RESEARCH ARTICLE

Oxidative Stress Mediates the Association between Thyroid Dysfunction and Breast Cancer

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Abstract

BACKGROUND: Breast Cancer (BC) and thyroid dysfunction are commonly observed ailments in females, and two may occur synchronously. The present study was conducted to find the role of oxidative stress and its association with thyroid dysfunction and BC.

METHODS: In this cross-sectional study, 288 and 100 subjects were included in case and control groups, respectively. Serum samples were obtained from consented subjects. Thyroid profile, thyroid antibodies, antioxidant and oxidant profiles, as well as cathepsin S (CTSS), prolactin, and estradiol levels were estimated using specific enzyme-linked immunosorbent assay kits. The data was analyzed using independent Student's t-test and Pearson correlation test.

RESULTS: BC cases had higher levels of thyroid antibodies and thyroid stimulating hormone than controls. Prolactin and estradiol levels were also deranged in the case group. Higher oxidative stress biomarkers were evident in the case group; 8-hydroxy-2'-deoxyguanosine (8-OHdG), a DNA damage marker, increased concomitantly. Correlation analysis showed a positive correlation between the antioxidant (catalase) and the oxidant (8-OHdG) levels. Furthermore, the higher level of CTSS in BC cases than in the controls is the hallmark of this study, demonstrating the pathogenesis and progression of the disease.

CONCLUSION: Results suggest the mediating role of oxidative stress in the association between thyroid dysfunction and BC. It concludes that the parameters assessed in this study could be indicative of disease progression and metastasis in BC as well as thyroid dysfunction.

KEYWORDS: breast cancer, thyroid, oxidant, antioxidant, ROS

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Introduction

Thyroid carcinoma and breast cancer (BC) are prevalent malignancies primarily affecting women. Clinical observations have consistently suggested a potential association between the two diseases, occurring sequentially and simultaneously. Some of these findings imply the presence of shared physiological and etiological factors between thyroid disorders and BC.(1) The coexistence of these conditions can be attributed to the hypothalamic-pituitary axis's mutual regulation of the thyroid gland and breast tissue.(2) Approximately 14.5% of women experience some form of thyroid dysfunction. Extensive

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research has provided substantial evidence supporting the documented association between thyroid dysfunction and BC.(2-3)

Reproductive factors are significant in both BC initiation and thyroid cancer development. The higher incidence of thyroid cancer in females can be attributed to the upregulation of estrogen receptors (ERs), which activate cellular signaling pathways and promote the growth and invasiveness of thyroid cells.(4) Estrogen is also crucial in angiogenesis and metastasis, critical factors in thyroid cancer outcomes.(5) However, the relationship between thyroid hormone and BC remains a topic of ongoing debate, necessitating further molecular-level evidence.(2)

Oxidative stress, characterized by the production of reactive oxygen species (ROS), has been implicated in cancer development. The effects of ROS on cancer cells are dual, with high concentrations causing DNA damage and cell death, while lower concentrations can result in epigenetic impairments and growth arrest.(6-7) Biomarkers of oxidative stress, such as 8-hydroxy-2'-deoxyguanosine (8-OHdG), hold clinical significance for evaluating oxidative DNA damage and its role in carcinogenesis. (8) Another established oxidative stress marker, namely malondialdehyde (MDA), is utilized to assess lipid peroxidation.(9-11)

Both endogenous and exogenous antioxidants are crucial in repairing ROS-induced damage and reducing the risk of malignancy. Enzymatic antioxidants, such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-P), neutralize superoxide and other peroxides that accumulate within cells.(11)

The other key player, identified as a potent metastasis agent, is cathepsin S (CTSS), classified under the papain-like cysteine-derived peptidases group. Interestingly, it is also identified in the micro milieu of the local tumor, where it is secreted extracellularly and has a crucial role in extracellular matrix remodeling, cell death, and survival. CTSS has been associated with various malignancies, including BC, and is linked to poor clinical outcomes and prognosis.(12,13)

Oxidative stress markers provide valuable insights into the severity and progression of diseases. Further exploration of the mediating role of oxidative stress as well as the involvement of antioxidants and CTSS holds promise for a deeper understanding of the complex relationship between thyroid dysfunction and BC. This study was conducted to find the role of oxidative stress and its association with thyroid dysfunction and BC simultaneously.

