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Exploring the Link between Type 2 Diabetes Mellitus and Triple Negative Breast Cancer: Insights from mRNA Expression Analysis in Tertiary Care Hospital

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Abstract: ***Background: Type 2 diabetes mellitus is associated with hyperinsulinemia, hyperglycaemia, adipokine changes (increased leptin and decreased adiponectin), chronic low-grade inflammation (increased interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-), and interferon γ). (INF-), increased levels of oxidative stress. These T2DM-related factors are thought to enhance tumour growth by engaging in signalling pathways involved in cell proliferation, migration, angiogenesis, inflammation, invasion, and apoptosis. However, the mechanisms of association between T2DM and breast cancer are still not fully understood. Aims/Objectives: Toanalyze the evaluation of role of diabetes mellitus related mRNA in triple negative breast cancer population of Bihar, whether the presence of diabetes in breast cancer patients led to a different mRNA expression before and after chemotherapy. Materials/Materials: Breast cancer and aged matched healthy control blood sample were taken in Paxgene tube. Total RNA was extracted from the breast cancer and healthy controls using PAX-gene Blood RNA Kit (Qiagen). ncRNAs and mRNAs were sequenced using the high-throughput and high-sensitivity Novaseq 6000 sequencing platform (Illumina, Inc.). Fast-QC version 0.11.8 was used to evaluate the quality of the pre-processed data. Gene expression was quantified via reads per kilo-base per million mapped reads, which was calculated using the DESeq2 package in R. Normalization of the read counts was performed and the differentially expressed genes for the treatment groups are filtered according to log2FC values (>0) and P-value <0.05. Results: There was more upregulation of genes like HLA-DPB1, HLA-DQB1, ABCA1 etc. as compared to downregulated genes in pre-treated group of breast carcinoma with to post-treated group. Most upregulated genes in pre-treated group with respect to control was HLA-DPB1 and HLA-DQB1 with log2fold change of 11.92 and 9.45 respectively. Most downregulated gene was ITLN1 Gene - Intelectin 1 (associated with type 2 diabetes mellitus and pleuropneumonia) with log2fold change of -7.74 with respect to control group. Conclusion: In order to arrive at more efficient and trustworthy therapies, potentially within a highly personalized and tailored pharmacotherapeutic framework, scientists and healthcare providers can additionally employ pharmacogenomic correlation as a vital method to determine the underlying pathophysiology and metabolomics of the particular fundamental disease.***

Keywords: Breast Cancer, Type 2 Diabetes Mellitus, mRNA, Gene Expression

1. Introduction

Obesity and type 2 diabetes mellitus (T2DM) are now on the rise. Population decline is a major concern worldwide, and both diseases are associated with an increased risk of various types of cancer, including breast cancer.[1,2]In 2018, breast cancer accounted for 11.6% of all cancers worldwide and about 7% of cancer deaths. It is the second most common cancer in men and women combined, after lung cancer, the second leading cause of cancer death, the most common cancer diagnosed in women, and the leading cause of cancer death[3]. Breast cancer accounts for about 30% of all cancers attributable to high BMI and T2DM in women [2]

T2DM is not only a risk factor for breast cancer but is also associated with breast cancer progression and a poor prognosis[3,6] Proposed biological mechanisms underlying the association between T2DM, obesity, and cancer include altered levels of T2DM-related factors that influence tumour initiation, progression, and/or response to treatment.[6] Specifically, T2DM is associated with hyperinsulinemia, hyperglycaemia, adipokine changes (increased leptin and decreased adiponectin), chronic low-grade inflammation (increased interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-), and interferon γ). (INF-), increased levels of oxidative stress.[6,7] These T2DM-related factors are thought to enhance tumour growth by engaging in signalling pathways involved in cell proliferation, migration,

angiogenesis, inflammation, invasion, and apoptosis.[6] However, the mechanisms of association between T2DM and breast cancer are still not fully understood.

Cancer prognosis may also be influenced by medical disparities among people with diabetes. In fact, studies have shown that women with diabetes are less likely to be screened for breast cancer [12] and have more advanced disease than women without diabetes.[2,9,13]. Women with diabetes and other comorbidities have less aggressive cancers.

Treatment methods, especially those related to chemotherapy.[2,8, 14-15]However, studies in settings with potential barriers to accessing care did not consider cardiovascular disease. Some chemotherapy regimens are known to be cardiotoxic, so doctors may choose more conservative chemotherapy for patients with cardiovascular disease. Because women with diabetes are at increased risk of cardiovascular disease, it is unclear to what extent the presence of nondiabetic cardiovascular disease influences physicians' decisions when choosing cancer treatment regimens.

