Full Length Research Article

Decoding the association between breast cancer prevalence and obesity-induced metabolic disorders

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Amer Alasadi[1],*, Noor Fadhil[2], Enas Abdul Kareem Jabbar[1]

1. Department of Medical Basic Science, College of Nursing, University of Thi-Qar, 10 University Campus West, Al-Muhia, Thi-Qar, 00964, Iraq
2. Department of pharmacology, College of Pharmacy, Al- Kut University, 212 Alanwar, Wasit, 00964, Iraq

* dr.amer@utq.edu.iq

ABSTRACT

Background: Breast cancer (BC) is the most common malignancy diagnosed among women worldwide, constituting approximately one- third of all recorded female cancers. It is also the prominent cause of cancer- related mortality among women. This study aimed to investigate the correlation between BC prevalence and certain metabolic disorders such as obesity and Insulin Resistance (IR) as well as hormonal disorders.

Methods : A cross- sectional study was conducted to identify potential metabolic risk factors that were associated with BC prevalence. The study included 203 BC patients from the breast clinics at medical and oncology centers and 80 healthy subjects (HS). BC patients were divided into four groups according to their body mass index (BMI). Baseline characteristics, Lipid profile, IR, leptin- adiponectin ratio, and Inflammatory biomarkers were evaluated in BC patients and HS

Results: Our data indicated that the highest prevalence rates of BC were observed among participants aged 40-47 years and those aged 48 years and above. 54 patients were classified as obese I (BMI 30.0-34.9), whereas 84 patients were Obese II (BMI 35.0-39.9). There was a prominent association between BC prevalence and family history, and estrogen receptor (ER) positively. Dyslipidemia and IR indices were significantly elevated in obese BC patients compared to HS. Overweight BC patients (BMI 25.0-29.9) also revealed significantly increased leptin levels, and clear decline in adiponectin levels. In addition, patients with higher BMI "had significantly increased in levels of C-Reactive Protein (CRP), IL-6, IL-1β, TNF-α, Resistin, Nesfatin-1 and Lipocalin-2.

Conclusion: BC prevalence is associated with obesity- IR axis and its consequences. Our data demonstrate that IR indices, adipokines and inflammatory biomarkers could serve as feasible predictors in oncology for monitoring the BC risk and progression in obese women.

EDITORIAL NOTE

Editorial Note on Version of Record

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INTRODUCTION

The association between BC prevalence and obesity- IR crosstalk is complex and heterogeneous, including several biological mechanisms, which contribute to BC growth and progression. Obesity has been constantly identified as the major threat for BC, especially in postmenopausal women [1-3]. Several studies indicated that obesity is linked with an increased chance of BC due to various factors, including age, family history (FH) and, alterations in hormone levels in postmenopausal women, especially estrogen, that is produced in excess by adipose tissue [4-7]. During postmenopausal stage, estrogen is mainly converted to androgen in adipose tissue through aromatization, which promoted increasing the estrogen level in blood circulation, consequently encouraging the development of hormone receptor-positive BC [8,9]. In addition, obesity contributes to about 9% of all BC deaths globally [10-12]. Together obesity and overweight situation are connected to a higher prevalence of ER+ BC hormones [13]. Furthermore, obese patients have been diagnosis with advanced BC, large tumor size, lymph node metastasis and poor survival outcome compared to non-obese women [14,15]. Moreover, data from many clinical trials indicated that obesity adversely impacts free survival and overall survival of BC patients [16]. Additionally, metabolic syndromes play pivotal roles in BC epidemiology, which frequently escorts obesity prevalence that has been accompanied with BC prevalence [17-19]. Notably, metabolic syndrome consists of complex conditions such as IR, hyperglycemia, dyslipidemia and hypertension that are considered the more important contributor for BC prevalences [20-22]. A study confirmed that obesity contributes to about 11% of BC in high income countries [23]. In addition, Obesity is one of the major inducers for inflammatory process, and it is considered as the foremost feature of fatty (adipose tissue) malfunction. Also, adipose tissue is not only the central storage for excess fatty acid such as triglycerides but also the active and the essential endocrine part to secrete different peptides as known as adipokines [24]. Specifically, these inflammatory adipokines such IL-6, IL-1β and TNF-α that are highly produced and expressed in the obese subjects [25]. Mechanistically, the Inflammatory process in adipose tissue of obese subjects is induced by specific macrophage, which promotes the site-specific inflammation. Moreover, the limited inflammation induces different metabolic disorders that promotes the general inflammation [26]. Among these metabolic problems, IR is a severe pathological and physiological malfunction of insulin roles in adipose tissue that occurs in obese patients. Through IR, Insulin levels dramatically rise in the blood circulation to avoid high blood sugar [27]. Therefore, hyperinsulinemia is highly correlated with increased BMI. From clinical view, several studies demonstrated that the elevation of IR indices, different inflammatory biomarkers such C-reactive protein, Resistin, Nesfatin-1, and Lipocalins-2 are correlated with poor prognosis in BC patients [28-31]. Therefore, we designed this cross-sectional study to investigate the effects of obesity-IR interaction on the BC prevalence among Iraqi women, with specific focus on assessing dyslipidemia, IR, inflammatory biomarkers (CRP, Resistin, Lipocalin-2 and Nesfatin-1), and leptin/adiponectin ratio as potential predictors of BC threat, development and disease progression.

