Diagnostic and Prognostic Value of Serum Vitronectin and Galectin-3 levels in Thyroid Tumors

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Abstract

Objective: Increased expression of Galectin-3(Gal-3) and Vitronectin (VN) molecules has been the subject of research, since it may be a biological marker that can be used for the separation of benign and malignant tissues. We aimed to evaluate serum Gal-3 and VN expression levels in the presence of thyroid tissue, and evaluate the predictive and prognostic value of these molecules in the differential diagnosis of malignant tissues.

Materials and Methods: 44 patients with thyroid nodules were included in this prospective study. Benign and malignant lesions were distinguished from thyroidectomy materials.

Results: Mean preoperative Gal-3 and VN values measured in malignant lesions were statistically significantly higher than preoperative Gal-3 and VN values in benign lesions (p-values: 0.007 and 0.009, respectively). Also, mean Gal-3 and VN values measured in serum were significantly reduced after operation compared to preoperative values (p-values<0.001 and 0.001, respectively). Mean preoperative Gal-3 and VN values were found statistically significantly higher if there is capsular invasion (p-values: 0.033 and 0.026, respectively).

Conclusion: The serum Gal-3 and VN concentrations are increased in thyroid cancer and in the presence of capsular invasion. And also decreased during the postoperative period significantly. Our findings will contribute to the literature in order to improve correct diagnosis and mortality rates in thyroid lesions.

***Keywords*:** *Thyroid cancer, thyroid nodules, Vitronectin, Galectin-3, Prognosis, Diagnosis*

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Introduction:

Thyroid cancers are the most common tumors of the head and neck and are also the most common endocrine malignancy. Although preoperative evaluation of thyroid lesions could be performed, it is important to evaluate prognosis determination, optimal therapeutic intervention and improvement of survival rates [1].

Galectins are a family of proteins with beta-galactosides affinity. Galectin-3 (Gal-3) is a subtype with different origins that is found on the cytoplasm, nucleus and cell surface and interacts with the extracellular matrix [2]. Cytoplasm and nuclear Gal-3 concentrations with the changes in thyroid cell gene transcription, proliferation, differentiation, apoptosis regulation, angiogenesis, adhesion, invasion, and tumor progression has been reported active in the area, such as many physiological and prognostic role [3]. However, Gal-3 expression has been reported to be up-regulated in thyroid, liver and stomach cancers. Therefore, the value of Gal-3 protein as a biological marker for the separation of benign and malignant thyroid tissues is widely investigated [4].

Vitronectin (VN) is an adhesive extracellular matrix glycoprotein associated with tumor progression, angiogenesis and metastasis in malignancies such as breast cancer, melanoma, hepatocellular carcinoma [5,6,7]. Integrins, which are also adhesive molecules, are a VN ligand. Integrin-VN complexes were revealed to trigger hypoxia resistance, neovascularization and tumor cell invasion [8]. Therefore, we aimed to examine the VN and Gal-3 expression levels in thyroid masses and the predictive and prognostic value of these molecules in the differential diagnosis and differentiation of malignant tissues, which would prevent unnecessary operations.

Materials and Methods

Subjects

Forty-four patients with a thyroid mass were included in this study. Approval from the local ethics committee (2018/1450) was obtained for this prospective study. In addition, verbal and written consent has been obtained from all patients, that their medical findings can be used for research purposes.

After clinical evaluations, the features of the mass or nodules was evaluated with thyroid ultrasonography (US), such as size, contour arrangement, calcification, echogenicity and vascularization. As a result of cytological and histopathological evaluation, benign and malignant lesions were determined after thyroidectomy. The patients evaluated as malignant were staged using the TNM system. Demographic data, as well as prognostic features such as lesion size, capsular invasion and lymph node (LN) involvement were analyzed with VN and Gal-3 serum levels.

