Original Article

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Adiponectin: A Predictor for Breast Cancer Survival?

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ABSTRACT

Objective: Breast cancers in women with low serum adiponectin levels have been reported to show phenotypes that are more aggressive. In 2008, we investigated the relationship between serum adiponectin levels and breast cancer in our case-controlled study involving 83 patients, in which serum adiponectin levels were measured preoperatively. In this study, we aimed to investigate the relationship between serum adiponectin levels and breast cancer-specific survival among these 83 patients.

Materials and Methods: All 83 patients with stage I-III breast cancer, whose adiponectin levels were measured preoperatively in 2008 were enrolled in this study. The patients had no history of medications influencing insulin resistance prior to collecting the blood samples. Serum adiponectin concentrations were measured after overnight fasting (≥12 hours) by drawing a venous blood sample of 30 mL from the arm. ELISA (B-Bridge Human Adiponectin ELISA kit) was used for testing.

Results: The mean adiponectin level was found to be 15,300 ng/mL. When the adiponectin levels of the patients were analyzed according to the stage of the disease, adiponectin levels tended to be significantly lower as the stage increased. The stage of the disease was an important determinant for both Diseas Free Survival (DFS) (p=0.003) and Overall Survival (OS) (p=0.005). A significant relationship between adiponectin levels and OS was also observed (p=0.025), and levels of adiponectin above the mean value of 15,300 ng/mL were associated with improved DFS (p=0.001).

Conclusion: Preoperative adiponectin levels may be useful to predict survival rates in breast cancer or may be used as a marker/predictor for defining patients who require more aggressive treatment. In order for adiponectin to be used as a practical clinical marker for breast cancer, large database studies are should be conducted.

Keywords: Adiponectin, breast cancer, survival

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Introduction

Adipose tissue serves as the energy storage of the body. However, it is understood that adipose tissue is also an important endocrine organ and secretes many different biological molecules. Adiponectin, leptin, C-reactive protein, tumor necrosis factor-alpha (TNF-alpha), and interleukin-6 (IL-6) are the main adipokines produced by adipocytes. The primary role of adipokines is to regulate energy storage and consumption. Since adipocytes are the natural components of the breast tissue, it has been postulated that signaling proteins released from breast adipocytes may have a potential relationship with breast cancer development (1). The most popular of these molecules is adiponectin, which epidemiological studies have shown that its reduced levels are associated with increased breast cancer risk (2). Adiponectin is a 257-aminoacid polypeptide hormone coded by a gene on chromosome 3q27. Adiponectin's relation with breast cancer is thought to be through alterations in insulin sensitivity and immunological pathways (3). It is also considered that low serum adiponectin levels might be associated with colorectal cancers, gastric cancer, kidney, and prostate cancer, which are also associated with insulin resistance and obesity (4, 5).

Breast cancers in women with low serum adiponectin levelshave been reported to show phenotypes that are more aggressive (6). There are only a few studies probing the relationship between serum adiponectin levels and breast cancer related survival in the English literature. In 2008, we investigated the relationship between serum adiponectin levels and breast cancer in our case-controlled study involving 83 patients, in which serum adiponectin levels were measured preoperatively (7). In this study, we aimed to investigate the relationship between serum adiponectin levels and breast cancer-specific survival among these 83 patients.

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Table 1. Patients' characteristics according to mean adiponectin level

		Adiponectin levels (ng/mL)		p
		<15.300	≥15.300	
Age	<50	26 (31.3%)	15 (18%)	0.08
	≥50	28 (33.7%)	14 (16.8%)	
Tumor grade	I	6 (7.2%)	7 (8.4%)	0.1
	II	30 (36.1%)	16 (19.2%)	
	III	18 (21.6%)	6 (7.2%)	
BMI	<25	20 (24%)	11 (13.2%)	0.4
	≥25	34 (40.9%)	18 (21.6%)	
Menopause status	premenopausal	25 (30.1%)	16 (19.2%)	0.3
	postmenopausal	29 (34.9%)	13 (15.6%)	
ER	negative	11 (13.2%)	6(7.2%)	0.8
	positive	43 (51.8%)	23 (27.7%)	
PR	negative	29 (34.9%)	10 (12%)	0.6
	positive	25 (30.1%)	19 (22.8%)	
Her-2	negative	31 (37.3%)	20 (24%)	0.8
	positive	23 (27.7%)	9 (10.8%)	

BMI: body mass index; ER: estrogen receptor; PR: progesterone receptor

Table 2. Mean adiponectin levels with respect to the stage and survival

Stage	Serum adiponectin level (ng/mL)	5-year DFS	5-years OS	p
I	33.454±29.467	86%	100%	
II	12.256±6.542	72.6%	78.1%	p<0.001
III	3.065±2.166	46%	65.2%	

Material and Methods

All 83 patients with stage I-III breast cancer, whose adiponectin levels were measured preoperatively in 2008 were enrolled in this study.

