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Serum Visfatin Levels and Tissue Visfatin Expression in Patients with Breast Diseases

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Abstract

Objective: This study aims to evaluate if serum visfatin levels and tissue visfatin expression have an importance in patients with either benign or malign breast masses.

Patients and Methods: The patients with complaints of breast masses and have diagnosis of either invasive ductal carcinoma or fibroadenoma were enrolled. Serum visfatin levels were measured by ELISA and tissue visfatin expressions were evaluated by immunhistochemistry.

Results: There were 29 patients with invasive ductal carcinoma and 14 patients with fibroadenoma. Immunhistochemical visfatin staining was positive in all patients with fibroadenoma and invasive carcinoma. When the patients with malignancy were evaluated separately, the patients with positive ER and PR were seen to have higher levels of serum visfatin than the patients with negative hormone receptors (p=0.023 and p=0.034 respectively). Serum visfatin levels were also high in patients with lymph node involvement and T2 tumors in diameter (p=0.04 and p=0.037 respectively).

Discussion: Serum visfatin levels were high in patients with positive hormone receptors, nodal involvement and T2 tumors. Visfatin staining was positive in both benign and malign diseases of the breast; it is not possible to declare visfatin as a prognostic tool in breast cancer.

Keywords: Breast; Breast cancer; Visfatin

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Introduction

Visfatin, an adipocyte hormone- also known as nicotinamide phophoribosyltransferase is a pre-B cell colony-enhancing factor. Hypoxia, inflammation and hyperglycemia upgrade; but insulin, somatostatin and statins down regulate the visfatin levels. Although it has been identified in many different tissue and organs, visceral adipose tissue preferentially expresses visfatin. It has many important well known functions in cell proliferation, biosynthesis of nicotinamide mono- and dinucleotide and hypoglycemia [1]. It has many other functions such as promoting vascular smooth muscle cell maturation and inhibiting neutrophil apoptosis. The associations between visfatin and different cancer types also have been reported [2-7]. Worldwide, breast cancer is one of the most common cancers in women. The well-known risk factors of the breast cancer are high body mass index, sedentary lifestyle, increased alcohol consumption, hormone replacement therapy for menopause, exposure to radiation, early age at menarche, and giving birth late or not at all. Few studies showing the relationship between visfatin and breast cancer have been reported up to now [8-17]. The aim of this study is to determine whether serum visfatin levels and tissue visfatin expression have an importance or not, in patients with either benign or malign breast masses.

Material and Methods

Newly diagnosed 29 patients with invasive ductal carcinoma and 14 patients with fibroadenoma were enrolled in this study. The clinicopathologic features of the patients were obtained from their oncologic charts. The staging of breast cancer was determined according to the tumor-node-metastasis (TNM) system. Visfatin (400-450) (Human) - antibody for immunohistochemistry (Phoenix Pharmaceuticals, Inc) was used for immunohistochemical staining. The detailed protocol was obtained from product description (Catalog No.: H-003-84). Finally, the slides were counterstained with hematoxylin and then examined under a light microscope by two independent pathologists. Only the cytolasmic staining in tumor cells (approximately 1,000 cells in 3–4 hpf) was

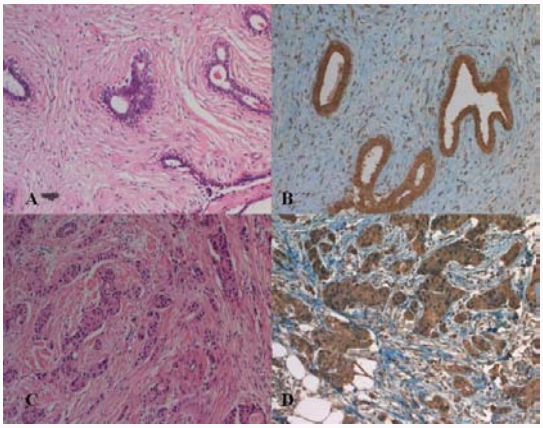

Figure 1: Immunhistochemical visfatin staining: **A:** Fibroadenom HE x 200 B: Fibroadenom Visfatin x 200, C: İnvaziv duktal karsinom HE x 200, D: İnvaziv duktal karsinom Visfatin x 200.

