

## ARAŞTIRMA

# Serum levels of VEGF and EGF in thyroid gland tumors

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### Abstract

**Purpose:** VEGF and EGF are involved in the pathogenesis of thyroid gland tumors and their growth. We decided to find whether changes in the production of these cytokines by thyroid tumor cells are reflected by changes of their peripheral blood. **Methods:** Using ELISA kits, we measured the concentrations of growth factors in the peripheral blood serum in 20 patients with thyroid gland tumors (10 adenomas, 10 papillary carcinomas) and compared these concentrations with those in healthy people.

**Results:** We found significantly higher serum levels of VEGF and EGF in patients with thyroid adenoma and papillary carcinoma compared with those in healthy subjects. But, these parameters, we were not different between groups of investigated subjects.

**Conclusion:** Changes in the production of these cytokines by thyroid gland tumor cells are reflected

in their peripheral blood levels. Also, significant differences of VEGF and EGF serum levels can be explained by their very high production by thyroid tumor cells and by their strong effect on the follicular and endothelial cell proliferation.

**Key Words:** Thyroid gland; Thyroid adenoma; thyroid papillary carcinoma; growth factors

### Troid bezi tümörlü hastalarda serum EGF ve VEGF düzeyleri

#### Özet

**Amaç:** VEGF ve EGF serum düzeyleri troid bezi tümörlerinin patogeneğinde ve onların büyümesinde rol oynar. Hipotezimiz troid tumor hücreleri tarafından üretilen bu sitokinler periferik kanda düzeylerini yansıttığını savunmaktayız.

**Metod:** ELISA kit kullanarak troid bezi kanserli 20 hastanın ve sağlıklı bireylerimizin periferik kanında bu sitokinleri ölçtük.

**Bulgular:** Biz 10 troid adenomalı ve 10 troid papillar karsinomlu hastaların serum VEGF ve EGF düzeylerini sağlıklı bireylerimize göre, istatistiksel olarak yüksek bulduk. Ancak, troid adenomalı ve troid papillar karsinomlu hastalar arasında ise bu sitokinlerin konsantrasyonları arasında bir fark göremedik.

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**Sonuç:** Tirodi bezi tumor hücreleri tarafından bu sitokinlerin üretimindeki değişikliğin peripher kan düzeylerini yansıttığını düşünmekteyiz. Aynı zamanda VEGF ve EGF serum düzeyleri arasındaki farklılık, tiroid tumor hücreleri tarafından üretimini yüksek olması şeklinde açıklanabilir ve foliküle ve endotelial hücre proliferasyonunu güçlü etkisini vurgulamaktadır.

**Anahtar Kelimeler:** Tiroid bez; Tiroid adenoma; Tiroid papillar karsinoma; Büyüme faktörleri.

Growth factors and their receptors are products of oncogenes. Most of them have proliferative and dedifferentiating effects. They ensure autonomic growth of the tumor cell population by their autocrine and paracrine effects. Growth factors affect tumor growth not only by their direct effect upon cell proliferation, but also indirectly by influencing immunity and angiogenesis.

Vascularization of enlarging tumor mass is ensured by higher production of angiogenic growth factors, such as VEGF (Vascular Endothelial Growth Factor), EGF (Epidermal Growth Factor).

VEGF is a strong mitogen for endothelial cells and raises vascular permeability. It takes part in the neo-vascularization of the tumor tissue (1, 2). It has a similar effect on the proliferation of follicular cells. The VEGF production is increased in thyroid gland adenomas and especially carcinomas so that histological type of the tumor thus regulates its own vascularization intensity (3, 4). VEGF also takes part in the lymphatic vessel formation and affects tumor cell dissemination into regional lymphatic nodes (3, 5).

EGF stimulates follicular cell growth and has mitogenic and dedifferentiating effects. It is a very strong activator of angiogenesis, it activates endothelial proliferation, epidermal cell proliferation, and migration (5, 6).

The aim of our study was to find out whether differences in the growth factors production by the cells of thyroid gland tumor adenoma and papillary carcinoma described in the literature are reflected by their peripheral blood levels.

## Material and methods

The study involved 20 patients (11 women and 9 men) with a thyroid gland tumor, who were operated at the Clinic of II. General Surgery, Haseki Training Hospital, Istanbul from December 2008 until November 2009. In all these patients, total thyroidectomy was carried out and then the thyroid gland tissue was histologically investigated. In 10 persons a benign thyroid

adenoma (7 women, 3 men) and in other 10 subjects papillary carcinoma (6 women, 4 men) was found.