Diabetes mellitus, cachexia, liver impairment, renal dysfunction and cardiovascular disease were defined as exclusion criteria. The patients had no history of medications influencing insulin resistance prior to collecting the blood samples. Serum adiponectin concentrations were measured after overnight fasting (≥12 hours) by drawing a venous blood sample of 30 mL from the arm. ELISA (B-Bridge Human Adiponectin ELISA kit) was used for testing. Blood samples from the patients were obtained preoperatively. Menopausal status, tumor stage and estrogen and progesterone receptor (ER-PR) status were also recorded.

Patients were followed up by medical oncologists and surgical oncologist postoperatively. Routine follow-ups were planned as follows: every 3 months for the first year, every 6 months for the next 3 years and annually thereafter. Physical examinations, annual mammograms (contralateral breast and diseased breast if breast-conserving surgery was performed) and carcinoembryonic antigen (CEA) and CA 15.3 measurements were the mainstays of the control visits, with additional workup when necessary.

No further institutional review board approval was needed apart from the approval that was granted in 2008. This study was performed in compliance with the Declaration of Helsinki. For this type of study, formal patient consent is not required.

Statistical analysis were performed using Statistical Package for the Social Sciences (SPSS) for Windows version 17.0 (SPSS Inc., Chicago, IL, USA). Kaplan Meier's test was used to investigate stage/survival relationship and Cox regression analysis was used to investigate the association between adiponectin levels and survival. A p value of ≤0.05 was sought for significance.

Results

The mean follow-up period was 80.7 months (18-136). The mean age of 83 patients included in the study was 51.9±12.5 (28-78). Forty-nine percent of the patients were premenopausal and 51% were postmenopausal. In terms of tumor characteristics; 15.7% grade 1, 53% grade 2 and 28.9% grade 3 tumors were encountered. The rate of ER (+) tumor was 80.7% and the rate of PR (+) tumor was 53%. Preoperative adiponectin levels did not differ according to menopausal or hormone receptor status. Of 83 patients; 26.5% was stage I, 44.6% was stage II and 28.9% was stage III according to the American Joint

Committee on Cancer Staging system. DFS and OS rates for stage I, II, and III were calculated as 86%, 72.6%, 46% and 100%, 78.1%, 65.2% respectively. The mean adiponectin level was found to be 15,300 ng/ml. Patient characteristics are given in Table 1. When the adiponectin levels of the patients were analyzed according to the stage of the disease, adiponectin levels tended to be significantly lower as the stage increased (Table 2). The stage of the disease was an important determinant for both DFS (p=0.003) and OS (p=0.005). A significant relationship between adiponectin levels and OS was also observed (p=0.025), and levels of adiponectin above the mean value of 15.300 ng/mL was associated with improved DFS (p=0.001) (Figures 1, 2). Cox regression results are shown in Figures 3 and 4.

Discussion and Conclusion

The relation between low serum adiponectin levels and risk of breast cancer has been well documented in epidemiologic studies. This association is thought to occur through obesity, hyperinsulinemia and insulin resistance (8). As adiponectin levels decrease, insulin resistance increases in peripheral tissue and as a result, circulating insulin levels increase. As a matter of fact, hyperinsulinemia and insulin resistance have been suggested to be factors that increase the risk of breast cancer (9, 10). Insulin activates signaling pathways necessary for cell growth by binding to cell membrane receptors (11). This activation is true for both breast cancer and normal cells. The greater the amount of adipose tissue, the lower the levels of adiponectin, because the increase in the amount of adipose tissue leads to a decrease in serum adiponectin levels (12). This explains the inverse relationship of adiponectin levels with body mass index. Alterations in the levels of estrogen are at the basis of the relationship between obesity and breast cancer. In the premenopausal period, the main source of estrogen is ovaries, thus estrogen plasma levels are not directly affected by the amount of adipose tissue. Besides, it is known that plasma estrogen levels are lower in premenopausal obese women. During the postmenopausal period, adrenal androgens transform into estrogen by peripheral aromatization in obese patients.