calculated. The results for visfatin staining were scored according to the percentage of positively stained cells in 4 quantitative categories: score 1, 25% or less positive cells; score 2, 26% to 50% positive cells; score 3, 51% to 75% positive cells; and score 4, 76% or more positive cells [9]. Blood samples for visfatin from the patients with invasive ductal carcinoma and fibroadenoma were obtained in preoperative period. Serum visfatin levels were measured using a commercial enzyme immunoassay kit (Phoenix Pharmaceuticals, Belmont, CA) according to instructions of Manufacturer Company. The study was approved by the ethics committee of Selcuk University, and informed consent was obtained from each patient. For statistical assessment; The Statistical Package for Social Sciences (SPSS for Windows version 13.0, Chicago, IL, USA) program was used. Median values were used to analyze demographic characteristics. The parametric data is given as arithmetic means ± standard deviation (SD) and non-parametric data is given as median (minimum–maximum). For comparing categorical variables Pearson chi-square test was used and comparison between groups was assessed by Student's *t* test or Mann–Whitney *U* test (parametric data, non-parametric data respectively). In the statistical evaluations, a *p* value was regarded as significant if <0.05.

Results

There were 14 patients with fibroadenoma and 29 patients with invasive ductal carcinoma. The age of the patients with fibroadenoma were ranging from 15 to 53 years with a median age of 37 years while the age of the patients with invasive ductal carcinoma ranged from 27 to 87 years with a median age of 51 years. The diameters of the tumors were between 6 mm and 135 mm (median 25 mm) in patients with fibroadenoma and 15 mm to 60 mm (median 23 mm) in patients with invasive ductal carcinoma. In patients with malignancy, 24 of 29 patients had nodal involvement and 3 had Stage IV diseases at the time of diagnosis. Estrogen receptor was positive in 24 patients, progesterone receptor was positive in 24 patients and HER2 was positive in 12 patients. Immunhistochemical visfatin staining was positive in all patients with fibroadenoma and invasive carcinoma (Figure 1). The serum visfatin levels of the patients with fibroadenoma and invasive ductal carcinoma were 24.56 ± 3.13 and 25.03 ± 3.06 ng/ml, respectively. There were no differences between the patients with malign and benign breast masses in the means of serum visfatin levels (p=0.64). In patients with invasive ductal carcinoma, when the patients with malignancy were evaluated separately, serum visfatin levels were also high in patients with T2 tumors in diameter and lymph node involvement (p=0.038 and p=0.039 respectively). The patients with positive ER and PR were seen to have higher levels of serum visfatin than the patients with negative hormon receptors (p=0.033 and p=0.033 respectively), (Table 1). Also, the serum visfatin levels of 3 patients with T3 tumor were 22.06, 25.52 and 27.72 ng/ml. Both ER and PR negative patients' serum visfatin levels (n: 3) were 24.31, 20.44 and 23.76 ng/ml. The serum visfatin level of the patient with triple negative disease was 24.59 ng/ml.

Table 1: The serum visfatin levels according to the subgroups of the patients with invasive ductal carcinoma.

	Visfatin levels (ng/ml)	P value
Body mass index		
<30 (n:16)	25.19 ± 3.02	NS
≥30 (n: 13)	24.88 ± 3.23	
Tumor size		
≤ 2 cm (n: 13)	23.75 ± 2.88	0.038
2-5 cm (n: 13)	26.45 ± 2.91	
Lymph node		
Negative (n: 5)	25.69 ± 2,94	0.03
Positive (n: 24)	22.54 ± 2,36	
Receptor status		
Estrogen receptor		
Negative (n: 5)	22.72 ± 2.07	0.033
Positive (n: 24)	25.6 ± 3.03	
Progesteron receptor		
Negative (n:5)	22.92 ± 1,83	0.032
Positive (n: 24)	25.56 ± 3.1	
HER-2 receptor		
Negative (n: 17)	25.18 ± 3.07	NS
Positive (n: 12)	24.87 ± 3.18	

NS: Not Significant

Discussion

The most common malignancy in women especially in developed countries is breast cancer, unfortunately its prevalence is increasing rapidly, and it is the leading cause of cancer related death among women. So, it becomes more and more critical to discover new prognostic parameters; therefore new therapeutic targets; to overcome this worldwide problematic disease. Epidemiologic studies have demonstrated many well-established risk factors as age, hormone-associated reproductive factors like earlier age at menarche, later age at menopause, older age at first birth, decreased parity and use of hormone replacement therapy, increased body mass index, ratio of the waist-to-hip circumference, family history of breast cancer, lesions with atypical cells in mammary gland, and high breast density on mammographic screening. The established prognostic factors for breast cancer exist including tumor size, nodal involvement, histologic grade, histologic type, and hormone receptor status besides with obesity, insulin resistance and serum adipocytokine levels. Recent studies indicate that obesity is both significant risk and prognostic factor for breast cancer with poor prognosis. Adipocytes produce adipocytokines; growth factors and cytokines; including adiponectin, leptin, resistin and visfatin. The influences of obesity and increased adiposity on the risk of breast cancer are partially explained by the changes in adipocytokines secreted from adipose tissue and from the epithelial tissue of breast tumors [18]. Visfatin regulates cell cycle, apoptosis and angiogenesis in mammalian cells [9]. There have been many studies showing the correlation between high expression of visfatin and various cancers including central nervous system, gastrointestinal and genitourinary systems [2-4]. The over expression of visfatin in human vascular smooth muscle culture and endothelial cells is positively correlated with acute oxidative stress, delayed

