.[35] Additionally, Ahn et al (2020) have also reported a significant

difference for 5-year relapse-free survival rates (92.0 vs. 82.3%) and survival rates (94.6 vs. 92.0%) in the euglycemia and hyperglycemia groups.[36] Together, these observations clearly indicate that hyperglycemia during adjuvant chemotherapy influences the clinical outcome and elevates the risk of death.[35,36]

When compared with primary diabetes, factors contributing to the development of treatment-induced or secondary diabetes are less understood and are believed to be sequelae to interaction and interplay of multiple risk factors such as genetic predisposition, xenobiotic/drug interaction, lifestyle, and dietary patterns.[37–39] In lieu of these observations, a practical and simple scoring system that can indicate the future risk of secondary hyperglycemia and diabetes will be useful as then suitable intervention can be planned and introduced to reduce or delay the chances of development of treatment-induced hyperglycemia during the active treatment. In this regard, important diabetes risk scores such as the Finnish Diabetes Risk Score (FINDRISC) developed in Finland,[40] the Indian Diabetes Risk Score (IDRS),[41] the diabetes risk calculator developed in the United States,[42] Australian Type 2 Diabetes Risk Assessment Tool (AUSDRISK) developed in Australia,[43] CANRISK (Canadian Diabetes Risk Assessment Questionnaire) prognostic model, developed in Canada,[44] the SLIM (St. Luke's Internal Medicine) diabetes risk test[45] are useful in predicting the chances of development of T2DM in large population-based studies.

Of these, the IDRS, also known as Madras Diabetes Research Foundation (MDRF)–IDRS developed by the eminent endocrinologist Mohan et al[41] by taking into account four vital end points (age, abdominal obesity, family history, and physical activity) has been field tested by multiple investigators and shown to be effective in predicting the chances of hyperglycemia and diabetes in different population in India[37,41,46–61] and in the United States.[38] The most important aspect of IDRS is that the risk score considers only four factors (age, abdominal obesity, family history, and physical activity), is easy to administer, time effective, and inexpensive.[41] Studies have also shown it to be useful in distinguishing type II from non-T2DM (GDRC-3) diabetes.[37] Additionally, it is also validated in Indians, Americans, including Hispanic, non-Hispanic white, non-Hispanic black, and other American populations.[38] In the current study, attempt was made to understand whether IDRS could be useful in predicting treatment-induced hyperglycemia in women undergoing curative adjuvant chemotherapy for their breast cancer.

Materials and Methods

This was a prospective study conducted at—, after obtaining permission from the hospital ethics committee (MIO/IEC/2018/02/07) from January 2019 to February 2020. All procedures performed in this study were in accordance with the ethical standards of the institutional and national research committee, the 1964 Declaration of Helsinki and in accordance to the guidelines stipulated by Indian Council of Medical Research 2018 for research. The subjects were also informed that their participation was completely voluntary, free, and that nonwillingness to be a part of this study would not deprive them of the planned investigations, treatment, and medical care. The willing patients were then included in the study, and a written informed consent was obtained.

The inclusion criteria included women between the ages of 20 and 65 years, who were not diabetics and were required to undergo adjuvant chemotherapy using the cytotoxic drugs anthracycline, paclitaxel/docetaxel, and HER2-targeted therapies (when required). As diet is known to have a vital role in diabetogenesis, we selected women who were residents of Udupi, Dakshina Kannada district of Karnataka, and Kasargod district of Kerala. These three areas were considered principally because the diet and lifestyle are the same, and the diet is rice-based. The exclusion criteria included men who needed treatment for breast cancer, women known to be diabetics (type I and/or type II), hypertensive or dyslipidemic, and were under medication for it; women who were newly diagnosed to have diabetes before the start of the treatment (during their fitness test before surgery) or during the postoperative period; volunteers who had pulmonary tuberculosis, human immunodeficiency virus, hepatitis C virus, or hepatitis B virus and had undergone treatment for tuberculosis in the past; women who required only surgery or surgery and radiation, women who discontinued the planned treatment of chemotherapy or radiation were not included.