Laboratory analyzes:

The determination of human Gal-3 and VN levels (ng/mL) was assessed by the quantitative sandwich enzyme-linked immunosorbent assay (ELISA) kits (Elabscience Biotechnology Inc., USA) according to VN and Gal-3 patients' peripheral venous blood samples the manufacturer's instructions.

Statistical analysis:

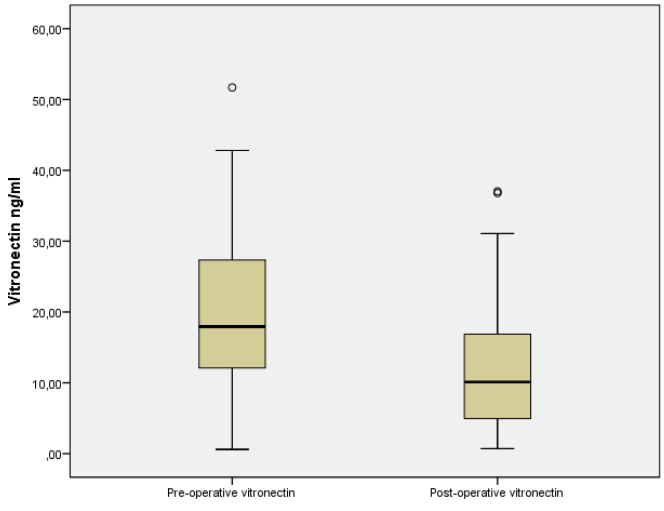
All data were evaluated with SPSS software for Windows (v21.0; IBM, Armonk, NY, USA). Mean, standard lead, median (min-max), distribution frequencies and percentages were analyzed. Normalization of the data distribution was evaluated by the Kolmogorov-Smirnov test. Comparison of variables that were not normally distributed was evaluated by Mann Whitney and Kruskal Wallis tests. P-value <0.05 was considered statistically significant.

Results:

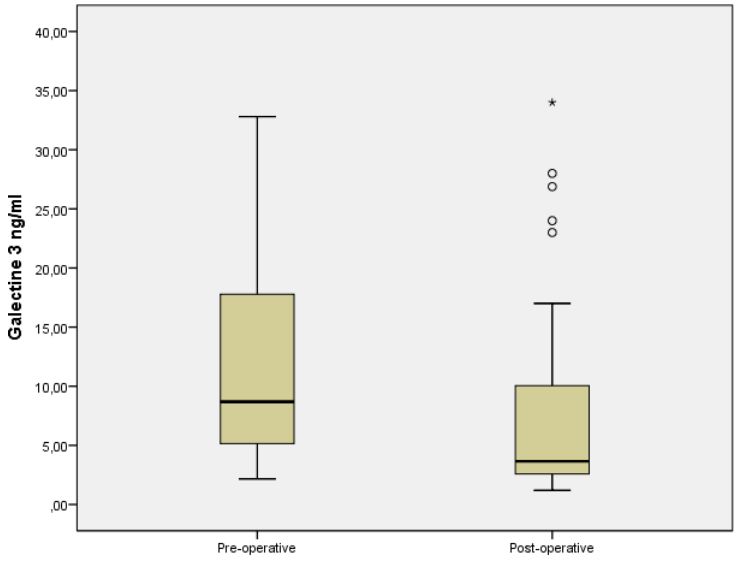
Mean age was 46.2 ± 11.5 (range: 26-78 years) and, 32 patients were female (72.7%) and 12 (27.3%) were male. While 40.9% (n: 18) of the subjects were under the age of 45 years, 59.1% (n: 26) of the subjects were the age of ≥45 years. There was no statistically significant difference (p: 0.679) between male and female patients in terms of mean age. According to histopathological analysis 56.8% (n: 25) of the lesions were benign and 43.2% (n: 19) were malignant. The most common tumor in our group was benign adenomatous nodules (58.8%, n: 25). This was followed by a papillary Ca (38.6%, n: 17), and followed by follicular Ca and medullary Ca (both 2.3%). While multicentricity was observed in 31.6% (n: 6) of the patients; angioinvasion was observed in 47.4% (n: 9), thyroid capsule invasion in 42.1% (n: 8), extra-thyroidal invasion in 5.3% (n: 1) and LN metastases was detected in 31.6% (n: 6) of the cases.

