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RESEARCH ARTICLE

Increased Fasting Plasma Glucose and Breast Cancer Risk in Sudanese Women: Association with Premenopausal Status and High Body Mass Index

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Abstract

Background: Female breast cancer is the most common cancer in Sudan, however little data is available about breast cancer in Sudanese. We aimed to assess whether fasting glucose and insulin levels are associated with the risk of having breast cancer in Sudanese women. **Methods:** This study was conducted at the National Cancer Institute – University of Gezira (NCI-UG), Sudan. A total of 174 females were enrolled, the patient group included 77 newly diagnosed untreated breast cancer women and a control group of 97 healthy women. Overnight fasting blood samples were collected to measure fasting plasma glucose and serum insulin levels. **Results:** The fasting plasma glucose level was significantly increased in the breast cancer patients (101.94±2.94 mg/dL) than the controls (90.75±2.02 mg/dL), p=0.002. Overweight-obese and premenopausal breast cancer patient's subgroups revealed significant elevation of fasting glucose levels (105.35±4.06 mg/dL); (99.64±4.06 mg/dL) compared to controls (89.44±2.62 mg/dL), p=0.001; and (86.38±2.44 mg/dL), p=0.007 respectively. Only in the non-obese patients the insulin level was significantly lower (3.76±0.40 µU/ml) than in the control (6.11±1.00 µU/ml) p=0.034. The patient group was more likely to have 2.5 times higher fasting glucose level than the control (p=0.005). Moreover, the overweight-obese and premenopausal breast cancer patients subgroups were more likely to have 4.4 times and 4.5 times respectively elevated fasting blood glucose level, both with p=0.002. The non-obese breast cancer patients were tended to have 4.3 times decreased insulin level (p=0.019). **Conclusion:** The elevated fasting plasma glucose levels are associated with high risk of breast cancer in Sudanese women especially in the premenopausal individuals and those having BMI more than or equal to 25 kg/m^2. Consequently, adjusting blood glucose level and controlling body weight by changing the lifestyle are suggested to reduce the risk of breast cancer in Sudanese women.

Keywords: Breast cancer- Fasting glucose- Insulin- Sudanese women- Obesity

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Introduction

Female Breast cancer is the most frequently diagnosed cancer and is the fifth leading cause of cancer deaths worldwide [1]. There is a global increase in the incidence of breast cancer; in 2008, the estimated number of breast cancer new cases was 1.4 million [2], this number rose to 2.3 million new cases in 2020 [1]. An increase of incidence occurs as well in regions where the rates have been formerly low such as observed in many African countries [3, 4]. This rise could be attributed to westernization of lifestyle and health behaviours including the changes in dietary habits and lack of physical activity [5,6].

Sudan is one of the low income African countries that lack a reliable national cancer registry, this results in unidentified incidence, prevalence, and death rates of breast cancer. A few studies [7-10] were conducted in Sudan and shed some light on the burden, pattern and

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distribution of the disease, although not covering the whole country. The main source of data is the two specialized oncology centers (Radiation Isotope Center Khartoum (RICK) and National Cancer Institute- University of Gezira (NCI-UG)), both are located in central Sudan. Hospital-based case series revealed that the burden of breast cancer is noticeably increasing accounting for almost one third of the cancer problem. Sudanese women with breast cancer are characterized by young age, late stage and high grade tumors [11,12].

Established risk factors of breast cancer include family history and many reproductive factors [13-15]. Obesity contributes to development of breast cancer, and this may be due to its associated metabolic changes such as high estrogen level, hyperinsulinemia, insulin resistance, high levels of insulin-like growth factor-1, and metabolic syndrome [16-19].

Malignant cells are characterized by high uptake of nutrients especially glucose because it is the principal fuel for them, besides they change their metabolic pathways to produce the macromolecules needed to support their proliferation. For their energy production process, malignant cells preferentially depend on converting glucose into lactate rather than mitochondrial glucose metabolism even under high oxygen environments [20]. Hexose Mono Phosphate shunt is one of the main oxidative pathways of glucose in cancer cells because it is essential for nucleic acid synthesis and many other synthetic pathways [21].

Inconsistent findings about the link between blood glucose and the risk of breast cancer were reported by studies that explored this relationship. Some studies revealed a relationship between elevated fasting blood glucose levels and increased breast cancer risk [22-24]; however, others showed no association [25,26].