The Indian Diabetes Risk Score

IDRS developed by Mohan et al (2005) is based on the multiple logistic regression model and uses the four vital parameters—age, abdominal obesity, physical activity, and the history of diabetes in the family, all of which are well-known proven factors associated with the development of T2DM.[40,41,62] The domain of age is categorized into three groups as age < 35 years coded as 0 point, 35 to 49 years as 20, and $\geq$ 50 years as 30.[41] The second parameter of abdominal obesity for females was waist circumference < 80 as 0 point, between 80 and 89 cm as 10, and those with $\geq$ 90 cm as 20.[41] Regarding family aspects, individuals with no family history of diabetes in parents are coded as 0, those with one parent as 10, and those with both parents diabetic as 20.[41] The physical activity was categorized as 0 if the individual did leisure-time exercise and in addition, had physically demanding work in their occupation; 20 for individuals who either did exercise or performed physically demanding work and 30 for those who did not exercise during leisure time and had sedentary work.[41] The minimum possible score was 0, while the maximum was 100.[41] The IDRS is easy to administer, time effective, inexpensive, and well validated in multiple studies in India and abroad.[37,38]

Conduct of the Study

The dietitian explained the nature and purpose of the study to eligible patients satisfying the inclusion criteria in either English or their mother tongue (Kannada, English, Tulu, or

Table 1 Demographic details of women who had dysglycemia after curative chemotherapy on their first follow-up visit 3 months after the completion of treatment

Parameters	Groups	All	Glycemic state		*p*-Value
			Normal (127; 61.05)	Hyperglycemic (81; 38.93)	
Age	< 30	15 (7.2)	12 (9.4)	3 (3.7)	0.003
	30–40	40 (19.2)	28 (22)	12 (14.8)	
	41 to –50	60 (28.8)	30 (23.6)	30 (37)	
	51 to –60	51 (24.5)	24 (18.9)	27 (33.3)	
	> 60	42 (20.2)	33 (26)	9 (11.1)	
	Total	208 (100)	127 (100)	81 (100)	
Place	Village	33 (15.9)	28 (22)	5 (6.2)	< 0.001
	Town	92 (44.2)	80 (63)	12 (14.8)	
	City	83 (39.9)	19 (15)	64 (79)	
	Total	208 (100)	127 (100)	81 (100)	
BMI	< 18	33 (15.9)	24 (18.9)	9 (11.1)	< 0.001
	18–22	83 (39.9)	63 (49.6)	20 (24.7)	
	> 22	92 (44.2)	40 (31.5)	52 (64.2)	
	Total	208 (100)	127 (100)	81 (100)	
Married	Yes	200 (96.2)	123 (96.9)	77 (95.1)	
	No	8 (3.8)	4 (3.1)	4 (4.9)	
	Total	208 (100)	127 (100)	81 (100)	
Child	Nil	61 (29.3)	39 (30.7)	22 (27.2)	
	1	17 (8.2)	11 (8.7)	6 (7.4)	
	2	76 (36.5)	48 (37.8)	28 (34.6)	
	> 2	54 (26)	29 (22.8)	25(30.9)	
	Total	208 (100)	127 (100)	81(100)	
Diet	Vegetarian	11 (5.3)	7 (5.5)	4(4.9)	
	Nonvegetarian	75 (36.1)	47 (37)	28(34.6)	
	Mixed	122 (58.7)	73 (57.5)	49(60.5)	
	Total	208 (100)	127 (100)	81(100)	

Abbreviation: BMI, body mass index.