In our patients, preoperative mean VN value was 21.46 ± 15.23 ng/ml (median: 17.93, range: 0.59-73.48) and Gal-3 value 12.22 ± 8.78 ng/ml (median: 9.10, range: 2.16-38.47). Post-operative mean VN value was 11.96 ± 9.14 ng/ml (median: 10.11, range: 0.71-37.03) and Gal-3 value was 7.70 ± 8.25 ng/ml (median: 3.65, range: 1.20-34.0). The decrease in the mean VN and Gal-3 levels following surgery was statistically significant (p< 0.001, and <0.001, respectively) (Graph 1 and 2).

Graph 1.



Graph 2.



When the clinical characteristics were evaluated according to preoperative serum level of VN and Gal-3 change; mean preoperative values of VN (21.92 ± 15.77 ng/ml) and Gal-3 (14.15 ± 7.73 ng/ml) measured in malignant lesions; mean preoperative values of VN (11.23 ± 7.36 ng/ml) and Gal-3 (8.99 ± 7.08 ng/ml) measured in benign lesions was found to be statistically significantly different (p-values: 0.007 and 0.009, respectively). The mean preoperative VN and Gal-3 values were found to be statistically significantly different in patients with capsular invasion (p-values: 0.033 and 0.026, respectively) (Table 1).

Table 1. Comparison of preoperative vitronectin and galectin 3 values between clinical and histopathological features of the patients.

	Clinical Variables	n (%)	VN (Mean±SD)	P-value	Gal-3 (Mean±SD)	P-value
Tumor Type	Benign Malign	25 (%56.8) 19 (%43.2)	12.03±9.49 11.87±8.92	0.955	14.47±11.09 9.25±1.95	**0.030***
Age	< 45 years ≥ 45 years	18 (%40.9) 26 (%59.1)	11.62±9.60 12.50±8.62	0.759	10.84±8.65 14.40±8.79	0.071
Tumor Size	< 4 cm ≥ 4 cm	17 (%89.4) 2 (%10.6)	15.28±10.22 8.09±5.58	0.079	8.88±1.71 9.67±2.21	0.497
Gender	Female Male	32 (%72.7) 12 (%27.3)	10.67±8.09 15.42±11.15	0.126	13.51±8.55 8.77±8.80	**0.011***

Malign Lesions Foci	**Unifocal** Multicentric	13 (%68.4) 6 (%31.6)	13.07±9.90 9.28±6.30	0.406	9.29±2.00 9.17±2.02	0.826
Angioinvasion	Absent Present	10 (%52.6) 9 (%47.4)	11.47±6.86 11.19±11.66	0.948	8.28±2.34 9.75±2.35	0.306
Thyroid Capsular Invasion	Absent Present	11 (%57.9) 8 (%42.1)	14.41±11.02 30.99±17.75	**0.033***	7.06±2.79 16.27±10.07	**0.026***
Extra Thyroidal Extension	Absent Present	18 (%94.7) 1 (%5.3)	11.71±9.28 4.68	0.465	8.89±2.44 10.50	0.410
LN Involvement	Absent Present	13 (%68.4) 6 (%31.6)	10.85±6.65 14.09±13.11	0.478	9.18±2.07 9.42±1.83	0.692

VN: Vitronectin, Gal-3: Galectin 3, LN: Lymph Node *p<0.05 statistically significant

Preoperative mean Gal-3 levels (8.77 ± 8.80) in men was statistically significantly lower than women (13.51 ± 8.55) (p: 0.011). In cases where malignant lesions were detected (n: 19), the total tumor diameter was determined as 2.0±1.2 cm (range: 0.3-4.5 cm).