Up to one-third of breast cancer patients have diabetes [2], and research shows that women with diabetes have a 40% higher risk of dying from breast cancer than women without diabetes.[2-6]Diabetes affects both non-cancer and breast cancer-specific mortality due to diabetes-related complications.[8] Because of the estrogenic effects of obesity or metabolic factors, including the growth-promoting effects of hyperinsulinemia and insulin resistance, which may lead to more severe disease, women with diabetes may have a poorer prognosis for developing breast cancer [6,9]. Evidence suggests that the presence of diabetes is a predictor of poorer health. The contribution of cancer treatment disparities in breast cancer prognosis, relative to other factors, is unclear. The effect of diabetes on breast cancer mortality can be particularly pronounced when adherence to guideline-recommended treatments is low among those most likely to benefit.[10,11]

In this study, we analyzed the evaluation of role of diabetes mellitus related mRNA in triple negative breast cancer population of Bihar, whether the presence of diabetes in breast cancer patients led to a different mRNA expression before and after chemotherapy. mRNAs, plays a significant role in diabetes mellitus, a metabolic disorder characterized by high blood sugar level. It plays a role in understanding the genetic factors associated with Diabetes mellitus in breast cancer mRNA analysis helps in studying gene expression patterns and identifying the gene involved in the disease process. It helps uncover the molecular underpinning of these complex conditions and paves the way for targeted and personalized treatments in future.

2. Materials & Methods

The present study was approved by the Institutional ethics committee of IGIMS, Patna, Bihar9(IEC-99). Breast cancer and aged matched healthy control blood sample were taken in Paxgene tube. Diseased sample were clinically proved by histopathological report and healthy controls were included in study, no history of malignancy or any other comorbid disease.

***cDNA library construction and Sequencing*:** Total RNA was extracted from the breast cancer and healthy controls using PAX-gene Blood RNA Kit (Qiagen). The RNA integrity and purity was determined using Nanodrop 2000 (Thermofisher Scientific, Massachusetts, USA) and agarose gen electrophoresis. The cDNA library was constructed using KAPPA Hyper-Prep Kit. rRNA was removed to obtained purified RNA. Subsequently, mRNA and ncRNA were separated by poly(A) splicing. The 1st strand cDNA was synthesized along with the 2nd strand cDNA using Kappa Hyper pre kit following the manufacturer's instructions. After purification, end-repair, A tailing and addition of adaptor sequences, the cDNA was fragmentated using uracil glycosylase.

cDNA fragments were subjected to PCR amplification, and the complementary cDNA library was constructed. ncRNAs and mRNAs were sequenced using the high-throughput and high-sensitivity Novaseq 6000 sequencing platform (Illumina, Inc.). Sequenced data were analysed and processed to dynamically remove the sequence fragments at the 3'-end and low-quality fragments using Trim Galore - 0.6.5 software. Finally, Fast-QC version 0.11.8was used to evaluate the quality of the pre-processed data.

Comparison with reference sequences: Using the HISAT2 tool the mapping of the RNA 00Seq reads to the reference genome GRCh38 (Ensembl) is performed. The genome index is built which is followed by mapping the reads to the genome index to obtain alignment files in.bam format.

***Analysis of differentially expressed genes*:** Gene expression was quantified via reads per kilo-base per million mapped reads, which was calculated using the DESeq2 package in R. Normalization of the read counts was performed and the differentially expressed genes for the treatment groups are filtered according to log2FC values (>0) and pValue<0.05.

3. Result

Comparison of down-regulation and up-regulation of various genes in patients of pre-treated or post-treated group of breast carcinoma with respect to control group is summarized in following tables.

Table 1: Down regulated genesinpre-treated group with respect to post treated

IDS	log2FoldChange	pvalue	Gene.name	Associated Disease
ENSG00000049239	-1.9645495	0.018532	H6PD	Type 2 Diabetes Mellitus
ENSG00000175061	-1.7455773	0.0167	SNHG29	Type 2 Diabetes Mellitus
ENSG00000062282	-1.7041245	0.04019	DGAT2	Type 2 Diabetes Mellitus