METHODS

Patients and Methods

A cross-sectional study was conducted at oncology centers in Thi-Qar province from January 2022 to October 2023. The data were collected from 203 female patients with newly diagnosed early-stage BC and 80 HS. The diagnosis of BC and estrogen receptor (ER) +/- or status were confirmed depend on histopathological examination by qualified pathologists. ER profile was assessed immunohistochemical analysis of BC specimens and categorized as (ER+ or ER-) based on the established criteria utilized by the pathologists. Data were collected by direct interview and from the registration records at the oncology centers. Patients age, sex, social state, proper history of disease and investigations results were recorded. Body Mass Index (BMI) was calculated from body weight and height measurements recorded by health care provider at the period of admission using Quetelet's index method (presented in kg/m2) [32]. The patients were divided the into four groups according to their BMI as indicated here, normal weight (18.5–24.9), overweight (25-29.9), obese I (30-34.9) or greater Obese II (35-39.9).

Exclusive and Inclusion Criteria

A participant was defined as follows: female's age starting at age 18 and up, exclusively for women residents of Thi- Qar Province, confirmed cases of breast cancer, visiting clinics for breast disease consultants at breast clinics at two medical and oncology centers. We included only patients with newly diagnosed, untreated early-stage BC, and excluded those who had heart diseases, other cancers and infectious diseases".

Ethical Consideration

The Research Ethics Committee at College of Nursing / University of Thi- Qar approved this project (approval no. NUR001R1023) prior to the project start. All participants in study provided informed consent, with the understanding that they would always have the option to withdraw. Confidentiality and individual privacy were fully protected.

Biochemical Parameters

Fasting blood samples were collected from all BC patients and healthy subjects. Serum used to measure lipid profile status such as Total cholesterol (TC), Triglycerides (TG,), Low Density Lipoprotein Cholesterol (LDL- C), High Density Lipoprotein cholesterol (HDL- C), Fasting Blood Glucose (FBG) and Fasting Insulin (FI) using colorimetric assay and ELISA kits performed according to company's instructions (Elabscience, China). IR and TyG indexes calculated according to following equations: HOMA-IR = Fasting Insulin (FI) (μU/mL) ×FBG (mmol/L)/22.5, TyG index =Ln [TG (mg/ dL) × FBG (mg/ dL)/2] respectively [30]. We measured the following parameters used ELISA Kit for all the following order with all catalog numbers (Leptin, Adiponectin, and Resistin) (ARG83643), Nesfatin-1- (Cat.NO.MBS705593) and Lipocalin-2 (ng/ ml) (Cat. No. DY8556), CRP (mg/L), IL-6 and IL-1β and TNF-α (pg/ml) measured from Uscn Life Science Inc. (Hubei, China).

Statistical Data Analysis

The data of the present study was analysed using analysis of variance (ANOVA) to find the significant differences between groups, and Tukey test (post hoc test) used to find the significant differences among groups. For the descriptive analysis we used frequencies and percentage %. Significant data was considered if *p < 0.05, with emphasis on (p value **p<0.01 and ***p<0.001) for highly significant data.

RESULTS

To identify correlation between several characteristics and breast cancer risk, we conducted a cross-sectional study to achieve this goal.

First, based on demographic variables, our data revealed the distribution and percentage of patients with BC as shown in Table 1. The results showed the frequency and percentage of age for all patients, the age group of 40-47 and 48+ years showed the highest prevalence rate of BC as shown 72 (35.46%) and 102 (50.24%) respectively.

