RESEARCH ARTICLE

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Investigation of Serum Seladin-1/DHCR24 Levels in Breast Cancer Patients

ABSTRACT

Objective: Seladin-1, an enzyme that catalyzes the cholesterol formation reaction from desmosterol, has been shown to be expressed at different levels in various types of tumor. The purpose of this study was to investigate the relationship between serum seladin-1 levels and clinical characteristics of patients with non-metastatic breast cancer, and to examine the prognostic value of seladin-1 in breast cancer.

Methods: Patients aged 18 and over diagnosed with breast cancer using histopathological methods at our medical oncology clinic, whose tumor tissue had been surgically removed and who had not yet received any oncological treatment, and with no distant organ metastasis or additional malignancy, and healthy women volunteers as a control group were included in the study. Demographic and laboratory data were recorded. Serum seladin-1 levels were compared between the patient and control groups.

Results: Seventy-three women, 46 patients and 27 controls, were enrolled. Mean ages were 56±12 years in the patient group and 62±12 in the control group (p=0.055) Seladin-1 levels were lower in the patient group than in the control group (p=0.038). No statistically significant relationship was observed between tumor size and seladin-1 levels (p=0.138). No relationship was also determined between patient grades and stages and seladin-1 (p=0.720; p=0.092, respectively).

Conclusions: Seladin-1 levels were lower in the serum of breast cancer patients than in the control group. However, no statistically significant relationship was found between breast cancer prognostic factors and seladin-1 levels. Further research is needed to clarify the mechanisms underlying the low seladin-1 levels in breast cancer patients.

Keywords: Breast Cancer, Seladin-1, DHCR24, Prognostic Value

Meme Kanserli Hastalarda Serum Seladin-1/DHCR24 Düzeyinin Araştırılması

ÖZET

Amaç: Meme kanseri kadınlarda önemli bir morbidite ve mortalite nedenidir. Desmosterolden kolesterol oluşum reaksiyonunu katalizleyen enzim olan Seladin-1 daha önce çeşitli tümör türlerinde farklı düzeylerde exprese edildiği gözlenmiştir. Çalışmamızda; serum seladin-1 düzeyleri ile metastatik olmayan meme kanseri hastalarının klinik özellikleri arasındaki ilişkiyi ve seladin-1'in meme kanserinde prognostik değerini araştırmayı amaçladık.

Gereç ve Yöntem: Tıbbi onkoloji kliniğimizde, 18 yaş üstü, histopatolojik olarak meme kanseri tanısı almış, cerrahi olarak tümör dokusu çıkarılmış, herhangi bir onkolojik tedavi henüz almamış, uzak organ metastazı ve ek malignitesi olmayan hastalar ile kontrol grubu olarak sağlıklı kadın gönüller çalışmaya dahil edildi. Demografik veriler ve laboratuvar verileri kaydedildi. Serum seladin-1 düzeyleri hasta ve kontrol grupları arasında karşılaştırıldı.

Bulgular: 46 hasta ve 27 kontrol grubu olmak üzere toplam 73 kadın hasta çalışmaya dahil edildi. Hasta grubunun yaş ortalaması 56±12 yıl, kontrol grubunun 62±12 yıldı (p=0.055) Seladin-1 düzeyleri gruplar arasında karşılaştırıldığında; hasta grubunda kontrol grubuna göre daha düşük seviyede saptandı (p=0.038). Tümör boyutları ile Seladin-1 düzeyi arasında istatistiksel bir ilişki yoktu. (p=0.138). Bunun yanında, hastaların stage ve gradelerine göre seladin-1 düzeyi karşılaştırıldığında istatistiksel fark olmadığı görüldü (p=0,720; p=0,092, sırasıyla).

Sonuç: Çalışmamızda meme kanseri hastalarının serumlarında seladin-1 düzeyi kontrol grubuna göre daha düşük saptandı. Ne var ki, meme kanserinin prognostik faktörleri ile seladin-1 düzeylerinin ilişkili olmadığı görülmüştür. Seladin-1'in meme kanserli hastalarında düşük olmasının altında yatan mekanizmaların aydınlatılabilmesi için daha ileri araştırmalar gerekmektedir.