Malayalam). They were also informed about the study and that their nonwillingness would not deprive them of the proposed treatment planned by the tumor board. The willing patients were then included in the study, and written informed consent was obtained. The dietitian collected the demographic details such as age at the time of breast cancer diagnosis, domicile, type of diet, marital status, number of children, previous history of chronic ailments, history of diabetes in the family and specifically in parents, whether they did exercise regularly and on how physically demanding their work (occupation) was before being diagnosed with cancer. The weight, height, and weight circumference were also measured, and BMI was calculated as per the standard guidelines. The clinical data (histopathological details such as TNM staging, hormonal receptor status [estrogen, progesterone], and HER2/Neu status ascertained by immunohistochemical [IHC] methods and fluorescence in situ hybridization [FISH] assay to further validate the HER2-positive status were collected when available from the files. The chemotherapy regimen and prescribed steroid dose and duration advised by the medical oncologist were collected from the patient records.

Blood Glucose Evaluation and Consideration

The blood glucose levels are always evaluated before the start of every chemotherapy cycle and on the first follow-up 6 weeks after curative radiotherapy, that is, 3 months after the last chemotherapy cycle. Patients with fasting blood sugar values of $\geq$ 126 mg/dL were considered diabetic. Fasting blood glucose levels $\geq$ of 100 mg/dL or random blood glucose levels $\geq$ of 140 mg/dL during the treatment were considered chemotherapy-induced hyperglycemia (World Health Organization, 2006). The standard practice for the management of diabetes is in accordance with standard

guidelines. It includes dietary measures and prescription of oral hypoglycemic depending on the clinical condition and the judgment of physicians.

Statistical Analysis

The data entered into Microsoft Excel was exported to SPSS for Windows, Version 17 (IBM Corp, Armonk, New York, United States). Data were presented with the help of tables. The descriptive data were subjected to frequency and percentage and subjected to chi-square test. The association between the demographic details and development of hyperglycemia occurrence was done using the Fisher's exact test. The receiver operating characteristic (ROC) curve was plotted, and the area under the curve (AUC) was used to find out the accuracy of this scoring system. The chi-square test was used for testing the significance of the difference between two or more proportions in the IDRS. All tests of statistical significance were based on a two-sided test, and a p-value of <0.05 was considered significant.

Results

The results of the study are presented in ►Tables 1 to 3 and ►Figs. 1 and 2. Of the total 208 women treated with chemotherapy, 127 (61.05%) were normoglycemic, 32 (15.38) were prediabetic, and 49 (23.55%) were diabetic during the first follow-up visit conducted 3 months after the completion of chemotherapy. For statistical convenience and understanding, the analysis was conducted as normoglycemic 61.05% (127/208) versus dysglycemic 38.93% (81/208). The demographic details indicate that most of the women were married (96.2%), had two children (36.5%), and were used to a nonvegetarian diet (94.7%) (►Table 1). With regard to development of hyperglycemia, majority of the women who developed the condition were from town (44.2%), in the age group of 41 to 50 years (28.8%) and with BMI more than 22 (44.2%) and statistically significant (►Table 1).

With regard to the tumor data,70.7% (147/208) women had T2 stage, 35.1% (73/208) had N0 nodal state; 97.1% had M0 stage (202/208), and 31.7% (66/208) in stage IIA (►Table 2). With regard to the hormonal receptor status, of the 154 women who had the reports, 51.3% (79/154) were ER negative; 55.2% (85/154) were PR negative; 47.4% (73/154) had both ER and PR-negative status, while 40.9% (63/154) had both ER and PR-positive status (►Table 2). With regard to the HER2/Neu status, 16.9% (26/154) had enriched status as confirmed by IHC with confirmatory FISH analysis. In the study, 29.9% (46/154) had triple negative,13.6% (21/154) had triple-positive status, while 56.5% (87/154) had a mixed status (►Table 2).

The results of the India diabetic scale showed a significant difference in the total ($p =< 0.001$) and domains of family ($p < 0.017$), activity ($p =< 0.001$) and waist diameter ($p =< 0.001$) but not in the age (►Table 3). With regard to the age, the results suggest that there was no significant difference between the two groups (►Table 3). In the domain of family history, 67.1% (100/127) in the normal group did not have a history of T2DM in the parents. In contrast, in the dysglycemic group, it was observed that the incidence of T2DM in one or both parents was more and was statistically significant ($p = 0.017$; ►Table 3).