If obesity and related low adiponectin levels were only to be related to breast cancer because of increased estrogen levels, this effect should be limited to postmenopausal women with ER (+) tumors. In our study from Turkey and Kawai et al. (13) studies, however, decreased adi-

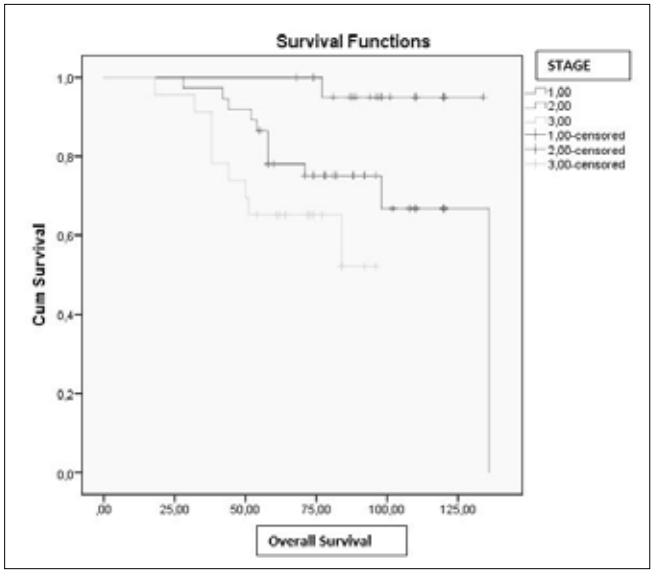

Figure 1. Kaplan-Meier curve for stage vs disease free survival

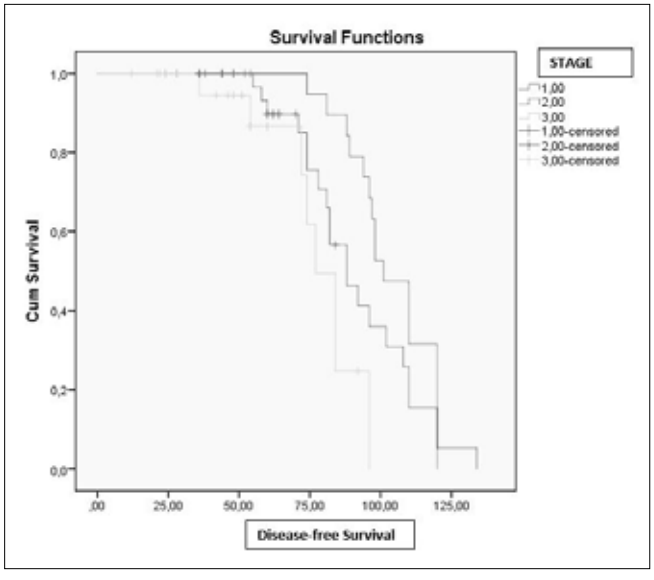

Figure 2. Kaplan-Meier curve for stage vs overall survival

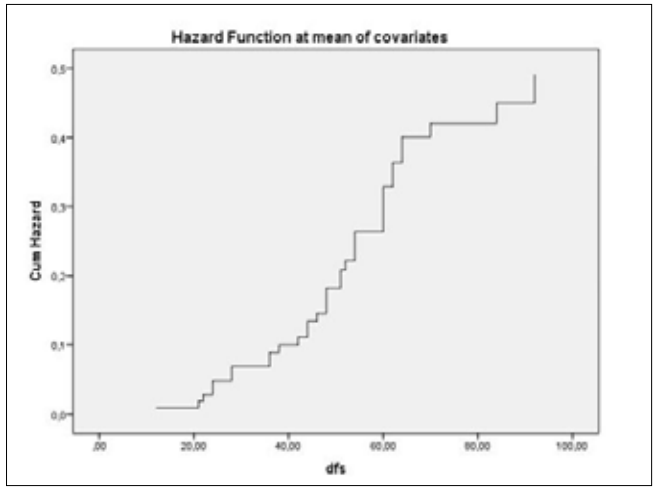

Figure 3. Cox regression model for adiponectin levels and disease-free survival

DFS: disease free survival

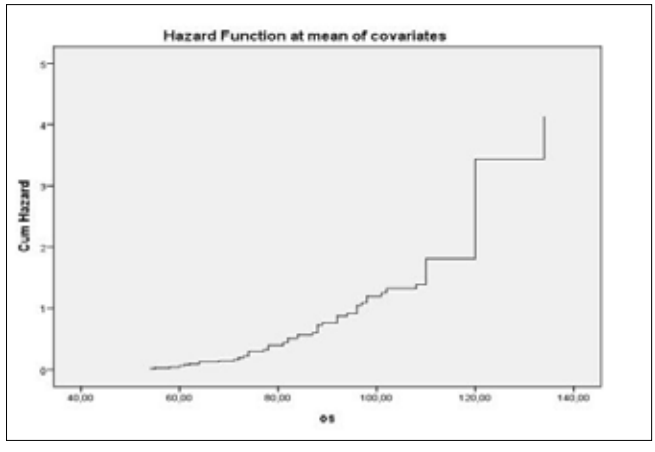

Figure 4. Cox regression model for adiponectin levels and overall survival

OS: overall survival

ponectin levels were associated with breast cancer for both premenopausal and postmenopausal women (7). It should be noted that these 2 studies reflect the Asian-Pacific population and Western studies have failed to show the same relation in premenopausal women (14, 15). Similar to our study, other studies have also shown that adiponectin levels and breast cancer association is independent from the receptor status of the tumor (6, 16).