Methods

Study Design and Recruitment of Subject

A cross-sectional comparative study was conducted at the Institute of Molecular Biology and Biotechnology, Lahore, Pakistan. Experimental protocols were approved by Research Ethical Committee (No. UOL/1336/03/19). Subjects were rigorously screened at the Institute of Nuclear Medicine and Oncology (INMOL), Lahore, Pakistan. The duration of the study was from 2020-2022. Clinically diagnosed 288 subjects with BC and were on stage II to III disease, aged 40 to 50 years, were included in the study. One hundred age-matched women with no history of any disease were taken as control. None of the control subjects included in the study were on medications. They had no history of chronic illness, malabsorption, malnutrition, depression, or metabolic dysfunction, which could hinder their oxidative metabolites. In the control group, these confounding factors were ruled out when filling out the demographic data, which was recorded in a questionnaire designed for this study.

Blood Sample Collection

For biochemical parameters, after precautionary measures, a blood sample was collected from the antecubital veins, and within three hours of its collection, it was centrifuged at 4,000 rpm. The serum was collected and stored at -80^{o}C until it was assayed.

Enzyme-linked Immunosorbent Assay (ELISA)

Different variables were analyzed using commercially available standard ELISA kits according to the manufacturer's instructions. QuantiChromTM ELISA kits (BioAssay Systems, Hayward, CA, USA) were used for the measurement of malondialdehyde (MDA) (Catalog No.: DTAC-100), glutathione (GSH) (Catalog No.: DIGT-250), and nitric oxide (NO) (Catalog No.: D2NO-100). GSH-P, 4-hydroxynonenal (4-HNE), glutathione reductase (GSH-R), advanced glycation end products (AGEs), prolactin, Cathepsin S (CTSS), and estradiol were measured using Glutathione (Catalog No.: ab65322), Lipid Peroxidation (4-HNE) (Catalog No.: ab238538), Glutathione Peroxidase (Catalog No.: ab102530), and Advanced Glycation End Products (AGEs) (Catalog No.: ab273298) Assay Kits, as well as Human Prolactin (Catalog No.: ab108679), Human Cathepsin S (Catalog No.: ab155427), and 17 beta Estradiol (Catalog No.: ab108667) ELISA Kits (Abcam, Cambridge, UK), respectively. EnzyChromTM ELISA kits (BioAssay Systems) were used for the measurements of CAT

(Catalog No.: ECAT-100) and SOD (Catalog No.: ESOC-100). Free Thyroxine (FT4) (Catalog No.: SE120122), Triiodothyronine (T3) (Catalog No.: SE120132), Thyroid Stimulating Hormone (TSH); (SE120135), Thyroglobulin (TG) Antibody (Catalog No.: SE120123), and Thyroid Peroxidase IgG (Catalog No.: SE120124) ELISA kits (Sigma-Aldrich, St. Louis, MO, USA) were used to measure FT4, free triiodothyronine (FT3), TSH, thyroglobulin antibody (TG-Ab), and thyroid peroxidase antibody (TPO-Ab), respectively. TSH receptor Autoantibody (TSHr-Ab) was measured using TSH Receptor Autoantibody ELISA Kit (Catalog No.: DEIA1670, Creative Diagnostics, Shirley, NY, USA). Advanced oxidation protein products (AOPP) were measured with AOPP-Human Serum Albumin (AOPP-HSA) (Catalog No.: STA-319, Cell Biolabs, San Diego, CA, USA). Oxidative DNA damage marker, 8-OHdG, was measured using DNA Damage (8-OHdG) ELISA Kit (Catalog No.: SKT-120-96S, StressMarq Biosciences, Victoria, Canada).