With regard to the aspect of waist diameter, it was observed that in the normal group, 81.6% had less than <80 cm as against 18.4% in the dysglycemic cohort ($p =< 0.001$; ►Table 3). The number of women who were not into regular exercise and had sedentary work was also observed

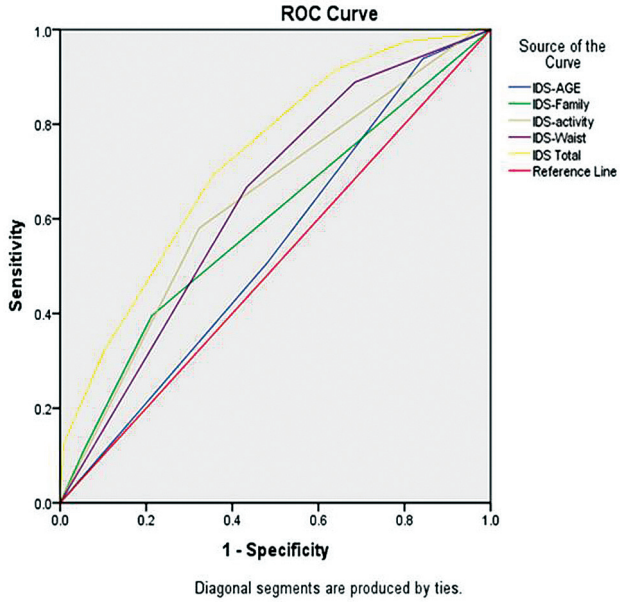

Fig. 1

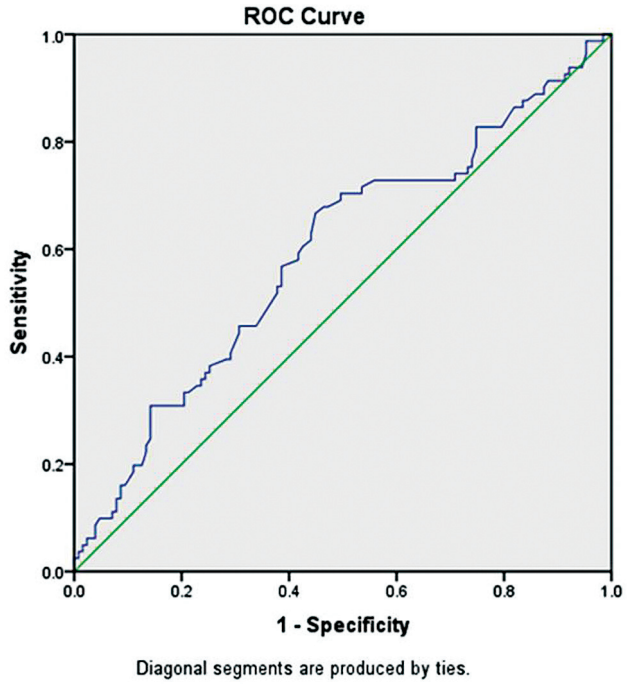

Fig. 2

Table 2 Tumor pathology details of the women who had dysglycemia after curative chemotherapy on their first follow-up visit 3 months after the completion of treatment