From every patient, 20 ml of blood were withdrawn from cubital vein in the operating-room before the start of the operation. After 30 min this peripheral blood was centrifuged for 10 min at 2600 rpm. The serum thus obtained was frozen in liquid nitrogen and stored in a closed plastic tube at -80 ° C. Measurements of serum concentrations of VEGF and EGF were performed by the ELISA method.

Tests for statistical differences were carried out with the Mann-Whitney *U* analysis, and Kruskal-Wallis test. Logistic regression was used for multivariate analysis. P values below 0.5 were considered significant.

## Results

Table 1 shows individual data of all patients. There was anamnesticly no other tumor disease, or any acute or chronic inflammation (including autoimmune disease) where production of cytokines can be changed (7).

Average values of serum concentrations of individual growth factors are shown in table 2.

We found significantly higher serum concentrations of VEGF and EGF in patients with thyroid adenoma and papillary carcinoma compared to the healthy population ( $p < 0.001$ ). There were no significant differences in serum VEGF and EGF levels between the groups of patients with thyroid adenoma and papillary carcinoma.

## Discussion

Several studies have described the production of particular growth factors in thyroid gland tumors. In these studies, the expression or occurrence of growth factors in thyroid gland was examined by their direct detection in the thyroid tissue, using PCR, immunohistological methods or in situ hybridization. We tried to elucidate, how these changes in the growth factor production by the thyroid gland tissue can be reflected by changes of their serum concentrations. Peripheral blood is still the most accessible biological material for routine screening investigation.

The role of VEGF in thyroid gland tumors is not yet quite clear. It stimulates follicular cells proliferation, it also supports angiogenesis and tumor tissue vascularization (8, 9). It is proved that VEGF is produced only in the isolated follicles of the normal thyroid gland. Its production rises in thyroid adenomas and

**Table 1.** Particular serum concentrations of growth factors in patients with thyroid adenoma and papillary carcinoma and in healthy subjects.

Group	Patient	VEGF (pg/ml)	EGF(ng/ml)
Adenoma	1	201.5	3.7
	2	178.3	4.1
	3	232.5	3.5
	4	257.1	2.9
	5	249.0	4.0
	6	231.7	3.6
	7	225.9	3.1
	8	209.2	3.8
	9	210.3	4.0
	10	198.5	3.7
Papillary carcinoma	1	199.4	3.2
	2	187.3	3.6
	3	234.1	3.9
	4	260.5	3.2
	5	248.2	3.5
	6	225.9	3.6
	7	198.2	4.0
	8	203.1	3.8
	9	209.5	3.5
	10	200.4	4.1
Healthy	1	56.4	2.1
	2	87.9	1.8
	3	65.3	2.5
	4	49.1	1.9
	5	52.0	2.2
	6	48.7	1.5
	7	59.5	2.0
	8	61.4	2.5

**Table 2.** Mean values of growth factors serum concentrations in patients with thyroid adenoma and papillary carcinoma and in healthy subjects.

Cytokine	Adenoma	Papillary carcinoma	Healthy
VEGF (pg/ml)	219.5 ± 28.4	216.7 ± 34.5	69.5 ± 9.9
EGF (ng/ml)	3.7 ± 1.1	4.5 ± 2.0	2.06 ± 1.2

Data are means ± SD.

especially in carcinomas (3, 10). Our VEGF serum concentrations are in accordance with these data. We have shown that VEGF serum levels are enhanced (3, 10).

EGF stimulates the proliferation of thyroid follicular cells. It has also dedifferentiating effects and it is a very strong activator of angiogenesis. Higher EGF production has been

described in thyroid adenomas and carcinomas, while this production is minimal in the normal thyroid gland tissue (6). We also found higher VEGF and EGF serum levels in patients with thyroid adenoma and papillary carcinoma compared to the healthy population.

Growth factors, such as other cytokines, have primarily autocrine and paracrine effects. Their

production in the organism is ubiquitous; they are not specific for particular tissues or diseases. Their serum concentrations express all physiological and pathological process in the organism. This fact may explain the results of our measurements, because some of them are not in agreement with literary data describing growth factor production directly in the thyroid gland tissue. Significantly higher VEGF and EGF serum levels in patients with thyroid gland tumors, compared to healthy subjects, can be explained by their very high production in thyroid tumor cells. These two growth factors have a very strong effect on the thyrocytes and endothelial cell proliferation. If it will be confirmed in more extensive studies, VEGF, EGF could be accepted as sensitive peripheral markers of thyroid gland tumors.

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