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Is there any venous gradient in serum thyroglobulin levels in patients with differentiated thyroid cancer?

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Some patients with differentiated thyroid cancer (DTC) have high serum thyroglobulin (Tg) levels although no evidence of disease can be detected on radioiodine scanning or other imaging methods. The aim of this study is to determine whether a gradient exists between the Tg levels of venous samples adjacent to primary tumour and systemic circulation.

Twenty-six patients underwent thyroidectomy and/or lymph node dissection for primary and recurrent DTC. To detect Tg levels, blood samples were concurrently collected via venipuncture from the internal jugular vein adjacent to the tumor and ipsilateral antecubital vein. Serum Tg level was measured by a chemiluminescence assay.

Tg levels were significantly higher in the adjacent internal jugular vein compared to the ipsilateral antecubital vein (p=0.001). The ratio of mean Tg values was higher 2.4-fold in the internal jugular vein than antecubital vein (median Tg ratio: 2.0:1; range, 0.7-29.6).

Documentation of a venous gradient in Tg levels in patients with DTC is a new investigational topic. According to the results of this prospective study, venous sampling for Tg may be a useful tool to localize recurrent or perhaps persistent DTC in the neck for patients who have no detectable disease on radioiodine scans or other imaging studies.

Keywords: thyroglobulin, thyroid cancer, venous gradient.

Serum thyroglobulin (Tg) protein is one of the best reliable tumor markers for papillary and follicular thyroid carcinoma, often termed differentiated thyroid carcinoma (DTC), during the follow-up [1]. It has shown that 10-15% of patients with DTC have high serum Tg levels after the treatment, which indicates persistent or recurrent disease, but no detectable disease on radioiodine scanning [2]. This discordance between serum Tg level and radioiodine scanning sometimes causes to empiric, high dose ^{131}I ablation and excessive work-up that includes neck ultrasound, computed tomography, magnetic resonance imaging, or positron emission tomography scans [2]. These imaging studies not only increase the cost, but also often display no disease and causes anxiety in some patients. According to some authors, Tg is not a reliable marker in patients who have high anti-Tg antibodies [1]. In these patients, some investigators suggest to measure serum Tg messenger RNA for the accurate determination of serum Tg levels [3].

Selective venous sampling for proteins secreted by endocrine tumors (parathyroid hormone, calcitonin, aldosterone, and insulin) has been used to localize tumors in the other studies [4–7]. However, the role of venous sampling for Tg in patients with DTC is clearly unknown. The purpose of this study is to determine whether a gradient exists between the Tg levels of venous samples adjacent to primary tumor and distant circulation.

Patients and methods

Twenty-six patients who underwent thyroidectomy and/or lymph node dissection for primary and recurrent DTC were included in the study. The inclusion criteria in this study included age more than 18; cytologically verified diagnosis of DTC of follicular cell origin that was proven later by histologic examination of the surgical material; tumor size equal or more than 1 cm; and suitable for thyroidectomy and/or lymph node dissection. The exclusion criteria also included patients with endogenous hyperthyroidism, liver failure or cirrhosis; use of anticoagulant therapy; and use of salicylate or nonsteroidal anti-inflammatory drugs for 7 days before the date of operation.

Twenty-five patients underwent total thyroidectomy for primary tumor. Two of 25 patients also had simultaneous

modified radical neck dissection together with thyroidectomy. One patient who had recurrent disease in the neck also had neck dissection with tumor excision. To detect Tg levels, 4 milliliters of blood were concurrently collected via venipuncture from the internal jugular vein adjacent to the tumor and ipsilateral antecubital vein on the same side prior to tumor resection. The venipuncture of the internal jugular vein was performed during the surgical procedure by an open neck and direct access to the internal jugular vein. Serum Tg level was measured by using the thyroglobulin immunoassay (Beckman Coulter Inc., USA). Futhermore, serum thyroid- stimulating hormone and anti-Tg antibody levels were measured in the systemic circulation by using the same method in all patients. This study was approved by our Board of Clinical Studies and written informed consent was obtained from all patients.

The difference in serum Tg levels between internal jugular vein and antecubital vein was calculated by Wilcoxon signed-rank test. Results are expressed as mean±SD. $P<0.05$ was considered statistically significant. Statistical tests were performed using the Statistical Package for the Social Sciences, version 10.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Clinical and pathologic charecteristics of the patients are shown in Table 1. Serum thyroid- stimulating hormone levels were in normal range in all patients (mean 1.7±0.9 mIU/mL). The serum anti-Tg antibody levels were measured high in two of 26 patients. One of these patients had a serum Tg gradient of 2.6-fold. On the other hand, mean serum Tg levels were 278±72 ng/mL in the internal jugular vein and 116±40 ng/mL in the antecubital vein. According to laboratory method used, the normal range of serum thyroglobulin level was from 0.58 to 625.1 ng/mL. Only 5 of 26 patients with DTC had an elevated serum Tg level according to the normal range in the internal jugular vein. Whereas, Tg level was higher than normal values in the antecubital vein in three patients. It was found that 23 patients had a higher serum Tg level in the internal jugular vein adjacent to the tumor than in the antecubital vein (Fig 1; $p<0.001$), in contrast Tg levels were higher in the peripheral veins of the other three patients. The ratio of mean Tg values was found to be 2.4-fold higher in the internal jugular vein than the antecubital vein (median Tg ratio: 2.0:1; range, 0.7-29.6). Although two patients had high serum anti-Tg antibody levels, one of these patients also had a serum Tg gradient (2.6-fold). We also determined that patient who had recurrent disease in the neck had markedly higher serum Tg level in the internal jugular vein (4.0-fold).

Table 1. Clinical and pathologic characteristics of patients.

		No.of patients	Percent
Age, y	<45/≥45	13/13	50/50
median (range)	44 (25-78)		
Sex	female/ male	20/6	77/23
Histologic type	Pure papillary / follicular variant	23/3	88/12
Multicentricity	yes/no	5/21	19/81
T Staging	T1/T2/T3	18/7/1	69/27/4
N Staging	N0/N1a/N1b	23/1/2	88/4/8
TNM Staging	1/2/3/4a	21/2/1/2	80/8/4/8

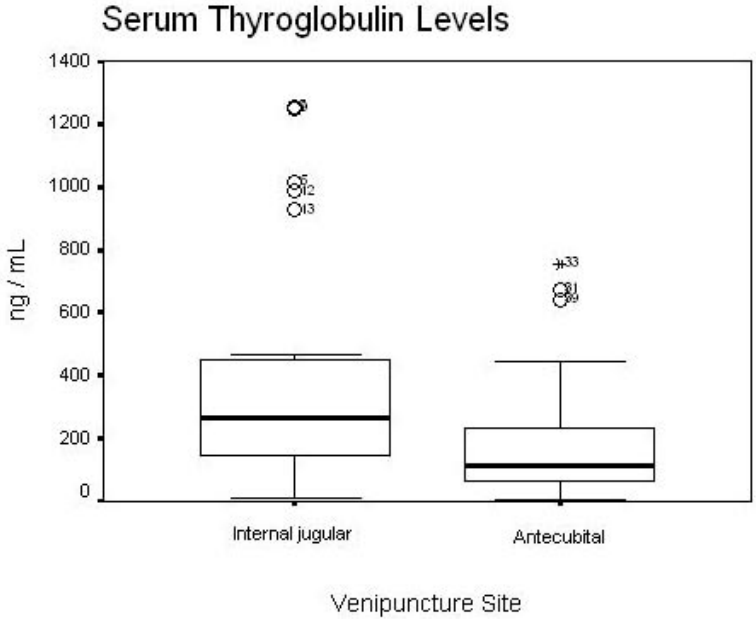

Figure 1. Distribution of serum thyroglobulin levels in the internal jugular vein and antecubital vein of patients with differentiated thyroid cancer (n=26; p=0.001).

The median follow-up period after the venous sampling process for all petients was 11 months. None of the 23 patients who had Tg gradient revealed any evidence of disease by serial mesurement of serum Tg levels or radioiodine scanning and the other imaging studies during the follow-up period.

Discussion

The long-term follow-up of patients with DTC is fundamental during the whole patient's life after the surgical treatment followed by ^{131}I remnant ablation and thyroid-stimulating hormone suppression [8]. Serum Tg level is the most commonly used biochemical marker to detect the persistent or recurrent disease in patients with DTC. It was reported that approximately 15% of thyroid cancer survivors have Tg-positive but radioiodine-negative tumors [9]. