Original Article
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Serum Endocan Level and Its Correlation with Clinicopathologic Features in Patients with Papillary Thyroid Cancer

Papiller Tiroid Kanseri Hastalarında Serum Endokan Düzeyi ve Klinikopatolojik Özellikler ile İlişkisi

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Abstract

Objective: Endocan, also known as endothelial cell specific molecule-1, is a vascular endothelium-derived factor and plays a key role in angiogenesis. The aim of this study is to assess serum endocan level in papillary thyroid cancer (PTC) patients which has not been investigated before. **Material and Methods:** This study included 48 patients with PTC who underwent total thyroidectomy between November 2018 and May 2019. As the control group, 40 age- and sex-matched cases with benign thyroid nodules were included. Serum samples were obtained from the patients before surgery. Serum endocan levels of the patients and controls were measured and the results were compared. The relationship between endocan levels and clinicopathological factors was investigated. Cases with benign thyroid nodules were included as the control group. **Results:** PTC patients had higher mean serum endocan level than control subjects (45.1±9.6 vs. 37.7±8.3 pg/mL, p<0.001). In PTC patients, there was no relationship between serum endocan levels and histopathologic variant, lymphatic or vascular invasion, surrounding thyroid tissue invasion, lymph node metastasis, surgical margin status, tumor-node-metastasis stage and American Thyroid Association risk stratification group, age and tumor size. **Conclusion:** This study suggests that, if supported by more comprehensive studies with a sufficiently large sample size in the future, serum endocan level may be used as an adjunctive test in the diagnosis of PTC in patients with thyroid nodules.

Keywords: Angiogenesis; endocan; papillary thyroid cancer; endothelial-cell-specific molecule-1

Özet

Amaç: Endotelyal hücre-spesifik molekül-1 olarak da bilinen endokan, vasküler endotel kaynaklı bir faktördür ve anjiyogenezde kilit rol oynar. Bu çalışmanın amacı, daha önce araştırılmamış olan papiller tiroid kanserli (PTK) hastalarda serum endokan düzeyini değerlendirmektir. **Gereç ve Yöntemler:** Çalışmaya, Kasım 2018 ile Mayıs 2019 tarihleri arasında total tiroidektomi uygulanan 48 PTK hastası dâhil edildi. Kontrol grubu olarak ise benign tiroid nodülü olan yaş ve cinsiyet uyumlu 40 olgu dâhil edildi. Hastalardan cerrahi öncesi serum örnekleri alındı. Hasta ve kontrollerin serum endokan düzeyleri ölçüldü ve sonuçlar karşılaştırıldı. Endokan düzeyleri ile klinikopatolojik faktörler arasındaki ilişki araştırıldı. Benign tiroid nodülü olan olgular kontrol grubu olarak alındı. **Bulgular:** PTK hastaları, kontrollerden daha yüksek ortalama serum endokan düzeyine sahipti (45,1±9,6 ve 37,7±8,3 pg/mL, p<0,001). PTK hastalarında serum endokan düzeyleri ile histopatolojik varyant, lenfatik veya vasküler invazyon, çevre tiroid dokusu invazyonu, lenf nodu metastazı, cerrahi sınır durumu, tümör lenf nodu metastaz evresi ve Amerikan Tiroid Birliği risk sınıflama grubu, yaş ve tümör boyutu arasında ilişki yoktu. **Sonuç:** Bu çalışma, gelecekte yeterince geniş örneklemli daha kapsamlı çalışmalarla desteklenirse, tiroid nodüllü hastalarda serum endokan düzeyinin PTK tanısında yardımcı bir test olarak kullanılabileceğini düşündürtmektedir.

Anahtar kelimeler: Anjiyogenez; endokan; papiller tiroid kanseri; endotelyal hücre-spesifik molekül-1

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Introduction

Papillary thyroid cancer (PTC), the most common histologic type of thyroid cancer, originates from thyroid follicular epithelial cells and is usually diagnosed by biopsy from a thyroid nodule detected by physical examination or neck imaging. The incidence of PTC increased dramatically from 4.8 to 14.9 per 100.000 people from 1975 to 2012 (1). In recent years, the incidence of thyroid cancer has increased more rapidly than other malignancies (2). This remarkable increase in the incidence of thyroid cancer is due to the widespread use of neck ultrasonography, fine needle aspiration biopsy (FNAB) of very small nodules and detection of small thyroid cancers (3-5). PTC is 2-4 times more common in women compared to men. The radiation exposure of the thyroid gland in childhood is the clearest known environmental factor leading to benign and malignant thyroid tumors (6). Thyroid cancer has a slow progression and good prognosis and is often treatable, but may show recurrence and metastasis. Age, sex, histopathologic variants of PTC, lymphatic or vascular invasion, lymph node involvement are among the factors affecting the occurrence of metastasis. Most patients achieve successful results with standard treatment such as radioactive iodine treatment or follow-up after surgery (7).