senescence, and increased replication in life cycle [19,20]. Visfatin is highly expressed in human breast cancer cells both *in vitro* and *in vivo* and it increases the proliferation rate and DNA synthesis of human breast cancer cells, suggesting that it may contribute to breast cancer growth and moreover it is present in mammary glands during lactation and milk [21]. Accumulating evidences suggest that visfatin has some roles in mammary epithelial cells and gland, unfortunately its probable role in breast cancer has not been understood clearly yet. Obesity is a risk and also a prognostic factor for breast cancer and the role of the visfatin on growth, apoptosis and angiogenesis were well described. In this study, we want to evaluate if serum visfatin levels and tissue visfatin expression have an importance in patients with either benign or malign breast masses. In a study with colorectal cell line HCT-116, Ghaemmaghami searched out that visfatin can affect colorectal cancer cells in an autocrine or paracrine and probably slightly in an endocrine manner. In a review by Shackelford et al. [6], the relation between increased serum visfatin levels and several types of human malignant tumors including colorectal, ovarian, endometrial, breast, gastric, prostate, thyroid, melanoma and astrocytomas were well established. Increased visfatin expression also had been noticed in malignant lymphomas. It also seems to have a role in hepatocellular carcinoma. Most studies documented increased visfatin levels between benign and malign tissue while several of them correlated visfatin expression with the changes in tumor behavior, like Long et al. [22] who had founded visfatin expression 13 folds high in gastric cancer tissue than in benign gastric tissue and concluded that higher visfatin expression is correlated with deeper tumor invasion, lymph node metastases, higher TNM stages and decreased survival rates. Interestingly in some researches they have found that visfatin expression also deals with chemotherapy resistance including doxorubicin, paclitaxel and fluorouracil [23,24]. High visfatin levels in breast cancer tissue were determined in patients with more malignant cancer behaviour as ER and PR negativity, which is indicators of poor prognosis and doubtless poor survival [11] and it, was shown to be an independent predictor of disease free and overall survival. Despite the absence of clear understanding of molecular mechanisms, the genetic studies validate visfatin as a novel oncogene with an important role in carcinogenesis [16]. These results may give chance to researchers to gain speed in improving new therapies for triple negative breast cancer by inhibiting the visfatin induced pathways and validating visfatin as a new therapeutic target.

Zhang et al. [2] indicated that their results suggest that serum visfatin level may serve as a biomarker of bladder cancer and an independent prognostic marker of non muscle invasive bladder cancer by their study in 2014. The similar correlation is also valid for gastric cancers. A study by Guo-Wen Lu [3] again in 2014, also showed that preoperative serum visfatin levels were higher in patients with gastric carcinoma than otherwise healthy persons. They suggested that visfatin levels were associated with invasion depth, lymph node metastasis, distant metastasis, peritoneal dissemination, tumor size and ultimately of course: stage. They revealed serum visfatin level as an independent predictor for overall survival and concluded that preoperative plasma visfatin level may play a role as prognostic biomarker in survival of the patients with gastric cancer. Contrarily; Skoczen et al. [5] showed that plasma visfatin concentrations were higher after stem cell transplantation in children with leukemia than before. The lower levels during complete remission before the transplantation may due to myelosuppression and immunsuppression so that the normalization of visfatin levels after recovery of stem cell transplantation is related with process of immune restoration. In our study, immunhistochemical visfatin staining was positive in all patients either with fibroadenoma or invasive carcinoma. In the patients with malignancy, the patients with positive ER and PR, assumed to have better prognosis, were determined to have higher levels of serum visfatin than the patients with negative hormone receptors. Vice versa serum visfatin levels were also high in patients with lymph node involvement and T2 tumors in diameter that indicates poor prognosis.

Conclusion

Visfatin is over expressed in several human malignancies where it is often associated with poor prognosis. Additionally some studies indicate visfatin as a novel oncogene and therapeutic target. Possibly it seems to play an important role both in carcinogenesis and treatment. However there are many poorly understood molecular mechanisms waiting to be solved. Further studies are needed to clear metabolism related carcinogenesis from the aspect of visfatin.

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