In Sudan, despite that breast cancer is the most common type of cancers among females, little is known about the factors related to the disease. Therefore, the present study was performed to assess whether markers of glucose specifically fasting plasma glucose and insulin levels are associated with breast cancer in Sudanese women.

Materials and Methods

This was a case-control study conducted at National Cancer Institute–University of Gezira (NCI-UG), Sudan, during the period from December 2012 to December 2014. A total of one hundred seventy four women were enrolled into the study. Seventy-seven women with newly diagnosed breast cancer in different ages, menopausal status, BMI, and stages of breast cancer were categorized as the patients' group. Patients who received chemotherapy and/or hormonal treatment, diabetic, hypertensive, cachexic, or patients on medications or have a disease that might interfere with study parameters were excluded. A control group of 97 healthy female volunteers participated in the study. Demographic and reproductive data were collected from all participants through a structured questionnaire. The study was conducted under the ethical guidelines approved by Ethics Committee at NCI-UG. All participants gave an informed consent before commencement of the study.

Blood samples were collected from all participants after an overnight fasting. For fasting plasma glucose measurement, samples were collected into fluoride acetate containers then plasma was prepared and measured immediately by Biosystems A15 automated analyzer (Biosystems, Barcelona, Spain) using glucose oxidase peroxidase method. The remaining blood samples were collected into plain containers. Sera were separated and stored at -20°C and used later for determination of insulin by electrochemiluminescence immunoassay (ECLIA) using Cobas e 411 automated analyzer (Roche Diagnostics, Germany). The Homeostasis Model Assessment for Insulin Resistance index (HOMA-IR) was used to estimate insulin resistance using the formula:

HOMA–IR= Fasting insulin (μU/ml) × *fasting glucose (mg/dL)* / 405

Anthropometric measurements i.e., weight (Wt), hight (Ht), and waist circumference (WC) were measured and the BMI was calculated.

Women having BMI less than 25 kg/m^2 were classified as a non–obese group, whereas women with BMI more than or equal to 25 kg/m^2 were categorized in the overweight-obese group.

The statistical analysis was done by statistical package for social science software (IBM SPSS version 20). Numerical data were presented as mean ± standard error of mean (SEM). Independent t-test was used to compare between means of patients and controls, and to compare between the mean levels of biochemical parameters in the subgroups of patients with their matched subgroups of the controls. To estimate the risk of breast cancer, binary logistic regression was done with dependent variables (patients versus controls), and independent variables (BMI, WC, age, menopausal status, glucose, insulin and HOMA-IR) to calculate odds ratios (OR) with 95% confidence intervals (CI). The cut-off values for BMI and WC were based on WHO classification. Glucose, insulin, and HOMA-IR were categorized according to 75th percentile of the study group. Further analysis was done by stratifying patient and control groups according to BMI (overweight-obese group vs. non-obese group) and menopausal status (premenopausal vs. postmenopausal group). Two-tailed p value was considered significant at 0.05.

Results

The main characteristics of the study groups

The mean age and BMI in the cases and control group were similar. The mean waist circumference was significantly higher in the patient group compared to the controls. Fasting plasma glucose mean concentration was significantly increased in the patient group than controls. Fasting serum insulin level in the patient group was lower than in the control group, though the difference was not

Table 1. Comparison of Age, Anthropometric and Biochemical Measurements between Patient and Control Groups

Variable	Mean ± SEM		p value
	Patient group (n=77)	Control group (n=97)	
Age (years)	45.32 ± 1.34	44.61 ± 1.21	0.692
Weight (kg)	63.59 ± 1.61	64.32 ± 1.41	0.734
BMI (kg/m^2)	25.20 ± 0.65	25.47 ± 0.51	0.576
WC (Cm)	90.93 ± 1.49	85.55 ± 1.28	0.007
Glucose (mg/dl)	101.94 ± 2.94	90.75 ± 2.02	0.002
Insulin (µU/ml)	5.69 ± 0.64	7.42 ± 1.14	0.187
HOMA-IR	1.50 ± 0.19	1.81 ± 0.35	0.439

SEM, standard error of mean. n, number. p, probability. BMI, body mass index, WC, waist circumference, HOMA-IR, homeostasis model assessment for insulin resistance

significant (Table 1).