Table 1 also showed the frequency and percentages correspondingly of the BC patients according to BMI as normal weight 30 (14.77%), overweight 35 (17.24%), obese I 54 (26.60%) and obese II 84 (41.37%). Also, the data revealed high frequency and percentage for BC prevalences related to living in urban places 138 (67.98%) rather than in rural places 65 (32.01%).

Furthermore, the data confirmed that the married women were the most susceptible patients to BC as indicated in Table 1 as 122 (60.09%) from 203 participants. Also, the results demonstrated the risk of cancer was associated with FH, the patients with BC were 123 (60.59%) from all cases. In addition, the data exhibited the frequency and percentage according to hormonal status and ER+ cases were the highest rate compared to ER- 158 (77.83%) and 45 (22.17%) respectively.

To investigate the differences in lipid profile and IR between HS and BC, we divided the BC

patients into four groups according to their BMI and compared the lipid profile status, IR indices and adipokines balance compared to HS as showed in Table 2.

The data confirmed there was a significant difference (p<0.001) between the HS group and BC patient groups (BMI overweight, BMI obese I and BMI obese II) and among groups in TC levels as indicated here 165.65±23.67, 219.93±16.62, 268.60±23.78 and 296.66±16.67 respectively. In addition, the data showed a significant (p<0.01 & p<0.001) elevation within and among the BC patients' groups in TG and LDL levels. Furthermore, the results indicated a significant increase (p<0.01) in TC/HDL and TG/HDL ratios among BC patients compared to the HS group. Whereas the data marked a significant (p<0.01) reduction in HDL-C concentration in BC patient groups (BMI overweight, BMI obese I and BMI obese II) and among groups rather than HS.

IR is an important landmark of obesity, to study the effect of IR as a risk biomarker for BC prevalence. We assessed the differences of IR indices through HOMA-IR and TyG index, and the data exhibited a significant increment (p<0. 01) in the above indices in BC compared to HS group shown in Table 2.

Leptin and adipokine balance have a remarkable connection with metabolic disorder, especially obesity and how this connection might act as a promoter factor for breast cancer prevalence. To understand this connection, we measured the levels of leptin and adiponectin in HS and BC patient's groups, our results revealed a significant increment / decline (p<0.01& p<0.001) in leptin/adiponectin level.

Obesity induces a notable chronic inflammation in adipose tissue; to explore the connection between the obesity induced BC and chronic inflammation, we measured some biomarkers of the inflammation in HS and compared the results with BC patients who have higher BMI. Our data confirmed a significant (p<0.01 & p<0.001) elevation in CRP, IL-6, IL-1β and Lipocalin-2 in BC patients compared to HS as shows Then, we tested TNF-α, Resistin and Nesfatin-1 is other indicators for persistent inflammation, obesity related inflammation and BC promotion respectively. The data showed a significant increase (p<0. 01) in the serum levels of all these parameters in BC patients compared to HS as shows in Table 3'. Taken together, these parameters could be a potential biomarker for obesity-associated BC risk.

In addition, in figure 1, schematic representation showing the roles of obesity- IR– chronic inflammation axis under the estrogen effect can increase the potential for breast cancer prevalence through activation of angiogenesis, genomic stability, epithelial mesenchymal transition and suppression of apoptosis.

Figures

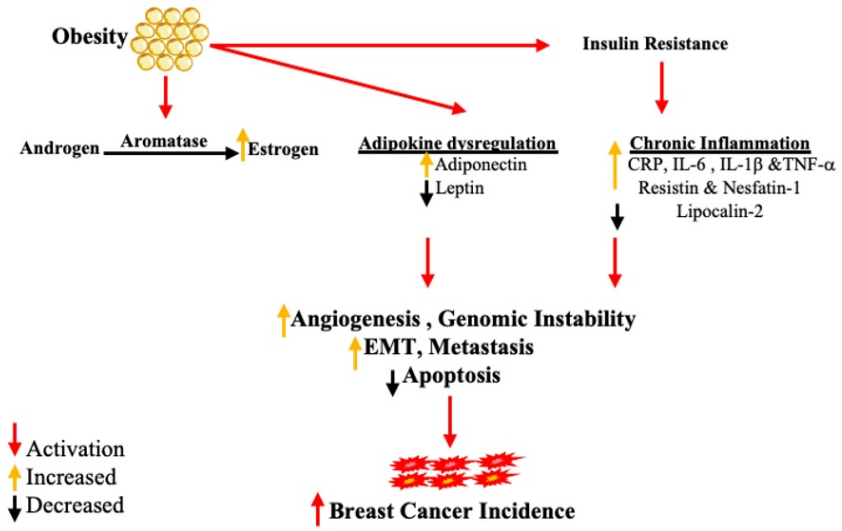

Figure 1: Schematic representation showing the roles of obesity-IR axis in increasing the potential for breast cancer prevalence through activation of angiogenesis, genomic stability epithelial mesenchymal transition and inhibiting the apoptosis pathway.

Tables

Characteristics	BC Patients Frequency/Percentage	Healthy Subjects (HS) Frequency/Percentage
Number	**203**	**80**
Age (Years)		
20-27	8(3.94%)	14(17.5%)
28-39	21(10.34%)	16(20%)
40-47	72(35.46%)	18(22.5%)
48 and above	102(50.24%)	32(40%)
BMI (kg/m²)		
Normal weight 18-24.9	30(14.77%)	20(25%)
Overweight 25-29.9	35(17.24%)	18(22.5%)
Obese I 30-34.9	54(26.60%)	16(20%)
Obese II 35-39.9	84(41.37%)	26(32.5%)
Place of living		
Rural	65(32.01%)	36(45%)
Urban	138(67.98%)	44(55%)
Marital Status		
Married	122(60.09%)	64(80%)
Single	41(20.19%)	16(20%)
Divorced	22(10.83%)	-
Widowed	18(8.86%)	-
Family History		
With B.C	123(60.59%)	-
Without B.C	80(39.40%)	-
Medical History		
Heart Diseases	-	-
D.M	-	-
Estrogen Status	158(77.83%)	-
ER+	45(22.17%)	-
ER-		

Breast Cancer (BC) , healthy Subjects (HS) Body Mass Index (BMI), Diabetes Mellitus (DM), Estrogen positive or negative (ER+, ER-)

Table 1: Baseline characteristics of breast cancer patients and healthy subjects. Data are presented as frequencies and percentages (%) for patients with breast cancer (BC; n = 203) and healthy subjects (HS; n = 80). Participants were categorized by age, body mass index (BMI), place of residence, family history, marital status, medical history, and estrogen receptor (ER) status.

Parameters	Healthy Subjects	BMI Normal BC	BMI Overweight BC	BMI Obese I BC	BMI Obese II BC	*P*value
TC (mg/dl)	165.65±23.67	165.67±23.68	219.93±16.62	268.60±23.78	296.66±16.67	<0.001
TG (mg/dl)	139.24±2.48	140.20±3.19	144.67±2.88	150.78±3.27	152.25±3.80	<0.001
HDL-C (mg/dl)	58.79±3.50	58.44±3.36	54.23±2.56	52.02±2.08	46.41±1.93	<0.01
LDL -C(mg/dl)	100.58±4.36	100.93±5.14	104.5±4.03	124.02±18.57	133.05±19.85	<0.001
TC/HDL	2.82±0.43	2.84±0.47	4.06±0.41	5.17±0.51	6.39±0.46	<0.01
TG/HDL	2.37±0.46	2.40±0.16	2.67±0.14	2.90±0.11	3.29±0.18	<0.01
FBG (mg/dl)	89.77±1.44	90.88±0.78	92.21±0.80	93.25±0.96	94.18±0.82	NS
Insulin (mU/l)	9.66±0.65	9.65±0.66	11.19±1.37	11.81±2.31	12.28±1.25	<0.001
HOMA-IR	2.13±0.15	2.17±0.15	2.54±0.30	2.71±0.53	2.85±0.30	<0.01
TyG Index	4.28±0.01	4.29±0.01	4.31±0.02	4.54±0.01	4.78±0.03	<0.01
Leptin (ng/ml)	6.42±0.23	6.43±0.19	7.30±0.14	8.91±0.77	9.94±0.49	<0.01
Adiponectin (mg/ml)	64.09±4.29	63.63±0.81	59.65±0.59	44.91±1.52	28.85±0.66	<0.001

BMI; Body mass Index; TC, Total cholesterol; TG, Triglyceride, HDL-C; High density lipoprotein cholesterol, LDL-C; Low density lipoprotein cholesterol, FBG; fasting blood glucose, HOMA-IR; homeostatic model assessment method insulin resistance; TyG; Triglyceride glucose index. Leptin normal range 4.0-6.0 ng/mL (women); Data are presented as mean ± standard deviation. Analysis of variance (ANOVA) to find the significant differences between groups, and a post hoc test used to find the significant differences among groups. Significant data was considered if *p* value* p<0.05, ** *p*<0.01 & *** *p*<0.001 vs. HS group. NS: not significant.

Table 2: Differences of lipid profile status, insulin, Insulin resistance indices and adipokines balance (adiponectin and leptin) between the BC patients' groups and Healthy Subjects (HS) group.

Parameters	Healthy Subjects (HS)	BMI Normal BC	BMI Overweight BC	BMI Obese I BC	BMI Obese II BC	*P* value
CRP (mg/L)	2.70 ±0.09	2.71±0.14	2.81±0.10	3.01±0.16	3.02±0.06	<0.01
IL-6 (pg/ml)	53.40±2.56	54.51±1.97	60.28±1.33	62.82±1.51	64.67±1.51	<0.01
IL-1β (pg/ml)	5.24±0.58	5.57±0.54	7.84±0.72	12.28±0.68	15.33±0.29	<0.001
Lipocalin-2 (ng/ml)	91.24±2.66	91.27±1.59	92.68±2.16	100.58±2.62	111.9±1.69	<0.001
TNF-a (pg/ml)	21.95±1.28	22.53±0.75	54.45±1.41	111.12±8.37	134.56±1.27	<0.001
Resistin (ng/ml)	9.93±0.42	10.01±0.73	10.74±0.82	12.65±0.72	14.45±0.69	<0.01
Nesfatin-1(ng/ml)	1.91±0.06	1.95±0.04	2.28±0.15	3.13±0.08	4.79±0.56	<0.01

CRP; C reactive protein BMI; Body mass Index, IL-6, interleukin-6; IL-1b, interleukin-1b; TNF-α, tumor Necrosis Factor-α. Data are presented as mean ± standard deviation. Analysis of variance (ANOVA) to find the significant differences between groups, and a post hoc test used to find the significant differences among groups. Significant data were considered if *p* value* p<0.05, ** *p*<0.01 and *** *p*<0.001. vs. HS group. NS: not significant.

Table 3: Differences of inflammatory parameters between the Breast Cancer patients (BC) groups and Healthy Subjects (HS) group.

DISCUSSION

The complex interaction between obesity, lifestyle, and hormonal changes promoting BC progression warrant further investigation to find innovative therapeutic targets.'. While risk factors for breast cancer can vary across different regions globally, acknowledging the specific factors that are associated with obesity-IR axis on BC risk remains essential.

The results of the current study confirmed that the risk and prevalence of BC was at advance age and high (40-48 and older). Our results are consistent with previous published data confirmed that BC prevalence increased with age, mostly after the third decade of life and into the postmenopausal period in many women [33-34]. Several research and clinical studies stated that the higher chances of BC with rising age, coherent with postmenopausal hormonal disturbances and aggregate exposure to environmental and hormonal risk factors [35-36]. Overall, our observation demonstrated that BC prevalence relates to older age and this data supported broadly concurring with worldwide patterns of BC prevalence by age.

Furthermore, the literature constantly connects greater BMI, mainly in postmenopausal women with enlarged BC chance, somewhat through adiposity-induced elevation in estrogen synthesis and production from fatty tissue accumulation and connected metabolic alterations. Other studies also showed a strong connection between higher BMI and BC Prevalence with ER+ BC [37-38].

Moreover, our finding showed that the prevalence of BC prevalence increased in the urban living places than the rural, this urban-rural variation in BC threat has been demonstrated in several studies and frequently show the variance exposure to the environmental pollution, modern lifestyle, physical activity, reproductive actions, and approach to diagnosis/treatment [33,39-40].

In the contexts of marital status, the data demonstrated that married women represent the greatest segment of BC patients plus FH related BC. Married status per se is not a straight etiologic element but can be a factor for reproductive behaviors, social/economic importance, and treatment-seeking patterns, all these factors have been unevenly allied with BC prevalence in diverse populations. The results of higher FH frequency among BC patients are consistent with the previous studies and literature that showed FH associated BC prevalence risk and can stimulate cancer initiation [36,41-42].

From the clinical perspective, ER+ BC is a worldwide and common BC, with highest prevalence at 70-80% in different populations and through many regions, age and diagnosis approach [43]. Notably, the data indicated ER+ cases as 158/203 (77.83%) and ER− as 45/203 (22.16%). Receptor status is clinically critical because ER+ tumors are typically more responsive to hormone therapies (e.g., tamoxifen, aromatase inhibitors) and generally have a better prognosis versus ER− tumors when treated appropriately [42-44]. The high ER+ percentage in our data was well-matched with ongoing observations in many women with BC cohorts, but living places, FH, BMI, age and environmental-endocrine problems related variances should be studied when concluding. Overall, the study emphasizes the significance of age, FH, obesity, and hormonal imbalance are the potential risk factors for BC prevalence.

In addition, our study compared lipid profile status and IR indices between HS and BC patients, with additional stratifying BC with BMI groups (overweight, obese I, obese II). The results showed a significant difference among groups in TC, TG, LDL-C, HDL-C, and consequential TC/HDL, TG/HDL ratios, along with prominent IR markers such as HOMA-IR and TyG index in BC patients rather than HS. This elucidation combines latest evidence on how IR and dyslipidemia-IR axis link to BC prevalence and tumor progression, including ER status– dependent arrangement where present. The growth and progression of cancer cells acquired the building substrates for new cancer cells. Therefore, the elevated TC and TG provide building subunit for cell membrane biosynthesis and lipid for different signaling pathways to promote cancer cells growth. In addition, increasing LDL- C is necessary for cholesterol structure that builds membrane structure and lipid rafts bioformation. Moreover, the decreased level of HDL-Cs in the BC patients with higher BMI indicated the metabolic disorder that was linked to obesity and the chronic inflammation [45,46].

Furthermore, the significant adiposity and IR within higher BMI (overweight, obese I, and obese II) in BC patients versus HS reveals the amplifying effect of adiposity in metabolic disarrangement in BC cases. This is aligned with the concept of fat tissue accumulation trigger proinflammatory, IR metabolic pattern that prevalence with BC and may cooperate with tumor microenvironment, mainly in estrogen favoring disease where adiposity- induced estrogenic environment plus adipokines can impact growth and progression signals and therapeutical response [45-47].

It's well-known that adipose tissue as endocrine organ and in the situation of obesity, adipose tissue alters the adipokine secretion (adiponectin and leptin), cytokines and the essential elements for insulin signaling pathway, all of them have an important roles BC prevalence and development in postmenopausal women. Our data explicitly demonstrated these events in the Table 2, this mechanistic explanation underpins why BC cases with abnormal BMI frequently exhibit worse and impaired metabolic status, IR biomarkers and why TyG index related data can be an informative biomarker for monitoring approach [48-51].

Moreover, the study evaluated the integration between adipokines (particularly adiponectin and leptin), inflammation status, and BC risk in the milieu of obesity. The results reported that BC patients showed a significant variation in adiponectin and leptin levels compared to HS, accompanied with significant increase in inflammatory biomarkers such as CRP, IL-6, IL-1β and TNF-α. Also, the data demonstrated a significant elevation in the levels of Resistin, Nesfatin-1 and Lipocalin-2 in BC patients with high profile of BMI versus HS. These results are relevant with previous reports and growing research, which linked the obesity and adipose tissue dysfunction to trigger IR, and chronic inflammation with different adiponectin/leptin signaling to BC chance prevalence, and development [52,53].

Furthermore, adiponectin-leptin balance plays a notable role as regulator for BC prevalence and development. Adiposity associate with significant elevation of leptin with marked declined of adiponectin creates a suitable milieu for tumorigenicity. During obesity, elevated leptin and reduction of adiponectin switch the signaling pathways to mitogenic, oncogenic and pro-inflammatory track. This modifiable balance of leptin/adiponectin is progressively implicated in the carcinogenesis and progression of BC via paracrine and endocrine mechanisms with clear connection with estrogen signaling, Insulin/insulin growth factor-1 and inflammatory cytokines [53,54].

Additionally, several studies demonstrated that the elevation of leptin and reduction of adiponectin correlate with worse and poorer prognosis to BC, especially women in postmenopausal where the adipose tissue accumulation promotes ER production and enhances signaling growth [54,55].Furthermore, elevated leptin activates its receptor as a known ObR signaling pathway in BC cells engaging PI3K/AKT, MAPK and JAK/STAT signaling pathway to stimulate growth, proliferation, progression and angiogenesis. Also, leptin receptor prominence in several BC samples reinforce the systemic importance of leptin/ adiponectin signaling in tumor initiation and progression [54-56].

Moreover, adiponectin commonly works as pro- apoptotic and has a double role as anti-inflammatory and anti-proliferative effect through AdipoR1/R2 and the related factors such as PPAR-α, NF-κB and AMPK. We observed a declined level of the adiponectin in obese patients,

eliminates the above roles and may enhance BC advancement, mainly in prevalence with additional mediators for pro- inflammatory and IR. This contrary link between leptin vs adiponectin is a frequently detected feature in obesity- induced cancer study and support our data. The interpretation that an adverse adipokine level associates with BC existence and inflammatory prevalence [53-57].

Clinically, several epidemiologic reports and reviews highlight that the balance of leptin/ adiponectin or complex adipokine signaling results. This is a good biomarker to detect tumor risk than each marker only, exhibiting adiposity problems. Our data prominence on leptin/ adiponectin ratio is coherent with above concept. The suggested models wherever the accumulative signal from anti-inflammatory roles of adipokines restrains BC prevalence [55-57].

The results showed a significant increase in TNF-α CRP, IL-6, IL-1β, and Resistin in BC patients compared to HS group, and this indicates this inflammatory alignment is constant with obesity-linked inflammatory process of BC etiopathophysiology [58]. We also investigated the role of Lipocalin-2 (LNC-2) in cancer prevalence and inflammation. LCN-2 is related to innate immunity and may acts as a regulator for inflammatory reactions and tumor biophysiology. We reported the level of LCN-2 elevated in BC patients compared to HS. Respective studies had linked the elevation of LCN-2 tumor progression and aggressiveness specially in women suffering from obesity and in menopausal period [59-61]. In addition, the elevation of the other inflammatory biomarkers such as TNF- α, Nesfatin-1 and Resistin, have been involved in promoting thrombogenesis via pro- angiogenesis, survival cascade, and metabolic rewiring [59-61].During the obesity, adipose tissue become infiltrated with immune system which increased the releasing of proinflammatory cytokines and mediator such as TNF-α, IL-6 ,IL-1β and LCN-2 with elevated level of leptin and decline adiponectin, this environment enhances IR, increases aromatase action and estrogen synthesis and production which can activate the different signaling pathway such as mTOR, PI3K/ AKT,NF-kB and JAK/ STAT which together enhance BC development and persistence, angiogenesis and invasion [55-61].

In conclusion, the data from our project highlight the basis for obesity avoidance and weight controlling as a prospective strategy to regulate adiponectin/ leptin balance and general inflammation, potentially diminishing BC risk or improving prognosis. Moreover, Improved lifestyle through mild aerobic exercise and avoiding high calories food and refined carbohydrates, which may be happened by increasing adiponectin levels and or stimulated the protective signaling of adiponectin to reduce the inflammatory prevalence can be mainly impactful for reducing BC prevalence on postmenopausal and obese women. A list of different inflammatory biomarker cytokines (CRP, IL-1β IL-6, TNF-α, Resistin, Nesfatin-1 and LCN-2), and adiponectin/ leptin balance that are significantly increased in BC related obesity. Whether these biomarkers offer independent prognostic value beyond BMI merits an additional analysis. In addition, the insight from our project could be a new avenue for oncology treatment implications by modifying adiponectin/ leptin balance or targeting the inflammatory signaling pathway such as NF/ kB or JAK- STAT mainly in obese patients with metabolic disorder. Furthermore, obese women should be aware of the risk factors for BC and take action to lower the risk via continuing a healthy lifestyle to sustain the overall well-being.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

Availability of data and materials

The data of this study is available and can be contacted the corresponding author.

AUTHOR CONTRIBUTIONS

A.A conceived and design the study. A.A Developed the methodology. A.A., N.F. & E.J Procurement and analysis the data. A.A wrote the manuscript draft; N.F & E.J reviewed and edited the manuscript. A.A supervised the study. All the authors have read and approved the final manuscript.

ETHICS STATEMENT

The current study was approved by Research Ethics Committee at College of Nursing / University of Thi- Qar and the approval no was (NUR001R1023). All participants in the study agreed to sign a written informed consent form, which contained permission to contribute to the

present study, use of their medical results for research purposes, as specified in the Declaration of Helsinki. The individual privacy was protected.

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