Statistical Analysis

A sample size of 288 consented BC women was determined using 95% confidence interval (CI). The sample size was estimated using an online webpage (https://clincalc.com/stats/samplesize.aspx). In addition, the power analysis was performed to estimate the sample size needed to detect the anticipated effect size with a desired level of statistical power of p=0.05 and the desired power level of 25%. The collected data was analyzed by SPSS v20 (IBM, Armonk, NY, USA). Variables of data were articulated as mean± standard deviation (SD). Independent Student's t-test was used to determine significant changes in different variables in both groups. Pearson correlation coefficient was used to find the correlation between the two studied variables. R-value of 0.3-0.5 was considered a significant positive association between the two parameters.

Results

The data assembled in Table 1 revealed the demographic profile, including age, socio-economic status, dietary habits, occupation, environment, family history, other comorbidities, addiction history, marital status, age at first full-term gestation, breastfeeding history, duration of reproductive years, *i.e.*, from menarche to menopause, site of cancer, the histological basis of cancer, period elapsed since diagnosis of cancer, ER status, metastasis and mode of treatment given in BC patients included in the study. Demographic data of the control subject were essentially helpful in getting background information.

Thyroid Hormone Profile

Higher levels of TSH were observed in the BC cases compared with the controls. Significant lower levels of FT3 and FT4 were recorded in the BC case group compared with the control group. TG-Ab, TPO-Ab and TSH-Ab levels were higher in the case group than in the control group (Table 2).

Oxidative Stress Markers and Hormonal Profile

The levels of oxidative stress biomarkers, namely AOPPs, AGEs, NO, and GSH-P, were raised in the BC cases compared with the controls. MDA and 4-HNE levels were also higher in the cases group compared with the control group. DNA damage marker, namely 8-OHdG, was higher in BC cases than in controls. Enzymatic antioxidants, namely SOD, GSH, CAT, and GSH-R were significantly lower in the BC cases as compared with controls. Levels of prolactin and estradiol persistently remained higher in BC cases when compared with controls (Table 3). Significantly higher CTSS levels were measured among BC cases compared with those in the control group (Figure 1). Correlation analysis between CAT, an antioxidant, and 8-OHdG, an oxidant showed a positive association in the BC group (Figure 2).

Discussion

Risk factors, including demographic, reproductive, hormonal, hereditary, breast-related, and lifestyle factors, contributed to BC incidence.(14) In a case-control study conducted in Morocco, 237 BC cases were included, and the results indicated a significant association between early menarche and nulliparity with an increased risk of BC. On the other hand, earlier age at first-term gestation was linked to a decreased risk of BC.(15)

Earlier studies involving 682 BC patients revealed a strong association between BC and total T3 and T4 levels. Premenopausal females showed decreased T4 levels and increased body mass index, while postmenopausal females exhibited the opposite pattern.(3) Another cohort study, which included 75,076 women aged 20-89 years over 28 years, indicated a positive association between hyperthyroidism and BC risk after age 60, but no such association was observed for hypothyroid females.(16) In the same study, FT4 levels were positively associated with a higher risk of BC, particularly in obese females. However,

Table 1. Demographic data of subjects.

Parameters	Control (n=100)	Case (n=288)	Parameters	Control (n=100)	Case (n=288)
Age (years), mean±SD	45.5±10.3	46.8±13.5	Age at menarche (years), mean±SD	14±1.86	14±2.13
Socio-economic status, n			Age at menopause (years), mean±SD	46±3.95	44±4.15
Economic class	47	215	Menopausal status, n		
Lower class	33	54	Premenopausal	41	119
Upper class	20	19	Postmenopausal	59	169
Occupation, n			Site of cancer, n		
Housewife	62	247	Right breast	0	141
Working women	38	41	Left breast	0	147
Family history, n			Histological diagnosis, n		
Posotive family history of BCRA in mother/siblings	13	53	Ductal carcinoma *in situ*	N/A	18
Other diseases, n			Lobular carcinoma *in situ*		27
Hypertension	0	96	Ductal invasive carcinoma		191
Diabetes mellitus	0	63	Lobular invasive carcinoma		29
Hypertension and diabetes mellitus	0	129	Mixed		7
Asthma	0	19	Miscellaneous		16
Addiction, n			Duration of cancer, n		
Betel leaves usage	0	54	< 2 years	N/A	98
Smoking	11	32	2-4 years		141
Betel leaves usage and smoking	0	3	>4 years		49
Marital status, n			ER status, n		
Married	93	265	Positive	N/A	201
Unmarried	7	23	Negative		87
Age at first pregnancy, n			Metastasis, n		
Nulliparous	0	17	Lymph node	N/A	186
<25 years	47	152	Bone		7
≥25 years	53	119	Liver		11
Breastfeeding history, n			Brain		6
Breastfed 1 child	20	116	No metastasis		78
Breastfed 2 children	39	88	Mode of treatment, n		
Breastfed >2 children	41	84	Radiotherapy	N/A	89
			Radiotherapy and chemotherapy		199