It can be postulated that adiponectin has a protective effect against tumorigenesis through intracellular mechanisms initiated via its receptors. Adiponectin is present in the blood stream in three different forms, of which high molecular weight (HMW) is the active form (17). After AdipoR1 and AdipoR2, T-cadherin was the third adiponectin receptor described. AdipoR1 and AdipoR2 are primarily expressed in the muscle and liver tissue; however, T-cadherin is expressed in the vascular tissue. It was suggested that depleted expression of adiponectin receptors in the colonic tissue is associated with colorectal tumor progression (18). In vitro and animal model studies have proved that adiponectin interacts also with estrogen receptors (19). Grossman et al. (20), have also shown that adiponectin directly interacts with breast cancer cells in vitro. Experimental studies investigating the protective effect of adiponectin against tumorigenesis, have shown that adiponectin reduces caspase-mediated endothelial cell proliferation and induces cell death. Adiponectin also inhibits Nuclear Factor NF-κB activation, which is a key pathway in breast cancer development (21). Genetic studies have demonstrated that single nucleotide polymorphism (SNP) in adiponectin gene located on 3q27 eliminates this protective effect (22). In an animal study by Lam et al. (23), reduced adiponectin levels have been shown to contribute to tumorigenesis through down-regulation of PTEN activity.Another protective mechanism against breast cancer is thought to be adiponectin's oxidative stress-reducingeffect. Increased oxidative stress induces mitosis, apoptosis, angiogenesis and cellular migration (24). In his study, Karimi showed indirectly that increased adiponectin levels are associated with decreased oxidative stress by measuring oxidative stress markers (25). Kim et al. (26), also speculated that increased adiponectin levels can limit cancer cell proliferation via AMP-activated protein kinase (AMPK).

Leptin and resistin are two other adipokines that are thought to be related to breast cancer. It has shown that leptin promotes the estrogen dependent cell proliferation and induces aromatase enzyme activity (27). In contrast to adiponectin,there is no sign that leptin has any effect on cellular function modulation, but increased levels of leptin are associated with breast cancer. It is also speculated that leptin and resistin may play as a growth factor in breast cancer cellular proliferation pathway (28). However, no relationship between leptin levels and breast cancer specific survival could be shown (29).

The largest study on serum adiponectin levels in breast cancer patients is reported from South Korea. Three hundred and seventy patients were enrolled in this study with a mean follow up period of 4.2 years. Patients having higher levels of serum adiponectin levels before the treatment is initiated are found to have longer DFS but similar OS. Serum leptin levels were also investigated in this study but no association between survival is found (30).

As a conclusion, the relationship between adiponectin and breast cancer is likely to be based on many different mechanisms. Since this relationship varies between Western and Asian-Pacific communities, survival studies should be conducted among different societies and ethnic groups. A study from the United States involving 527 patients has shown that patients with high adiponectin levels have a reduced mortality rate by 61% (HR, 0.39; 95% CI 0.16-0.95) (31).However, blood samples from the patients were obtained 24 months after the treatment has been completed. Therefore, the design of the study was different. Like Miyoshi et al. (6) study from Japan, our study also showed that as the stage of the disease increases, mean serum adiponectin levels decreases. In this case-control series lower serum adiponectin levels were related to increased tumor size and higher tumor grade.

Our initial findings indicated an indirect relationship between serum adiponectin levels and DFS and Osmic was shown through the stage of the disease. Thus, we searched for a more direct association by using quantitative levels of adiponectin in our recent retrospective observational study, which proved that adiponectin levels are directly proportional to OS and DFS in breast cancer. Preoperative adiponectin levels may be useful to predict survival rates in breast cancer or may be used as a marker/predictor for defining patients who require more aggressive treatment. To the best of our knowledge, this is the first study in English literature looking for an association between preoperative adiponectin levels and overall survival.

There are some drawbacks of our study. Firstly, it's unclear that which form of adiponectin molecule was measured. Since only preoperative adiponectin levels were measured, subsequent serum levels are not known. Physical activity status and weight changes of the patients were not investigated. In order for adiponectin to be used as a practical clinical marker for breast cancer, large database studies are should be conducted.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects" (amended in October 2013).

Informed Consent: N/A

Peer-review: Externally peer-reviewed.

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