When tumor diameters are grouped as smaller than 4 cm (n: 17, 89.4%) and ≥4 cm (n: 2, 10.6%), then the relationship between groups and the average preoperative VN and Gal-3 are examined; there was no statistically significant difference between each group (p-values: 0.079 and 0.497, respectively). In addition, when the mean preoperative VN and Gal-3 values were evaluated in terms of age, tumor localization, focal number, angioinvasion, out-of-capsule invasion, and LN involvement, no statistically significant difference was observed (p> 0.05) (Table 2). When the lesions were evaluated according to histopathology results as malignant and benign; no statistically significant difference was seen between the groups in terms of mean preoperative VN and Gal-3 values (p-values: 0.053 and 0.058, respectively) (Table 2)

Table 2. Comparison of preoperative Vitronectin and Galectin 3 values in lesion types.

	N	**%**	**VN(Mean±SD)**	**P-value**	**Gal 3(Mean±SD)**	**P-value**
Malignant	19	38.6	22.58±16.59	0.053	13.62±8.03	0.058
Benign	25	58.8	11.67±7.17		9.27±7.10	

VN: Vitronectin, Gal-3 Galectin 3, *p<0.05 statistically significant

Discussion:

The difficulties are well known, encountered during the histological analysis of thyroid lesions, as benign or malignant. Considering the clinical behavior and prognostic characteristics of thyroid carcinomas, nodules that appear to be very common in the general population, and the incidence of thyroid carcinomas increasing more rapidly than all other cancer types in recent years and management of the disease becomes difficult for clinicians [1,9]. In recent years, there are ongoing investigations about the immunohistochemical and molecular biological markers potential to discriminate lesions malignancy and prognosis [10]. Sumana et al., obtained histopathologically proven analysis of 30 malignant and 20 benign thyroid lesions, as well as the expression of Gal-3 in the tissue samples and reported that Gal-3 expression increased statistically significantly ($p < 0.0001$) in malignant lesions. In the same study, they reported sensitivity of 86%, specificity of 85%, positive predictive value of 89.7% and negative predictive value of 80.9% for benign and malignant distinction by Gal-3 expression, However, the researchers did not observe a significant difference between malignant histological subtypes in terms of Gal-3 expression [11]. Gal-3 has been reported as a critical component in the tumor microenvironment. Thus, many prognostic processes have been reported, such as tumor cell adhesion, proliferation, differentiation in the pre-cancerous process, angiogenesis and metastasis [12]. In their study involving 38 malignant and 26 benign thyroid lessions, Siderova et al 38 reported strong and diffuse Gal-3 expression in malignant lesions, and Gal-3 expression was negatively reported in normal and/or benign thyroid tissues [13]. Similarly; Weihui et al reported statistically significantly higher Gal-3 expression in patients' papillary thyroid cancer (PTC) with cervical LN metastases, than patients without LN metastasis [14]. Tang et al in a meta-analysis of PTC and non-PTC lesions consisting of 424 cases reported significantly increased Gal-3 expression in the presence of LN metastasis and capsular invasion, [15].

Increased Gal-3 expression was detected not only in tumoral tissues, but also in serum samples. It has been reported that, circulating Gal-3 may have a critical role in tumor aggregation, prognosis and metastasis due to adhesion susceptibility to vascular wall endothelium and, serum Gal-3 levels increase at least 1.5 times in head & neck, lung, breast and gastrointestinal cancers compared to healthy individuals. Moreover, the increase in serum levels observed in the presence of metastases has been reported to be much higher than the levels in localized tumors [16].