Endothelial cell specific molecule 1, also known as endocan, was first detected in endothelial cell cultures in 1996 (8). Endocan is produced in epithelial cells of the distal tubules of the kidney, cells lining the vascular endothelium, submucosal glands of bronchus and lungs (9). Vascular endothelial growth factor A (VEGF-A) and VEGF-C are growth factors with critical roles in angiogenesis, lymphangiogenesis and cancer progression. In the presence of these mediators, endocan production has been shown to increase more (10). Endocan is recognized as a new marker of angiogenesis (11). In recent studies, the role of endocan in many cancers including gastric cancer, non-small cell lung cancer, head and neck squamous cell carcinoma, colorectal cancer, clear cell renal cell carcinoma, hepatocellular carcinoma, pituitary adenoma, ovarian cancer, and brain cancers has been identified (12-20).

Serum endocan levels can be used in the early diagnosis of cancers because of the aforementioned characteristics. In addition, many studies have suggested that it can be a molecule of prognostic importance in various cancers (9). Although there are studies investigating endocan level in many cancer types, no studies have been reported on this subject in PTC patients. The aim of the current study was to compare preoperative serum endocan levels of patients diagnosed with PTC by thyroid FNAB and endocan levels of patients with no malignancy after thyroid FNAB.

Material and Methods

Forty-eight patients who were diagnosed as PTC by thyroid FNAB between November 2018 and May 2019 at Necmettin Erbakan University (NEU) Meram Faculty of Medicine Endocrinology and Metabolism outpatient clinic were enrolled in the study preoperatively. Control group consisted of 40 volunteers with benign thyroid FNAB results.

Demographic and laboratory findings of the patients and controls were recorded. The pathological findings of the patients after thyroidectomy were evaluated. Patients with comorbid disease and using drugs for any reason were excluded from the study. Subjects with any comorbid disease other than benign thyroid nodule were excluded for the control group. 5 mL of venous blood samples were taken from the controls and patients in the morning fasting. Blood samples of the patients were taken before total thyroidectomy operation. Blood samples were centrifuged in the NEU Meram Faculty of Medicine Biochemistry Department Laboratory and serum samples were stored at -80 °C until the time of study. After all samples were collected, serum endocan levels were measured by ELISA on the same day.

NEU Meram Faculty of Medicine Ethics Committee approved the study with the decision no 2018/1637 and the date 21.12.2018. Written "Voluntary Informed Consent Form" was obtained from the patient and control group who agreed to participate in the study. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later

amendments or comparable ethical standards.

Statistical Analysis

Statistical analysis were performed by the Statistical Package for Social Sciences (SPSS) software version 21.0 (SPSS Inc., Chicago, IL, USA)."program. Continuous variables were expressed as median (minimum-maximum) when the distribution was not normal, and as mean±standard deviation when the distribution was normal. The test we used to determine whether the distribution of the data was normal was the Kolmogorov-Smirnov test. For the comparison of independent group differences, the significance test of the difference between the two means (independent samples t-test) was used when parametric test assumptions were provided. When parametric test assumptions were not provided, the Mann-Whitney U test was used to compare independent group differences. Chi-square test was used for the comparison of categorical variables between independent groups. Pearson test was used for the correlation analysis between numerical variables showing normal distribution. Receiver operating characteristic (ROC) analysis was used to determine the cutoff value for optimal sensitivity and specificity of endocan level. For differences, $p<0.05$ was considered as statistically significant.

Results

Of the patients enrolled in the study, 38 (79.2%) were female and 10 (20.7%) were male, and the mean age was 48.5±14.1 years. In the control group, 36 (90%) were female and 4 (10%) were male, and the mean age was 48.7±15.8 years. The 2 groups were similar in terms of gender and age distribution, weight, height, body mass index and serum thyroid-stimulating hormone (TSH) levels (Table 1).

The mean serum endocan level was 45.1±9.6 pg/mL in the patients and 37.7±8.3 pg/mL in the controls. Endocan levels of the patients were statistically significantly higher than those of the controls ($p<0.001$) (Table 1).

All patients had PTC as a result of postoperative final pathology. In terms of histopathologic variants of PTC; 33 (68.8%) patients had classic, 11 (22.9%) patients had follicular, 3 (6.3%) patients had both classic and follicular and 1 (2.1%) patient had insular variant PTC (Table 2). There was no significant difference in serum endocan levels between the groups formed according to the parameters related to the clinicopathologic features of the PTC (Table 3). Correlation analysis showed no significant correlation between serum endocan level and the other parameters evaluated (Table 4).

In the ROC analysis, serum endocan level cut-off value was 40.84 pg/mL to predict PTC diagnosis. The specificity, sensitivity, negative predictive value and positive predictive value for this cut-off value were 67.5%, 68.8%, 64.3% and 71.7%, respectively. Area under curve (AUC) was 0.71 (Figure 1).

Discussion

Unlike other cancers, thyroid cancers occur earlier in life and are usually diagnosed in the fifth decade. In a study of 77,276 thy-

Table 1. Comparison of demographic and laboratory findings of patients and controls.

Parameter	Patient group	Control group	p value
Gender (female/male)	38/10	36/4	0.167
Age	48.5±14.1	48.7±15.8	0.932
Weight (kg)	70.7±9.6	72.5±8.9	0.372
Height (cm)	164.8±6.8	165.5±6.5	0.622
BMI (kg/m^2)	25.9±2.6	26.3±2.2	0.426
TSH (IU/mL)	2.1±1.3	2.2±1.3	0.846
Endocan (pg/mL)	45.1±9.6	37.7±8.3	<0.001

All values are presented as n or mean value±standard deviation. BMI: Body mass index; TSH: Thyroid-stimulating hormone.

Table 2. Clinicopathological features of the patient group.

Parameter	n (%)
Histopathologic variants	
Classical	33 (68.8)
Follicular	11 (22.9)
Classical+follicular	3 (6.3)
Insular	1 (2.1)
Lymphatic invasion (+)	14 (29.2)
Perineural invasion (+)	4 (8.3)
Vascular invasion (+)	26 (54.2)
Invasion of surrounding thyroid tissue (+)	46 (95.8)
Lymph node metastasis (+)	13 (27.1)
Presence of tumor at surgical margin (+)	9 (18.8)
TNM Stage	
1	32 (66.7)
2	2 (4.2)
3	8 (16.7)
4	6 (12.5)
ATA risk category	
Low	16 (33.3)
Intermediate	26 (54.2)
High	6 (12.5)
Tumor size (cm) (median, minimum-maximum)	2.5 (0.2-10.20)

All values are presented as n (%) or median value (minimum-maximum). TNM: Tumor-node-metastasis; ATA: American Thyroid Association.

roid cancer patients, Lim et al. reported a mean age at diagnosis as 48 years (1). In our study, the mean age at diagnosis was found to be 48. Thyroid cancers are more common in women than in men. In the literature, the incidence of thyroid cancer is 2 to 4 times higher in women than in men (1,21,22). In the current study, the female/male ratio was found to be 3.8. In our study, age at diagnosis and female/male ratio were consistent with the literature.

Among the histopathologic variants of PTC, follicular variant is the most common variant and its frequency has been reported in 23-40% in different studies (23,24). In our study, the most common variant was the classical variant (68%). Follicular variant was the second most common variant and detected in 22% of the patients. Thus, the histopathologic variant distribution was different from the literature.

Endocan is known as a proteoglycan secreted from the endothelium of the vessels. Unlike other large proteoglycan molecules, endocan has different biological functions. Recent studies have suggested that endocan plays a critical role in inflammation, healing and tumorigenesis (25). In many studies, endocan expression was increased in tumor vessels of cancers such as lung, brain, colon, liver and pituitary which are highly vascular (26). In addition, an association between increased endocan expression and overall survival has been reported, and endocan has been suggested to have prognostic significance (27).

In the current study, we found that serum endocan levels were significantly higher in patients with PTC compared to patients with benign thyroid nodules. Although there are studies designed to examine serum endocan levels in many types of cancer, very few studies have been reported in this regard in patients with PTC yet. Şahin et al. divided the patients into four groups as having PTC, multinodular goiter (MNG) on thyroiditis background, MNG and follicular thyroid cancer (FTC) and they found no significant difference between the 4 groups in terms of endocan level. When the authors grouped the patients as benign and malignant, they found that endocan levels was significantly higher in the malignant group, and they also reported that patients with FTC, which shows spreading via the hematogenous route, had higher endocan levels compared to PTC patients (28). In our study, in accordance with the literature, endocan levels were found to be significantly higher in patients with PTC compared to patients with benign thyroid nodules, but since patients with FTC were not included in our study, a comparison could not be made between different types of thyroid cancer in terms of endocan levels. The results of our study gave us the idea that the measurement of serum endocan level can be used as an adjunctive test in the diagnosis of PTC if supported by other studies with higher sample size.