Anahtar Kelimeler: Meme Kanseri, Seladin-1, DHCR24, Prognostic Değer

INTRODUCTION

Breast cancer is the most frequent cancer and the second major cause of cancer-related deaths in women (1, 2). The global prevalence of breast cancer is also increasing. However, despite this increase, survival rates have improved continually in recent years thanks to intensive research and new therapeutic modalities (3, 4). However, survival rates and quality of life can also decrease significantly once failure in treatment occurs. Finding a reliable prognostic factor capable of improving survival is therefore of great importance.

Selective Alzheimer Disease Indicator-1 (Seladin-1), also known as DHCR24 for 24-dehydrocholesterol reductase, is an enzyme that catalyzes cholesterol formation from desmosterol (5), The name derives from its being less expressed in brain specimens from Alzheimer's patients compared to healthy individuals (6). It has also been found to prevent neuron degeneration in the brain with its anti-apoptotic functions (7). Seladin-1 is a multifunctional protein expressed by the DHCR24 gene. It is associated with oxidative stress, cell proliferation, anti-apoptotic, and anti-inflammatory effects (8). Seladin-1 acts by inhibiting activation of caspase 3, an important apoptosis modulator (9). DHCR24 was determined to be associated with cell differentiation and senescence in a study of DHCR24 gene knockout mice (10) However, the cytoprotective mechanisms of seladin-1 have not been fully explained. For example, the response to acute and chronic oxidative stress differs. In acute oxidative stress seladin-1 expression is up-regulated by increasing intracellular cholesterol synthesis, while in chronic oxidative stress it is down-regulated (11). Due to the cytoprotective effect of seladin-1, its role in various cancers has also been investigated, including melanoma, adrenal cancer, bladder cancer, pituitary tumors, prostate cancer, and endometrium cancer (12-17). However, seladin-1 has been observed to be expressed at different levels in these cancer types compared to normal tissues.

The aim of this study was to investigate the prognostic value of serum seladin-1 by analyzing its levels and the clinical features of patients with non-metastatic breast cancer.

MATERIAL AND METHODS

Participants: Forty-six patients aged 18 and over diagnosed with breast cancer using histopathological methods at the Duzce University Medical Faculty Medical Oncology Clinic, whose tumor tissue had been surgically removed and who had not yet received any oncological treatment, and with no distant organ metastasis or additional malignancy, and 27 healthy women were included in the study.

Individuals aged under 18, pregnant women, and individuals with additional malignancy, distant organ metastasis, and acute or chronic infection were excluded. Informed consent forms were obtained from all participants. Demographic data and laboratory parameters of both groups were analyzed.

Sample Collection and Biochemical Analysis: Blood samples were collected following 12-14 h fasting. Serum was separated by centrifugation for 10 min at 4000 rpm. Routine parameters were investigated using photometric methods at the Biochemistry Laboratory Research Hospital with the help of an IDS B0728 auto Seladin-1 levels were determined using a commercially available ELISA kit (ABIN1129410, Biocompare, Georgia) with spectrophotometric methods. Concentrations of seladin-1 in samples were determined by comparison of ODs against a standard curve at 250 nm**.**

Statistical Analysis: Statistical analyses were performed on SPSS (Statistical Package for Social Sciences) for Windows 22 software. The Kolmogorov–Smirnov test was employed to assess the distribution of variables. Results were expressed as mean ± standard deviation and median (min-max). P data were compared using the independent-samples t-test in case of parametric parameters, or using the Mann-Whitney U test for non-parametric parameters. The chi-square or Fisher exact tests were applied for the comparison of qualitative data. $p<0.05$ was regarded as statistically significant.

Ethics: This study was performed in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants before enrolment. The study protocols and consent forms were approved by the ethics committee of the Duzce University Medical Faculty (approval number: 2019/136).

RESULTS

Seventy-three women, 46 patients and 27 controls were included in this study. The mean ages were 56±12 years in the patient group and 62±12 in the control group (p=0.055). Body mass index values were 30.60±5.49 kg/m^2 in the patient group and 29.43±4.23 kg/m^2 in the control group (p=0.374). No statistically significant difference was determined in lipid parameters between the groups (p>0.05). Seladin-1 levels were lower in the patient group than in the control group (0.28461±0.10181 ng/ml vs 0.40530±0.15130 ng/ml respectively, p=0.038). Basic characteristics and laboratory parameters of the patient and control groups are summarized in Table 1.

Table 1. A comparıson of patıent and control group parameters

Parameters	Patients n=46	Controls n=27	*P*
Age (year), mean±SD	56±12	62±12	.055
Comorbids (n)			
Diabetes Mellitus	12	3	.353
Hypertension	18	12	.299
Hyperlipidemia	4	1	.323
Weight (kg)	75.98±12.92	72.43±14.23	.423
BMI kg/m^2	30.60±5.49	29.43±4.23	.374
Waist circumference (cm)	98.07±14.64	95±12.3	.612
Glucose (mg/dl)	112.97±42.01	120.80±59.98	.563
HOMA-IR (mg/kg^2)	4.6±2.1	4.1±1.5	.683
Total cholesterol (mg/dl)	212.06±38.54	214.40±31.31	.907
LDL (mg/dl)	132.83±34.18	118.31±14.27	.355
Trygliseride (mg/dl)	163.70±96.44	162.14±80.61	.973
ALT (U/L) Median (min-max)	15.82(5.40-79.10)	16.77(7.45-38.51)	.494
Urea (mg/dl)	29.78±9.07	33.82±9.42	.119
Creatinin (mg/dl)	0.68±0.15	0.67±0.13	.812
WBC (mm^{3}x10^3)	6.09±1.92	7.33±2.98	.051
ESR (mm)	30.20±17.92	24.61±16.49	.415
Seladin-1 (ng/ml)	0.28461±0.10181	0.40530±0.15130	.038*

*p<0,05; BMI: Body Mass Index, HOMA-IR: Homeostatic Model Assessment of Insulin Resistance, LDL: Low-density lipoprotein, ALT: Alanine transaminase WBC:White Blood Cell ESR: erythrocyte sedimentation rate

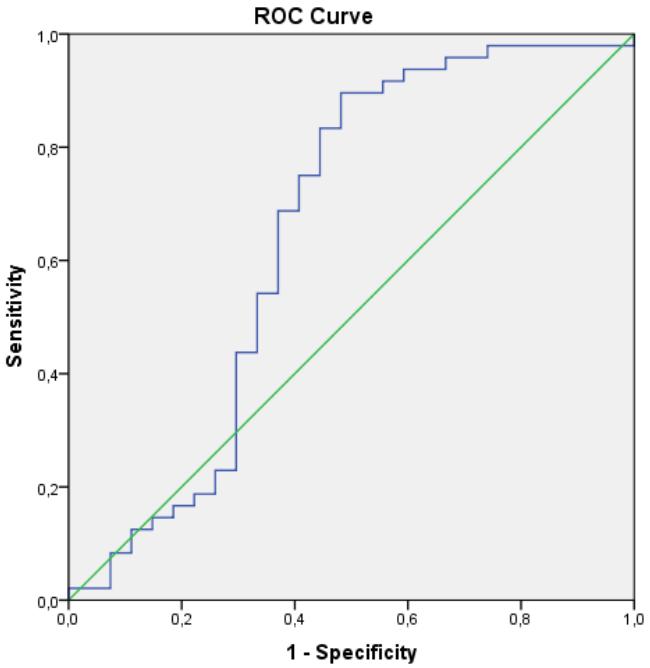
A family history of breast cancer was present in 20 patients (43.5%), but not in 26 (54.3%) (p=0.698). There was no statistically significant association between tumor size and seladin-1 levels (p=0.138). In addition, no statistically significant difference was observed when seladin-1 levels were compared in terms of patients' grades and stages (p=0.720 and p=0.092, respectively). A comparison of patients' seladin-1 levels and clinicopathological characteristics is summarized in Table 2.