females with higher levels of TPO-Ab had a relatively lower risk of BC.(17) Albeit, various studies concluded that hyperthyroid females have an increased risk of BC, while hypothyroid females have a slightly decreased incidence of BC.(18)

In the present study, BC subjects had significantly higher AOPPs, AGEs, and GSH-P levels than controls. Moreover, the level of NO was higher in the case group than control group, although no significant difference was observed between these groups. Additionally, as measured by MDA and 4-HNE levels, lipid peroxidation was significantly higher in BC patients compared to controls. 8-OHdG, a DNA damage marker, was also elevated in BC patients. Enzymatic antioxidant levels, including SOD, CAT, GSH, and GSH-R, were significantly decreased in BC patients compared with healthy individuals. Correlation

Table 2. Thyroid profile of control (n=288) and case (n=100) groups.

Variables	Control	Case	*p*-value
FT4 (pmol/L)	17.86±2.95	10.11±1.63	0.041*
FT3 (pmol/L)	4.71±0.16	3.73±0.19	0.032*
TSH (IU/L)	1.90±0.37	3.54±0.63	0.005*
TG-Ab (IU/mL)	24.10±6.81	62.07±9.65	0.032*
TPO-Ab (IU/mL)	5.26±1.49	10.19±1.95	0.019*
TSHr-Ab (IU/L)	1.23±0.21	3.16±0.49	0.022*

Independent Student's t-test, *$p<0.05$.

Table 3. Antioxidative and hormonal profile of control (n=288) and case (n=100) groups.

Variables	Control	Case	*p*-value
MDA (nmol/mL)	0.96±0.06	4.35±1.15	0.003*
8-OHdG (ng/mL)	1.03±0.09	6.59±1.44	0.001*
4-HNE (mmol/L)	0.64±0.02	5.29±1.08	0.003*
SOD (µg/dL)	0.65±0.06	0.16±0.09	0.011*
GSH (µg/dL)	9.77±1.16	5.88±1.29	0.018*
CAT (µmol/mol of protein)	6.58±2.59	4.59±1.53	0.017*
AOPPs (ng/mL)	0.78±0.01	1.55±0.06	0.026*
AGEs (U/L)	1.55±0.07	2.59±0.05	0.040*
NO (ng/mL)	28.25±4.59	35.29±6.35	0.091
GSH-P (µmol/mL)	10.59±4.59	15.66±5.29	0.017*
GSH-R (µmol/mL)	1.55±0.09	0.15±0.02	0.028*
Prolactin (ng/mL)	8.59±2.45	42.59±8.11	0.013*
Estradiol (pg/mL)	6.35±1.55	12.65±2.45	0.012*

Independent Student's t-test, *p<0.05.

studies revealed a positive correlation between CAT and 8-OHdG. A further molecular-level investigation is required to establish this correlation.