Considering the studies examining the value of Gal-3 as a potential serum marker for thyroid cancer; in a study involving 35 malignant and 55 benign lesions, significantly increased serum Gal-3 levels are reported in patients with thyroid carcinoma. Also, significantly decreased serum Gal-3 levels in post-op measurements compared to pre-op levels in PTC patients. Similarly, in another study involving 159 patients with 72 differentiated thyroid cancer (DTC), 87 benign lesions and 16 healthy controls; high serum Gal-3 levels have been reported in DTC patients compared to benign lesions and control groups [17]. In contrast to these studies, Inohara et al (58 DTC, 60 benign, 20 healthy controls) and Makki et al (43 PTC, 58 benign lesions) did not detect a statistically significant difference between serum Gal-3 levels in patients with benign and malignant lesions [18,19]. In our study, in accordance with the publications, mean preoperative serum Gal-3 levels in malignant lesions was found statistically significantly higher than the benign lesions. It is determined that the postoperative mean Gal-3 levels decreased statistically significantly compared to the preoperative period. On the other hand, mean preoperative Gal-3 values were found to be statistically significantly higher in patients with capsular invasion. And also, a statistically significant correlation was found between

postoperative Gal-3 levels and tumor size. However, in our study, mean preoperative Gal-3 values did not show a statistically significant difference between malignant tumor types.

In a limited number of studies about VN, which is a multifunctional adhesive protein, there are published data related to tumor progression, angiogenesis and metastasis in breast cancer, melanoma, hepatocellular carcinoma, and colorectal adenocarcinoma; but no relationship has been established in patients with thyroid carcinoma [5-7]. Yoshimura et al. have shown, in their study involving 62 epithelial ovarian cancer patients, 26 benign ovarian lesions and 20 healthy controls tumor cell invasion and tumor progression triggered by fibronectin and VN up regulation, in patients with epithelial ovarian cancer [20]. Yang et al. reported significantly higher serum VN levels in patients with HCC compared to other groups in their study, conducted on 105 HCC, 91 liver cirrhosis, 102 chronic hepatitis patients and 100 healthy controls. Moreover, increased serum VN levels have been reported to be directly related to the histological differentiation, vascular tumor thrombosis, nodal metastasis and decreased survival rates. Researchers have concluded that serum VN levels may be a useful diagnostic and prognostic marker in patients with HCC [21]. Hao et al showed that mean serum VN values in 93 breast cancer patients were significantly higher than the subjects with 30 benign breast lesions and 9 precancerous lesions, and 30 healthy controls. Moreover, they reported that serum VN levels correlated statistically significantly with tumor size, TNM and clinical stage [22]. In another study conducted by Niu et al., including 34 prostate carcinoma and 41 benign prostate hypertrophy patients, has been reported that serum VN rates were statistically higher in patients with prostate cancer ($p < 0.005$), and that serum VN rates significantly increased in metastatic cases ($p < 0.05$). In our study, to be compatible with all these data; it was found for the first time in the literature that the mean preoperative serum VN levels measured in patients with malignant thyroid tumors were significantly higher than the benign thyroid lesions. And also, statistically significant decrease was determined in postoperative mean VN levels compared to preoperative levels. In addition, mean preoperative VN levels were statistically significantly higher, in patients with capsular invasion. However, the mean preoperative VN values did not show a statistically significant difference according to histopathological tumor types.

In conclusion, in our study it was shown that serum Gal-3 and VN concentrations decreased during the postoperative period and increased significantly in patients with malignant thyroid lesions and especially in the presence of capsular invasion. The value of serum Gal-3 and VN as biomarkers were determined in patients with thyroid mass in the differential diagnosis and prognosis. Therefore, we believe that our findings will contribute to the literature in order to improve differential diagnosis and mortality rates in patients with thyroid mass, as well as to provide new therapeutic approaches with serum Gal-3 and / or VN targets.

Conflicts of interest statement: There are no conflicts of interest.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: E.A., **Design:** E.A., **Supervision:** E.A., G.A., B.O., D.S., F.D.C.T., A.V.S., K.U., **Data Collection and/or Processing** E.A., G.A., B.O., D.S., F.D.C.T., A.V.S., K.U., **Analysis and/or Interpretation:** E.A., G.A., B.O., D.S., F.D.C.T., A.V.S., K.U., **Literature Review:** E.A., **Writer:** E.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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