Increased serum endocan levels and/or upregulated tissue endocan expression have been demonstrated in various cancers (12-20). Lv et al. compared the serum endocan levels of 114 gastric cancer patients without neoadjuvant therapy and 55 healthy controls.

Table 3. The relationships between serum endocan level and papillary thyroid cancer clinicopathological features.

Parameter	Endocan (pg/mL) (mean±SD)	p value
Histopathological subtype		
Classical (n=33)	45±10.2	0.908
Follicular (n=11)	45.4±9.5	
Lymphovascular invasion		
Present (n=14)	43.1±8.6	0.363
Absent (n=34)	45.9±10.1	
Perineural invasion		
Present (n=4)	49.8±5.5	0.312
Absent (n=44)	44.7±9.8	
Vascular invasion		
Present (n=26)	45.9±8.9	0.555
Absent (n=22)	44.2±10.5	
Invasion of surrounding thyroid tissue		
Present (n=46)	45.1±9.8	0.678
Absent (n=2)	45.7±1.1	
Lymph node status		
N1 (n=13)	42±7.3	0.180
N0 (n=35)	46.2±10.2	
Presence of tumor at surgical magrin		
Present (n=9)	40.7±7.4	0.130
Absent (n=39)	46.1±9.9	
TNM Stage		
1 (n=32)	10±1.7	0.630
2 (n=2)	8.1±5.7	
3 (n=8)	10.2±3.6	
4 (n=6)	7.9±3.2	
ATA risk category		
Low (n=16)	43.6±11.6	0.457
Intermediate (n=26)	46.7±8.5	
High (n=6)	42.2±8.5	

All values are presented as mean value±SD. SD: Standard deviation; TNM: Tumor-node-metastasis; ATA: American Thyroid Association.

Endocan levels of the patients (83.7±16.2 pg/mL) were significantly higher than those of the controls (44.7±16.4 pg/mL). The authors determined a cut-off value of 55.3 pg/mL in their ROC analysis, and for this cut-off value, the specificity, sensitivity, negative predictive value and positive predictive value of endocan measurement were 80%, 98%, 93.6% and 91%, respectively, and the AUC value was 0.94. In addition, serum endocan levels were higher in advanced gastric cancer patients compared to early stages.

However, there was no relationship between endocan level and sex, age, tumor size, lymph node and distant metastasis (29). Ji et al. compared both serum endocan levels and endocan expression in tumor tissue of

Table 4. Correlation analysis with serum endocan level.

Parameter	r value	p value
Tumor diameter	-0.090	0.543
TSH	0.165	0.262
Age	-0.026	0.862
Weight	0.151	0.304
Height	0.069	0.643
BMI	0.143	0.333

r indicates Pearson correlation coefficient. TSH: Thyroid-stimulating hormone; BMI: Body mass index.

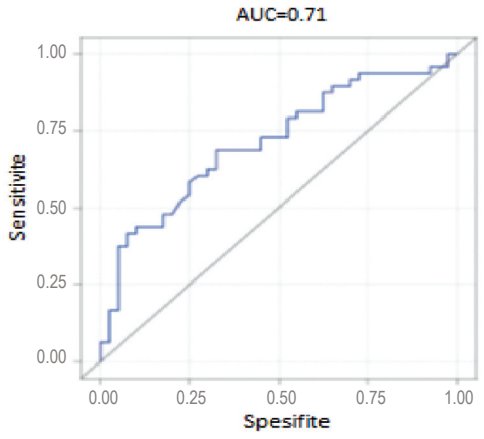

Figure 1. The predictive performance of endocan levels for papillary thyroid cancer according to the receiver operating characteristic curve.
AUC: Area under curve.

100 preoperative colorectal cancer patients with 78 healthy controls. The endocan level of the patients (70.1±29.7 pg/mL) was significantly higher than the endocan level of the control subjects (29.7±14.9 pg/mL). The authors determined a cut-off value of 33.3 pg/mL in their ROC analysis, and for this cut-off value, the specificity, sensitivity, negative predictive value and positive predictive value of endocan measurement were 73%, 99%, 95% and 63%, respectively, and the AUC value was 0.94. In addition, serum endocan levels were higher in patients with advanced colorectal cancer compared to early stages. However, there was no relationship between endocan level and sex and age (30). Laloglu et al. compared serum and urine endocan levels in 50 preoperative bladder cancer patients, 50 urinary tract infection patients and 51 healthy controls. Serum (631 pg/mL vs 472 pg/mL) and urine (1,514 pg/mg creatinine vs 627 pg/mg creatinine) endocan levels of patients with bladder cancer were significantly higher than endocan levels of healthy control subjects. Urinary endocan levels were significantly higher than serum endocan levels in both control and patient groups. The authors determined the cut-off value for serum endocan level as 630 pg/mL in their ROC analysis and determined the sensitivity and specificity of endocan measurement for this value as 50% and 77%, respectively. No significant difference was found between serum endocan levels of advanced and early stage bladder cancer patients (31). In these studies, the authors concluded that the measurement of serum endocan levels may be a marker that can be used in the early diagnosis of gastric, colorectal and bladder cancers. In our study, similar to other studies that investigated the relationship between endocan and cancer, serum endocan levels were significantly higher in patients with PTC than in control subjects. Although not studied in the same disease, similar to other studies, we could not find a relationship between age and gender and endocan levels. In our study, the cut-off value of serum endocan level was 40.84 pg/mL. The sensitivity and specificity for this cut-off value were 68.8% and 67.5%, respectively, and the AUC value was 0.71. Although the values found in our study are not as high as those of gastric and colorectal cancer studies, it is suggested that the measurement of serum endocan level may be a potential tumor marker that can be used in the diagnosis of PTC, if supported by large-scale studies.

Increased endocan expression was found to be associated with tumor progression and poor clinical outcomes. However, the results of the studies on this subject are contradictory. While the above-mentioned studies evaluating gastric and colorectal cancers showed a relationship between serum endocan level and tumor stage, this relationship was not found in bladder cancer (28-30). Furthermore, in a meta-analysis of Huang et al., 15 studies investigating the prognostic value of endocan expression in different types of cancer were evaluated. This meta-analysis found an association between increased endocan expression and worse overall survival in gastrointestinal cancers [hazard ratio (HR): 2.27] and hepatocellular carcinoma (HR: 2.61) (27). We conducted a cross-sectional study. Therefore, it was not possible to make an evaluation regarding prognosis and especially survival. However, important prognostic factors such as age, primary tumor size, soft tissue invasion, presence of lymph node and/or distant metastasis and histopathological subtype have been identified in PTC. In our study, we divided the patients into groups according to histopathological subtype of tumor, presence of lymphovascular, perineural, capillary and surrounding thyroid tissue invasion,

lymph node metastasis, surgical margin positivity, tumor-node-metastasis stage and American Thyroid Association risk category and compared the serum endocan levels of these groups. We investigated the relationship between age and tumor size and endocan level. No correlation was found between endocan levels and any of these parameters. FNAB applied to nodules detected in the thyroid gland is the most important step in the diagnosis of thyroid cancer (7). In recent years, with the widespread use of neck ultrasonography and FNAB, the number of nodules biopsied has increased considerably. Nodule size is one of the important determinants in deciding which nodule to take biopsy (7). In our study, although serum endocan level was found to be higher in patients with PTC than in controls, we think that the lack of a relationship between tumor size and endocan level may have clinical importance. This finding, if supported by other studies, suggests that after the detection of a thyroid nodule, the measurement of serum endocan level can provide valuable information about the need for FNAB by assisting features suggestive of increased cancer risk such as microcalcification, central vascularity, irregular borders, hypoechoic nodule and presence of cervical lymphadenopathy even if the size of the nodule does not meet the FNAB criteria.

There are some limitations of our study. First, the endocan level was studied in serum in our study. In previous studies examining the relationship between cancer and endocan, immunohistochemical methods were used to show endocan expression in cancer tissue. In order to establish a direct relationship between PTC and endocan, the demonstration of endocan expression in PTC tissue by immunohistochemical methods will provide more reliable information. Another important limitation of the current study is the small study population.

Conclusion

In conclusion, the fact that endocan levels were found to be significantly higher in patients with PTC compared to controls led us to think that endocan could be used as a marker for tumor development in the future. However, our findings need to be supported by more comprehensive studies with larger sample sizes to be conducted in this context.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and/or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Musa Kürşad Şener; Design: Melia Karaköse; Control/Supervision: Musatafa Kulaksızoğlu, Feridun Karakurt; Data Collection and/or Processing: Taha Ulutan Kars, Cihad Solak; Analysis and/or Interpretation: Fethi Yönet, Fatma Hümeyra Yerli kaya; Literature Review: Mehmet Emin Gerek; Writing the Article: Musa Kürşad Şener, Muhammed Kocabaş; Critical Review: Melia Karaköse, Muhammet Kocabaş; References and Fundings: Musa Kürşad Şener, Materials: Cihad Solak.

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