Parameters	Groups	All	Glycemic state		*p*-Value
			Normal (127; 61.05)	Hyperglycemic (81; 38.93)	
T	T1	7 (3.4)	4 (3.1)	3 (3.7)	
	T2	147 (70.7)	93 (73.2)	54 (66.7)	
	T3	43 (20.7)	22 (17.3)	21 (25.9)	
	T4	11 (5.3)	8 (6.3)	3 (3.7)	
	Total	208 (100)	127 (100)	81 (100)	
N	N0	73 (35.1)	42 (33.1)	31 (38.3)	0.029
	N1	59 (28.4)	29 (22.8)	30 (37)	
	N2	49 (23.6)	36 (28.3)	13 (16)	
	N3	27 (13)	20 (15.7)	7 (8.6)	
	Total	208 (100)	127 (100)	81 (100)	
M	M0	202 (97.1)	122 (96.1)	80 (98.8)	
	MX	6 (2.9)	5 (3.9)	1 (1.2)	
	Total	208 (100)	127 (100)	81 (100)	
Stage	IIA	66 (31.7)	39 (30.7)	27 (33.3)	
	IIB	45 (21.6)	23 (18.1)	22 (27.2)	
	IIIA	63 (30.3)	41 (32.3)	22 (27.2)	
	IIIB	5 (2.4)	3 (2.4)	2 (2.5)	
	IIIC	29 (13.9)	21 (16.5)	8 (9.9)	
	Total	208 (100)	127 (100)	81 (100)	
ER	Negative	79 (51.3)	44 (45.4)	35 (61.4)	
	Positive	75 (48.7)	53 (54.6)	22 (38.6)	
	Total	154 (100)	97 (100)	57 (100)	
PR	Negative	85 (55.2)	49 (50.5)	36 (63.2)	
	Positive	69 (44.8)	48 (49.5)	21 (36.8)	
	Total	154 (100)	97 (100)	57 (100)	
ER and PR status	ER −/PR−	73 (47.4)	41 (42.3)	32 (56.1)	
	ER −/PR+	6 (3.9)	3 (3.1)	3 (5.3)	
	ER +/PR−	12 (7.8)	8 (8.2)	4 (7)	
	ER +/PR+	63 (40.9)	45 (46.4)	18 (31.6)	
	Total	154 (100)	97 (100)	57 (100)	
HER2 enriched	Negative	128 (83.1)	44 (45.4)	35 (61.4)	
	Positive	26 (16.9)	53 (54.6)	22 (38.6)	
	Total	154 (100)	97 (100)	57 (100)	
Triple status	Mix	87 (56.5)	55 (56.7)	32 (56.1)	
	Negative	46 (29.9)	26 (26.8)	20 (35.1)	
	Positive	21 (13.6)	16 (16.5)	5 (8.8)	
	Total	154 (100)	97 (100)	57 (100)	

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor type 2; PR, progesterone receptor.

to be more in the hyperglycemia cohort and was significant ($p = < 0.001$). The ROC analysis indicated that an IDRS score above 60 increased the possibility of developing hyperglycemia with the sensitivity of 81.3%, specificity of 54.7%, and AUC of 0.727 (►**Fig. 1**). The analysis also showed that women with BMI above 25.03 were at high risk for developing hyperglycemia (sensitivity 70.4%, specificity of 50.4%, and AUC 0.593) (►**Fig. 2**).

Table 3 Number and percentage of normal, prediabetic, and diabetic in women who underwent curative radiotherapy on their first follow-up visit 3 months after the completion of treatment

Domain	IDRS details		Glycemic state		Chi-square/Fisher's exact test
	Grouping	Score	Normal	Hyperglycemic	
Age	< 35	0	20 (80)	5 (20)	
	35–49	20	46 (56.8)	35 (43.2)	
	≥ 50	30	61 (59.8)	41 (40.2)	
Family	No family history	0	100 (67.1)	49 (32.9)	0.017[a]
	Either parent	10	20 (46.5)	23 (53.5)	
	Both parents	20	7 (43.8)	9 (56.3)	
Activity	Exercise + strenuous work	0	4 (100)	0 (0)	< 0.001[a]
	Exercise or strenuous work	20	82 (70.7)	34 (29.3)	
	No exercise and sedentary work	30	41 (46.6)	47 (53.4)	
Waist	< 80 cm	0	40 (81.6)	9 (18.4)	0.001[a]
	≥ 80–89 cm	10	32 (64)	18 (36)	
	≥90 cm	20	55 (50.5)	54 (49.5)	
IDRS total		20	4 (100)	0 (0)	< 0.001[a]
		30	4 (80)	1 (20)	
		40	17 (94.4)	1 (5.6)	
		50	21 (80.8)	5 (19.2)	
		60	36 (66.7)	18 (33.3)	
		70	32 (51.6)	30 (48.4)	
		80	12 (42.9)	16 (57.1)	
		> 80	1 (9.1)	10 (90.9)	

Abbreviation: IDRS, Indian Diabetes Risk Score;
[a](significant difference).