Factors associated with risk of breast cancer

Regarding the BMI, 51.3% of patients were non-obese in contrast to 45.4% of controls. On the other hand, 48.7% of patients were overweight-obese and 54.6% were overweight-obese in their counterparts of controls. A percentage of 52.0% and 57.7% were premenopausal women in patient and control groups, respectively. Postmenopausal women represented 48.0% and 42.3% of the patients and controls, respectively. Patients with elevated fasting plasma glucose had a 2.5 fold increased risk of breast cancer (95% CI: 1.313 – 4.760, p= 0.005). Patients having higher waist circumference had a 1.7 times increased risk of breast cancer (95% CI: 0.891 – 3.1584, p= 0.109), however this was statistically not significant. Insulin level was inversely associated with breast cancer, but with no statistical significance (OR 0.6, 95% CI: 0.264 – 1.232, p= 0.153). Postmenopausal status was found to be linked to 1.3 times increased risk of breast cancer as for premenopausal status (95% CI: 0.688 – 2.312, p= 0.454), but with no statistical significance (Table 2).

Subgrouping of study groups according to BMI and menopausal status

To test whether or not there a relation between BMI and menopausal status on one hand and glucose and insulin levels on the other hand; the study groups were categorized according to BMI into two subgroups as non-obese and overweight-obese subgroups, and according to menopausal status into premenopausal and postmenopausal subgroups. Comparing the patients and controls within each subgroup, revealed that only the glucose level was significantly increased in the overweight-obese patients compared to controls. In the non-obese subgroup, serum insulin level was significantly decreased in patients. With regard to menopausal status subgroups fasting plasma glucose level was significantly increased in premenopausal patients compared to their control counterparts (Table 3).

Table 2. Association of Investigated Parameters with Risk of Breast Cancer in the whole Group of Participants

Parameters	Cut-off	Patient group N (%)	Control group N (%)	OR	95% CI	p value
BMI (kg/m^2)	< 25	39 (51.3)	44 (45.4)	1 (Ref)		0.437
	≥25	37 (48.7)	53 (54.6)	0.788	0.432-1.438	
WC	<88	26 (38.8)	50 (51.5)	1 (Ref)		0.109
	≥ 88	41 (61.2)	47 (48.5)	1.678	0.891-3.158)	
Age (years)	<45	40 (51.9)	51 (52.6)	1 (Ref)		0.934
	≥ 45	37 (38.1)	46 (47.4)	1.026	0.563-1.867	
Menopausal status	Pre	39 (52.0)	56 (57.7)	1 (Ref)		0.454
	Post	36 (48.0)	41 (42.3)	1.261	0.688-2.312	
Glucose (mg/dl)	< 97.75	42 (54.5)	72 (75)	1 (Ref)		0.005
	≥97.75	35 (45.5)	24 (25)	2.500**	1.313-4.760	
Insulin (µU/ml)	<7.86	64 (84.2)	73 (75.3)	1 (Ref)		0.153
	≥ 7.86	12 (15.8)	24 (24.7)	0.57	0.264-1.232	
HOMA-IR	<1.7	56 (73.7)	71 (74.0)	1 (Ref)		0.968
	≥ 1.7	20 (26.3)	25 (26.0)	1.014	0.512-2.011	

N, number. OR, odds ratio. CI, confidence intervals. p, probability. BMI, body mass index. Ref, reference group. WC, waist circumference. HOMA-IR, homeostasis model assessment for insulin resistance. **, significant at 0.05.

Table 3. Comparison of Insulin, Glucose, and HOMA-IR Levels According to BMI and Menopausal Status

Subgroup Parameter	Non-obese		p value	Overweight-obese		p value
	Patients	controls		patients	controls	
Glucose (mg/dl)	98.90 ± 4.38	92.30 ± 3.15	0.225	105.35 ± 4.06	89.44 ± 2.62	0.001
Insulin (µU/ml)	3.76± 0.40	6.11 ± 1.00	0.034	7.75 ± 1.17	8.50 ± 1.91	0.737
HOMA-IR	0.94 ± 0.11	1.59 ± 0.34	0.079	2.11 ± 0.35	2.00 ± 0.58	0.878
Subgroup Parameter	Premenopausal		p value	Postmenopausal		p value
	Patients	controls		patients	controls	
Glucose (mg/dl)	99.64 ± 4.06	86.38 ± 2.44	0.007	104.53 ± 4.51	96.88 ± 3.23	0.173
Insulin (µU/ml)	6.23 ± 0.79	8.16 ± 1.83	0.338	5.15 ± 1.09	6.41 ± 0.99	0.396
HOMA-IR	1.60 ± 0.23	1.80 ± 0.55	0.643	1.42 ± 0.33	1.72 ± 0.35	0.529

Variables are shown as (Mean ± SEM), SEM, standard error of mean. p, probability. HOMA-IR, homeostasis model assessment for insulin resistance.