Table 2. Relations between patients' clinicopathological factors and seladin-1

Charecteristic	n (%)	Serum Seladin-1 level. median (min-max)	*P*
Age			
≤45 y	10 (21.7)	0.2507 (0.1164-0.3309)	.456
>45 y	36 (78.3)	0.2430 (0.1977-1.6006)	
Family History			
Positive	20 (43.5)	0.2451 (0.1977-1.6006)	.698
Negative	26 (54.3)	0.2437 (0.1164-0.4961)	
Tumor size			
T1	21 (45.7)	0.2373 (0.1977-0.2978)	
T2	22 (47.8)	0.2455 (0.1164-1.6006)	.138
T3	3 (6.5)	0.3046 (0.2391-0.3654)	
Metastatic LAP			
Positive	12 (26)	0.2438 (0.2217-0.3654)	1.000
Negative	34 (74)	0.2472 (0.1977-1.6006)	
Stage			
I	15 (32.6)	0.2381 (0.1977-0.2978)	
II	15 (32.6)	0.2437 (0.1986-1.6006)	.720
III	16 (34.8)	0.2455 (0.1164-0.3654)	
Grade			
I	3 (7.7)	0.2250 (0.2225-0.2824)	.092
II	27(69.2)	0.2431 (0.1977-0.3309)	
III	9 (23.1)	0.2629 (0.1986-0.4961)	
ER			
Positive	39 (84.8)	0.2439 (0.1164-1.6006)	.771
Negative	7 (15.2)	0.2431 (0.1986-0.4961)	
PR			
Positive	38 (82.6)	0.2443 (0.1160-1.6006)	.908
Negative	8 (17.4)	0.2357 (0.1986-0.4961)	
CERBB2			
Positive	18 (39.1)	0.2434 (0.1164-0.4961)	.770
Negative	28 (60.9)	0.2443 (0.2102-1.6006)	
Ki-67			
<14%	14 (32.6)	0.2438 (0.2102-0.3135)	.876
≥14%	29 (67.4)	0.2431 (0.1164-0.4961)	
LVI			
Positive	24 53.3	0.2443 (0.1977-0.3654)	.802
Negative	21 46.7	0.2431 (0.1164-1.6006)	
PNI			
Positive	12 (26.1)	0.2530 (0.1164-0.3654)	.230
Negative	34 (73.9)	0.2430 (0.2211-1.6006)	

ER=estrogen receptor . PR=progesterone receptor

The area under the curve (AUC: 0.651) for seladin-1 was analyzed in all groups to confirm whether seladin-1 serum level may be a reliable predictor of breast cancer. The cut-off point identified for seladin-1 was 0.2735 ng/mL, and this exhibited 75% sensitivity, 59.2% specificity, a 76.5% positive predictive value (PPV), and a 57.1% negative predictive value (NPV) at receiver operator characteristic (ROC) analyses (p=0.031). The results are shown in Figure 1.



AUC	Cut-off	Sensitivity	Spesivity	PPV	NPV	*P*
0.651	0.2735	75%	59.2%	76.5%	57.1%	.031*

*p<0.05 **p<0.001

Figure 1. ROC analysis of seladin-1 levels between the patient and control groups

DISCUSSION

Our findings revealed lower serum seladin-1 in breast cancer patients than in the control group. Nonetheless, prognosis did not vary in line with serum seladin-1 levels. The present research is the first study to investigate seladin-1 in patient serum.

DHCR24, an enzyme that catalyzes cholesterol formation from desmosterol, was given the name seladin-1 due to its being downregulated from the brains of Alzheimer's patients and to its neuroprotective characteristics (18). Seladin-1 expressed at high levels from brain cells has also been shown to exhibit a protective role against oxidative stress-related neuron apoptosis (9, 14, 19). Seladin-1 is expressed at varying levels from different tissues and tumors (20, 21). It also contributes significantly to cell survival and death regulation (22).