Table 2: Up-regulated gene pre-treated with respect to post treated

IDS	Log2Fold change	P-value	Gene name	Associated disease
ENSG00000055332	1.943472837	0.0004	EIF2AK2	Type 2 Diabetes Mellitus
ENSG00000165029	2.010201596	7.54E-06	ABCA1	Type 2 Diabetes Mellitus
ENSG00000089127	2.405530475	1.30E-05	OAS1	Type 2 Diabetes Mellitus
ENSG00000163638	6.515172341	0.04101	ADAMTS9	Type 2 Diabetes Mellitus
ENSG00000164756	6.833266349	0.024859	SLC30A8	Type 2 Diabetes Mellitus
ENSG00000237767	6.858559593	0.044925	LINC01370	Type 2 Diabetes Mellitus
ENSG00000136267	7.283178859	0.026929	DGKB	Type 2 Diabetes Mellitus
ENSG00000162409	7.428921132	0.021106	PRKAA2	Type 2 Diabetes Mellitus
ENSG00000179344	10.33122781	4.01E-06	HLA-DQB1	Type 2 Diabetes Mellitus
ENSG00000223865	21.94583982	0.000225	HLA-DPB1	Type 2 Diabetes Mellitus

There was more upregulation of genes like HLA-DPB1, HLA-DQB1, ABCA1 etc. as compared to downregulated genes in pre-treated group of breast carcinoma with to post-treated group. Log2Fold change was highest for HLA-DPB1 and HLA-DQB1.

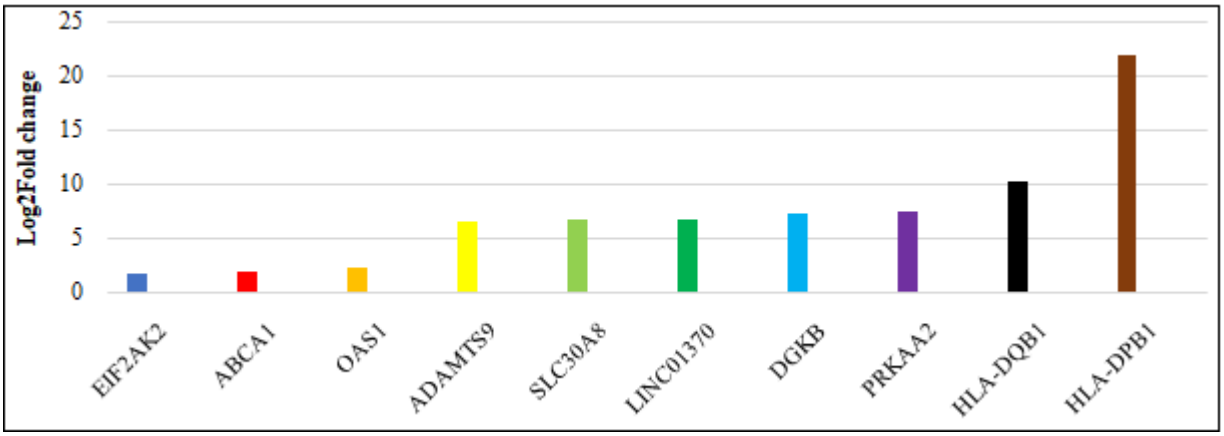

Figure 1: Up-regulated gene pre-treated with respect to post treated

Table 3: Up-regulated gene pre-treated with respect to control

IDS	log2FoldChange	p-value	Gene.name	Associated disease
ENSG00000196735	11.92271	3.60E-05	HLA-DQA1	Type 2 Diabetes Mellitus
ENSG00000179344	9.450604	4.14E-05	HLA-DQB1	Type 2 Diabetes Mellitus
ENSG00000248441	7.918878	0.002651	LETR1	Type 2 Diabetes Mellitus
ENSG00000226278	7.643213	0.018809	PSPHP1	Type 2 Diabetes Mellitus
ENSG00000255794	6.98027	0.018459	RMST	Type 2 Diabetes Mellitus
ENSG00000259520	6.482767	0.036972	SLC28A2-AS1	Type 2 Diabetes Mellitus
ENSG00000273079	4.27464	0.024796	GRIN2B	Type 2 Diabetes Mellitus

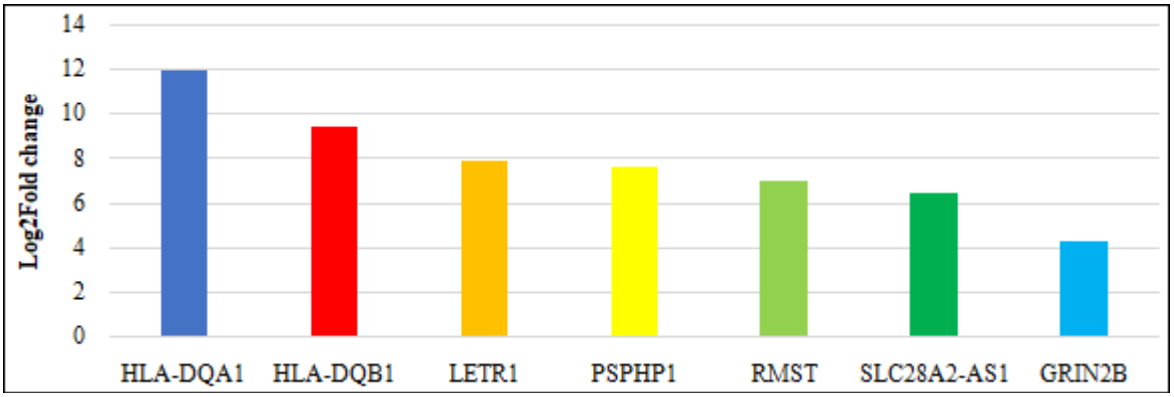

Figure 2: Up-regulated gene pre-treated with respect to control

Table 4: Down regulated genes in pre-treated group with respect to control

IDS	log2FoldChange	pvalue	Gene.name	Associated disese
ENSG00000179914	-7.737719552	0.040051	ITLN1	Type 2 Diabetes Mellitus
ENSG00000288722	-3.74768206	0.021996	F8A1	Type2Diabetes Mellitus
ENSG00000133069	-3.36917113	0.042736	TMCC2	Type 2 Diabetes Mellitus
ENSG00000233695	-3.17895196	0.03196	GAS6-AS1	Type 2 Diabetes Mellitus
ENSG00000133687	-3.087520908	0.000141	TMTC1	Type 2 Diabetes Mellitus

ENSG00000242324	-2.918266177	0.013176	Novel transcript	Type 2 Diabetes Mellitus
ENSG00000196205	-2.802674397	1.01E-05	EEF1A1P5	Type 2 Diabetes Mellitus
ENSG00000213839	-2.656059415	0.044745	TMX2P1	Type 2 Diabetes Mellitus
ENSG00000221983	-2.482638901	0.02653	UBA52	Type 2 Diabetes Mellitus
ENSG00000197465	-2.047255818	0.036314	GYPE	Type 2 Diabetes Mellitus
ENSG00000159346	-2.04231556	0.001616	ADIPOR1	Type 2 Diabetes Mellitus
ENSG00000233355	-1.750009329	0.004008	CHRM3-AS2	Type 2 Diabetes Mellitus
ENSG00000261614	-1.742644603	0.024801	YBX3P1	Type 2 Diabetes Mellitus
ENSG00000197324	-1.587825957	0.047972	LRP10	Type 2 Diabetes Mellitus
ENSG00000198888	-1.321576134	0.005286	MT-ND1	Type 2 Diabetes Mellitus
ENSG00000110090	-1.2979964	0.045062	CPT1A	Type 2 Diabetes Mellitus
ENSG00000266412	-1.182805337	0.015277	NCOA4	Type 2 Diabetes Mellitus

Most upregulated genes in pre-treated group with respect to control was HLA-DPB1 and HLA-DQB1 with log2fold change of 11.92 and 9.45 respectively. Most downregulated gene was ITLN1 Gene - Intelectin 1 (associated with type 2 diabetes mellitus and pleuropneumonia) with log2fold change of -7.74 with respect to control group.

4. Discussion

Breast cancer is 23% more likely to occur in diabetes patients than in non-diabetic patients [17] Breast cancer patients who have a history of diabetes have a 37% higher risk of dying from the disease. [18,19] Furthermore, diabetes can increase the severity of breast cancer symptoms, and in some women, diabetes symptoms might be mistaken for symptoms of breast cancer. Given that breast carcinoma survivors live longer than the general population, attention must be paid to how comorbid illnesses affect long-term outcomes. Distress, exhaustion, decreased physical well-being, anxiety, and reproductive problems are among the symptoms associated with diabetes and breast carcinoma that are similar in how they affect quality of life.[20,21]

Even though the causes of diabetes and breast carcinoma's symptoms are distinct, cohabitation can make them worse. Women with type 2 diabetes are somewhat more likely to get breast carcinoma. Any organ with a higher concentration of estrogen receptors, such as the ovaries, breast, and endometrial, is more likely to develop malignancy as a result of insulin resistance. [22] The emergence of breast carcinoma can be made more likely by certain cytokines, IGFBP-3, and IGF-1 concentrations[23] Some anti-diabetic medications can both prevent and promote the growth of various forms of breast carcinoma in women. The blood glucose-lowering medication metformin, which is prescribed to people with T2D, may lessen the risk of estrogen-positive (ER-positive) breast cancer in females.

The risk of acquiring estrogen receptor-positive breast cancer was 38% reduced in patients with type 2 diabetes who had used the medication metformin for at least ten years compared to non-diabetic patients, as per a research article published in Annals of Oncology. Furthermore, it was linked to a 74% increased probability of triple-negative breast cancer and a 25% increased risk of estrogen receptor-negative breast cancer in patients with type 2 diabetes.[24,25]

Numerous studies have emphasized the link between certain diseases and the HLA system. The association between HLA antigens and breast carcinoma has been demonstrated in numerous research.[26-29]Since the 1970s, a number of research examining the connection between HLA and breast cancer have been addressed[26-30] In their studies, Patel et al. and Iaffaioli et al. found a significant association between HLA B7 and breast carcinoma, and they found that those who carry such antigens frequently had pre-menopausal status, lacked hormonal receptors, and had primary cancers with high histological grades.[30-31]

Boulinelle et al.'s studies revealed a statistically significant association between breast carcinoma and HLA-A28 and revealed that post-menopausal women, particularly nulliparous ones, were the main carriers this particular antigen[32-16]. Breast cancer has been found to significantly correlate with HLA-B7 and DR4 by Casole et al 33] and Lavado 34], respectively. According to Chaudhuri et al. 26, the HLA-DRB1*1101, DQB1*03032 alleles are beneficial against breast carcinoma. The prevalence of the 12 allele on HLA DRB1 was definitively determined by Ghaderi et al to be considerably higher[27]. Breast carcinoma has been associated in reverse with the HLA-DRB1*02 and *07 alleles, according to Harrath et al. [28]

The multigene variants DR3/DQ2 and DR4/DQ8, in particular, were demonstrated to be crucial in the death of islet cells and pancreatic inflammation in type 1 diabetes mellitus and LADA (latent onset autoimmune diabetes in adults) in the decade of 1980[35,36]. Given the significance of HLA class II in the development and progression of type 1 diabetes, it is conceivable that variations in genes at the HLA locus may also be important for those with type 2 diabetes. A diet high in fat increases MHC class II expression in mouse fat tissue monocytes and fat cells, as shown in research models 38

This change emerged after the diet-induced large leptin release but before leukocytes invaded adipose tissue, and even before there was cellular inflammation. Cho et al. further demonstrated that adipose tissue-specific MHC knock-out animal models on a high-fat diet improved insulin resistance and decreased blood glucose, indicating a function for MHC genes in the progression of type 2 diabetes 39].

We may infer from gene-disease research that type 2 diabetes and breast carcinoma are linked to a wide range of illnesses, including pulmonary, cerebral, cardiovascular, hepatic, congenital, and certain cancers. Following radiation for breast carcinoma, pneumonia can occur and type 2 diabetes is linked to an increase in mortality related to lung infection. [39-40] Women who have breast cancer had a higher

likelihood of acquiring lung carcinoma later on, perhaps as a result of the interaction between smoking and radiotherapy and prior T2D 41-42 About 30% of people with hepatic cirrhosis also have T2D, and elevated estrogen levels have been linked to hepatic cirrhosis, which may be a contributing factor in breast cancer [43-44]. Hyperglycaemia specifically targets the lung, which exhibits fibrosis of the lungs [45].

It is important to note that our study had several restrictions. We didn't gather any additional diabetic datasets, and the datasets we used only had a small number of samples. Additionally, we excluded gender, age, race, and other relevant factors from our analysis. Therefore, further confirmation is needed in order to fully assess the biological significance of the research's findings.

5. Conclusion

Our research identifies T2D genes with variable expression that may play a crucial role in the emergence of breast cancer. In order to comprehend how these two diseases relate to one another, we employed mRNA analysis to find similar molecular processes and biomarkers among women with type 2 diabetes and breast cancer. They might also offer fresh data on these illnesses. In order to arrive at more efficient and trustworthy therapies, potentially within a highly personalized and tailored pharmacotherapeutic framework, scientists and healthcare providers can additionally employ pharmacogenomic correlation as a vital method to determine the underlying pathophysiology and metabolomics of the particular fundamental disease.

6. Future Scope

Drug targeting the common metabolites and pathways in breast cancer and type - 2 diabetes mellitus should be developed and tested. This could open the door for new therapeutic approach for treatment of metabolic syndrome and malignancy.

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