Discussion

The current study results clearly show that the IDRS developed by the MDRF is sensitive in predicting the development of treatment-induced hyperglycemia in women undergoing curative chemotherapy for their breast cancer. IDRS is one of the oldest and a well-investigated risk score questionnaires in the different study populations in India and the United States.[37,38] In addition to this, IDRS is also reported to be useful in differentiating T2DM from non-T2DM and to identify people at risk to develop coronary artery disease, peripheral vascular disease, and neuropathy among those with T2DM.[37,63–65] The ROC analysis indicates that an IDRS of above 60 could be a predictive cut point in this study. In their first study with IDRS scale, Mohan et al (2005) have reported that the AUC for ROC was 0.698 and that an IDRS value ≥ 60 had optimum sensitivity (72.5%) and specificity (60.1%) for determining undiagnosed diabetes with a positive predictive value of 17.0%, the negative predictive value of 95.1%, and accuracy of 61.3%.[41] Subsequent studies by the authors have shown it was also useful in distinguishing T2DM from non-T2DM and that the IDRS ≥ 60 was predictive of T2DM, while an IDRS <60 was predictive of non-T2DM.[37] Recently, Nugawela et al (2020) studied the usefulness of IDRS with different ethnic groups in the United States and reported that a cutoff ≥60 in the IDRS was observed for the American Indians, while a cutoff ≥70 had a good discriminative performance for the American Hispanics, non-Hispanic whites, and non-Hispanic blacks. Cumulatively, all these observations suggest that a cutoff of IDRS value > 60 was useful in predicting the chances of development of T2DM.[38]

Regarding BMI and waist circumference, the results suggest that in women who developed hyperglycemia, these indicators were significantly on the higher side (►**Table 3**). The ROC analysis also ascertained a predictive value of 25.03 (►**Figs. 1** and **2**). To further substantiate our observations, previous studies have shown that BMI cutoff of 22.7 to 23.8 kg/m^2 for women has been reported to have a significant association for the development of DM and cardiometabolic ailments.[66] To support this, a case–control study conducted by Awasthi et al (2017) have also shown that when compared with the controls, the BMI was more than 25 kg/m^2 in people affected with T2DM and was significant ($p < 0.05$).[67] Studies have shown that when compared with the white Caucasian population, South Asians are at higher risk for the development of non-communicable obesity-related ailments. Therefore, a BMI >23 to 24.9 kg/m^2 and central obesity are important anthropometric indicators.[68] Additionally, recent observations by Venkatrao et al (2020) have emphasized that both waist circumference and BMI are good predictors for the

risk of developing T2DM in the Indian population and that people with high values in both end points improved its accuracy and specificity as predictors.[69]

T2DM has been shown to have a genetic predisposition, and previous studies with adult Asian Indians have shown a significant association ($p < 0.001$) to the family history of diabetes.[70] Family history is a major risk factor, and strong family history is reported to early age onset of T2DM and to also develop complications.[71] Studies from Kancheepuram district, Tamil Nadu, India, have also shown that 68.8% of the people affected with T2DM had a family history of diabetes and that 25.1% had a mother and 15.3% had father affected with the ailment, respectively, and that 51.6% had diabetic complications.[72] Together with all these observations indicate that the family history had a strong association with both ages of onset and complications.[71,72] Large community-based studies have shown that when compared with those at average risk, people with a strong family risk were more likely to report a diagnosis of diabetes.[73] Studies done in Qatar also indicate that people with a family history of metabolic syndrome in parents, maternal aunt, maternal grandfather, and born in consanguineous marriages had high chances of developing T2DM.[74] Family history had a strong role in an increased risk of impaired fasting glucose/impaired glucose tolerance, T2DM, and increased levels of obesity.[75] Additionally, maternal history was shown to be associated with higher BMI, suggesting that in South East Asians, maternal transmission has a vital role.[75]