Risk estimation of breast cancer regarding BMI and menopausal status

Fasting blood glucose level was significantly increased in the presence of breast cancer by 4.4 times in overweight-obese and 4.5 times in premenopausal women. On the other hand, overweight-obese breast cancer patients had higher HOMA-IR scores by 1.9 times compared to their controls, but statistically this was not significant as shown in Table 4.

The non-obese women exhibit significant inverse relationship between insulin level and risk of breast cancer. Also, HOMA-IR showed an inverse relationship with the risk of breast cancer but did not reach statistical significance. Glucose levels are more likely to increase in non-obese patients by 1.7 times than the control although this was not significant (p=0.258). In the postmenopausal women subgroups, insulin level was inversely related to occurrence of breast cancer, yet statistically not significant (Table 4).

Discussion

The risk factors of breast cancer remain obscure among Sudanese women thus extensive research is needed in this regard. The current study was designed to assess the relation of high fasting glucose and insulin levels to the risk of breast cancer in Sudanese women.

In the present study we found higher levels of fasting plasma glucose in breast cancer patients than controls. Elevated glucose increased the risk of breast cancer by 2.5 folds similar to other studies [22] [24]. High glucose plays an essential role in the proliferation and progression of breast cancer cells [20] [27]. Moreover, high concentrations of glucose stimulate the in vitro invasiveness of human breast cancer cell line MDA-MB-435 by changing the expression of matrix metalloproteinase MMP-9/MMP-2/E-cadherin [28]. In breast cancer patients, hyperglycemia was shown to be associated with aggressive phenotype of disease [29], and increased mortality in hormone receptor positive cases [30]. It was reported that the elevation of fasting blood glucose levels reduced the response to neoadjuvant chemotherapy in diabetic and non-diabetic breast cancer patients [31], while use of metformin together with neoadjuvant chemotherapy in the treatment of diabetic patients with breast cancer improved their pathologic complete response [32]. Studies from Sweden and Korea showed that the glucose level was not associated with breast cancer risk [25] [33]. Other researchers showed a relationship in the diabetic patients but not in the non-diabetics [34].

Other factors that might affect the level of plasma glucose such as BMI and menopausal status were investigated by stratification of the whole study group. For this purpose, classification was made into two subgroups according to BMI (non-obese and overweight-obese subgroups). Another categorization was based on the menopausal status (premenopausal and postmenopausal subgroups) to ensure a more homogenous patients and controls within each BMI and menopausal status subgroup. We found that glucose level was significantly increased in the patients than controls in the overweight-obese subgroup, whereas no difference was seen between patients and controls in non-obese subgroup. It was shown that high fasting plasma glucose level was associated with breast cancer risk in the premenopausal patients and only in overweight postmenopausal women [22]. Increased blood glucose was found to be associated with poor prognosis in breast cancer patients; shorter overall survival time and shorter time to tumor recurrence were reported in patients with elevated random blood glucose [35].

Concerning the menopausal status, a significant association was shown between impaired glucose-insulin homeostasis and the risk of breast cancer in overweight and obese premenopausal women but not in normal weight premenopausal women [36]. In the current study, we showed higher fasting plasma glucose levels in premenopausal breast cancer patients compared to controls, in agreement with Muti et al [22]. We observed no difference in the postmenopausal subgroup. Previously, a significant relationship has been stated only in postmenopausal women with high BMI [22]. On the other hand, another study showed that high blood glucose level increases the risk of breast cancer in both pre- and postmenopausal women [24]. Manjer et al had reported no association between glucose levels and risk of breast cancer neither in premenopausal nor postmenopausal women [25].

Many studies showed an association of

Table 4. Association between the Biochemical Parameters and Breast Cancer Risk in the BMI and Menopausal status Subgroups