The role of seladin-1 in various types of cancer has also previously been investigated. In one such study, Wu et al. determined a high level of upregulation of endogenous seladin-1 levels in oxidative stress (23). One noteworthy finding in that study was that seladin-1 is also associated with the tumor suppressor gene p53. Seladin-1 binds to the p53 amino terminal following exposure to oncogenic and oxidative stress, and displaces E3 ubiquitin ligase Mdm2 from p53, thus leading to p53 accumulation. Additionally, in the light of these data, seladin-1 was shown to prevent senescence Ras/p53-mediated oncogenic signaling supporting the tumor suppression role of p53 (23).

A defect in seladin-1 converted into cholesterol from desmosterol can result in impairment of the lipid cell membrane, free radical activation, and thus cell death (24, 25). One striking piece of evidence for this is 'desmosterolosis syndrome,' a rare autosomal recessive entity characterized by desmosterol accumulation in the body and progressing with severe multiple congenital anomalies developing due to seladin-1 gene mutation. Lipid profiles in this study were similar between the patient and control groups since we anticipated that these might affect seladin-1 levels.

Serum seladin-1 levels were lower in the patient group in the present study. Luciani et al. compared seladin-1 levels in adrenal carcinoma, adrenal adenoma, and normal adrenal gland groups and observed lower seladin-1 levels in the adrenal carcinoma group than in the other groups (26). In another study involving adrenal carcinoma, Simi et al. also reported significantly lower seladin-1 mRNA expression in adrenal carcinomas compared to normal adrenal glands (27). Battista et al.

investigated the relationship between prostate cancer and seladin-1 and reported that seladin-1 expression increased in low-risk prostate cancer while decreasing in advanced prostate cancer (28). They attributed this to seladin-1 expression increasing in order to inhibit cell proliferation as the first stages of cancer develop (low-grade, Gleason grade 3), with this increase probably being in order to slow the progression of the cancer. However, seladin-1 is no able to longer interfere with the progression of high grade (Gleason grade 4 and 5) cancer, with seladin-1 expression being though to decrease as other factors leading to progression of the cancer assume control. This is also supported by Kuehnle et al.'s study of the response of seladin-1 to acute and chronic oxidative stress. Those authors determined that seladin-1 is up-regulated in acute stress, but gives a downregulated response in long-term oxidative stress (10). In that context, the cytoprotective effect of seladin-1 was explained in terms of intracellular cholesterol concentrations increasing by raising seladin-1 levels in exposure to acute oxidative stress (11). In agreement with the previous literature, seladin-1 levels were significantly lower in the patients with breast cancer than in the control group in the present study. However, in contrast to Battista et al.(28) we observed no statistically significant relation between disease prognosis parameters (tumor size, grade, stage, lymph node metastasis, etc.) and seladin-1 levels.

There are several limitations to the present study. Our patient number was low. It would also have been useful to have examined response seladin-1 levels following administration of oncological therapy. In addition, had long-term follow-up been performed an association might have been shown between prognosis and seladin levels depending on whether patients were metastatic or not. However, our patients consisted of newly diagnosed and not yet treated non-metastatic individuals. In addition, seladin levels being lower in the patient group compared to the control group despite the surgical removal of the tumor burden, may also be important in terms of monitoring the benefit of adjuvant oncological therapies.

CONCLUSION

To the best of our knowledge, this is the first study to investigate seladin-1 levels in human serum using ELISA. Selain-1 levels were lower in serum from breast cancer patients compared to the control group, but no association was observed between seladin-1 levels and cancer progression. There is a strong link between seladin-1 and cancer, but this association depends on the type and course of the cancer. Further research is therefore needed to clarify the underlying mechanism involved in the lower serum seladin-1 levels observed in breast cancer patients.

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