Physical activity has shown to have an inverse association with the development of cardiovascular diseases and regular physical activity such as exercise training and cardiorespiratory workouts reduced the all-cause mortality, especially in patients with T2DM.[76,77] In this study, it was observed that women who were less physically active were more likely to develop hyperglycemia (►Table 3). Most of the women in our study group were housewives and were restricted to household chores, and had reduced levels of physical activity when compared with men.[78] To substantiate this, reports by Padmanabha et al (2017) from the study have shown that at 29.6%, the incidence of T2DM was more in women than in men (25.4%).[79] Reports indicate that the incidence of diabetes was more in females than in men and that this was attributable to the sedentary lifestyle they lead.[80,81] Women living in rural areas had more physical activity when compared with women in urban areas.[82] A significant difference was also observed in the healthiness of the food and that women living in the urban area consumed a higher quantity of unhealthy diets leading to a proportionate presence of central obesity.[82] Indian women who were homemakers and were physically less active consumed a high-calorie diet and were more overweight than women working in the fields or as manual laborers.[78]

In this study, majority of the women (28.8%; 60/208) were in the age group of 41 to 50 years (►Table 1) and agreed with earlier studies published from the study area.[20,83–85] In the study, the majority of the women (84.1%) were from the urban areas (city + town) and only a small fraction (15.9%) from villages. Innumerable reports from around the world have clearly shown that the incidence of breast cancer is high in developed countries than in developing countries. That rate was also high in cities and towns than in the villages.[2,86] Also, in the study, it was observed that 93.8% of the women who developed hyperglycemia were from urban areas (►Table 1). The possible reason for this is that most women living in the urban localities in the study area have a sedentary lifestyle. To substantiate this, community-based reports published from the study area have shown that when compared with the males, females who had lower physical activity had higher BMI, indicating overweight and obesity.[87]

Conclusion

For the first time, the results of the study indicate that the IDRS can be useful in predicting the incidence of chemotherapy-induced hyperglycemia, and the association was seen with increased BMI, waist diameter, family history, and physical activity. There was no association with age, and this could be due to the fact that most women diagnosed with breast cancer were above the age of 40 years.

The biggest drawback of the study is that this study was done in a single center, and it is suggested that multicentric studies should be performed with IDRS and other validated diabetes risk questionnaires to understanding which is more sensitive in predicting the development of treatment-induced hyperglycemia and also diabetes.

The other important lacuna of the study is that emphasis was on treatment-induced hyperglycemia and during the period of active treatment. It is quite possible that the hyperglycemia seen is transient. It may revert after the treatment and as time progresses, provided woman follows a healthy and physically active life. In this regard being a cancer specialty hospital, a substantial number of patients referred for chemotherapy and radiotherapy are from other hospitals across the state and study area. Therefore, sizeable numbers of patients, especially from distant places, are lost from the follow-up analysis.

Treatment-induced hyperglycemia and diabetes are associated with negative prognostic factors such as increased chances for metastasis/recurrence.[88,89] Attempts are also underway to ascertain the long-term effect of treatment-induced hyperglycemia on the treatment end points, on the development of metabolic syndrome, musculoskeletal issues, and quality of life by contacting the long-term survivors lost to regular follow-up. Reports in these lines are lacking and will help understand the role of treatment-induced hyperglycemia on the cancer treatment outcome and will bridge the lacunae in the existing knowledge for the benefit of patients and the fraternity of oncoendocrinology.

Informed Consent

Informed consent was obtained from all participants included in the study.

Ethics Statement

This study was performed in accordance with the ethical standards of the institutional and national research

committee, the 1964 Declaration of Helsinki and in accordance to the guidelines stipulated by Indian Council of Medical Research 2008 for research after obtaining permission from the hospital ethics committee (MIO/IEC/2018/02/07).

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Conflict of Interest
None declared.

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