Subgroup	Parameters	Cut off	Cases N (%)	Control N (%)	OR	CI	p value
Non-obese	Glucose (mg/dl)	< 97.75	25 (59.52)	17 (40.48)	1 (Ref)	0.686-4.083	0.258
		≥97.75	32 (71.11)	13 (28.89)	1.674		
	Insulin (µU/ml)	<7.86	38 (90.48)	4 (9.52)	1 (Ref)	0.070-0.780	0.019
		≥ 7.86	31 (68.89)	14 (31.11)	0.233		
	HOMA-IR	<1.7	35(83.34)	7 (16.66)	1 (Ref)	0.175-1.388	0.18
		≥ 1.7	32 (71.11)	13 (28.89)	0.492		
Overweight-obese	Glucose (mg/dl)	< 97.75	16 (43.24)	40 (76.92)	1 (Ref)	1.750-10.935	0.002
		≥97.75	21 (56.76)	12 (23.08)	4.375		
	Insulin (µU/ml)	<7.86	27 (72.97)	41 (77.36)	1 (Ref)	0.480-3.337	0.634
		≥ 7.86	10 (27.03)	12 (22.64)	1.265		
	HOMA-IR	<1.7	22 (59.46)	38 (73.08)	1 (Ref)	0.754-4.542	0.179
		≥ 1.7	15 (40.54)	14 (26.92)	1.851		
Premenopausal	Glucose (mg/dl)	< 97.75	21 (53.85)	47 (83.93)	1 (Ref)	1.729-11.589	0.002
		≥97.75	18 (46.15)	9 (16.07)	4.476		
	Insulin(µU/ml)	<7.86	31 (79.49)	41 (73.21)	1 (Ref)	0.266-1.873	0.484
		≥ 7.86	8 (20.51)	15 (26.79)	0.705		
	HOMA-IR	>1.7	26 (66.67)	40 (71.43)	1 (Ref)	0.517-3.022	0.62
		≥ 1.7	13 (33.33)	16 (28.57)	1.25		
Postmenopausal	Glucose (mg/dl)	< 97.75	20 (55.56)	24 (58.54)	1 (Ref)	0.482-2.988	0.695
		≥97.75	16 (44.44)	16 (41.46)	1.2		
	Insulin (µU/ml)	<7.86	30 (83.34)	31 (75.61)	1 (Ref)	0.158-1.690	0.275
		≥ 7.86	5 (16.66)	10 (24.39)	0.517		
	HOMA-IR	>1.7	27 (75.00)	30 (73.17)	1 (Ref)	0.306-2.580	0.828
		≥ 1.7	8 (25.00)	10 (26.83)	0.889		

N (%), number of cases in group (percentage). OR, odds ratio.CI, confidence interval. p, probability. HOMA-IR, homeostasis model assessment for insulin resistance. Ref, reference.

hyperinsulinemia with the risk of breast cancer [16] [37, 38]. In our study, we found no association of insulin level with breast cancer in Sudanese women similar to other authors [34] [39]. Only in the non-obese subgroup of women, we observed a statistically significant association between insulin level and incidence of breast cancer, patients with increased insulin level had more than four-folds lower risk of breast cancer. A large prospective study with 5 years duration revealed the risk of breast cancer was associated with the levels of insulin-like growth factor-1 (IGF-1), but moderately associated with insulin level [22]. Insulin may exert its mitogenic effect mediated by insulin receptor or IGF-1 receptor. Insulin has critical roles in cancer development including stimulation of cell growth through activation of the insulin receptor and IGF-1 receptor [40,41]. Heredity has an important role in the association of glucose and insulin traits with the risk of breast cancer development [42].

HOMA-IR is a more valuable marker – than the measurement of insulin or glucose level alone – to identify patients with insulin resistance and those who have high risk of breast cancer [18]. In this regard, our results demonstrated a decreased HOMA-IR in non-obese breast cancer patients compared to controls, with a trend towards significance. Luque et al. (2017) showed a significantly increased HOMA-IR in the overweight breast cancer patients [36]. In the present study, neither premenopausal nor postmenopausal subgroups of patients revealed an elevation of HOMA-IR compared to controls, whereas another study had reported that especially in postmenopausal women [18]. However, the association between insulin resistance and breast cancer in premenopausal women is related to high BMI [36].

The limitations of this study are that it was a case-control study of a small sample size, with no follow-up of patients. A larger longitudinal prospective study could assess the relation of glucose markers to breast cancer incidence, prognosis, and response to treatment. To address questions about breast cancer risk factors, a cohort study design is more valuable and informative. However, our present findings draw attention to the link between glucose metabolism and female breast cancer in Sudanese.

In summary, our study revealed a significant association between high fasting plasma glucose levels and breast cancer in Sudanese women in the whole group of patients as well as in the premenopausal subgroup, and in the overweight-obese women. Thus, lowering of both blood glucose level and BMI by alteration of lifestyle is suggested to reduce the risk of breast cancer in Sudanese women, particularly in the premenopausal women in addition to the overweight-obese women.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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