CTSS has been implicated in intracellular signaling pathways and identified as a potential biomarker in triple-negative BC, a subtype associated with poor outcomes. Its overexpression may indicate defective DNA damage repair pathways and sensitivity to DNA-damaging agents.(19,20)

Imbalances between ROS production and enzymatic and non-enzymatic antioxidant defenses have been implicated in the pathogenesis of various diseases, including cancer. ROS can initiate and promote carcinogenesis by activating proto-oncogenes and inactivating tumor-suppressor genes. (21) A Lithuanian study involving 52 females found higher MDA levels and lower total glutathione levels in BC patients compared with controls, highlighting the importance of MDA as a predictor of oxidative stress in BC.(22) Oxidative stress also affects signaling pathways associated with cell proliferation.(13,23,24) ROS can impair the expression of p53, a factor involved in apoptosis, further contributing to tumor development and progression.(25,26)

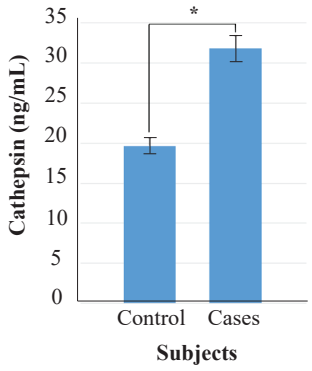

Figure 1. CTSS levels of control (n=288) and case (n=100) groups. Significant difference between groups is indicated by *p<0.01.

BC patients have been found to exhibit higher levels of 8-OHdG and reduced activity of antioxidant enzymes, suggesting higher oxidative stress and increased utilization of antioxidants.(27,28) Increased MDA levels have been associated with higher BC stages and metastatic potential. (29-31) The elevation of MDA is linked to reduced levels of antioxidants, potentially playing a crucial role in tumor progression.(32)

The overall association between BC and thyroid dysfunction suggests that excessive production of ROS and impairment of the antioxidant defense system result in permanent oxidative damage to macromolecules. Regulating the inflammation balance of antioxidant system is essential in managing oxidative stress in BC patients. Higher auto-antibodies levels reflect tendency to develop autoimmune thyroid disorders in BC patients. Higher biomarkers of oxidative stress implicate to have a role in disease progression. These interactive findings can be helpful in the development of multi-target, yet effective anticancer drugs intended for modulating the cell redox balance and monitoring the progression of cancer and metastasis.

To the best of our knowledge, this is the first study that has assessed the relationship between thyroid dysfunction

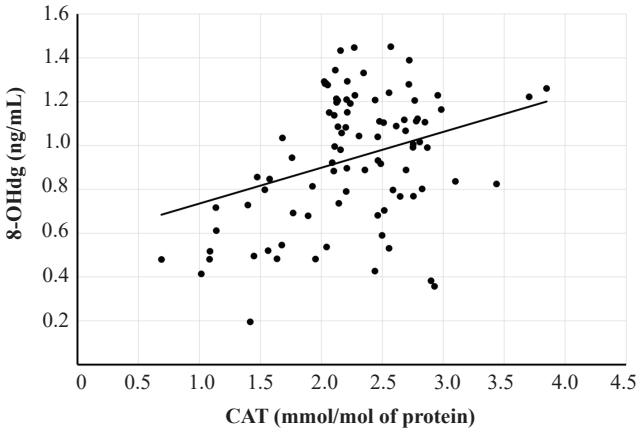

Figure 2. Correlation between CAT and 8-OHdG. A positive correlation was observed between CAT and 8-OHdG (R=0.53) and (p=0.043).

(hormonal and auto-immunity) and BC in women in Pakistan. The results of our study open a new line of research with which to assess the relationship between thyroid dysfunction and BC at the molecular and cellular levels. There is a need for preventive measures and thyroid profile screening in women suffering from BC. However, larger multi-center, multi-regional and multi-ethnicity studies are needed to reach a better conclusion.

Conclusion

Results suggest the mediating role of oxidative stress in the association between thyroid dysfunction and BC. It concludes that the parameters assessed in this study could be indicative of disease progression and metastasis in BC as well as thyroid dysfunction.

Authors Contribution

MAM was concepting of the idea for the study. MAM, MZM, FAA and ARJ were involved in the study design. AAM, RUK, and FAA were involved in the definition of intellectual content. MAM, MZM, AAM, RUK, and ARJ conducted the literature search. MAM, MZM, and RUK were involved in the data acquisition. MAM, MZM, AAM, RUK, FAA, and ARJ prepared the original draft of the manuscript. MAM, MZM, and FAA edited the manuscript. MAM, MZM, AAM, FAA, and ARJ reviewed the manuscript. All authors took parts in giving critical revision of the manuscript.

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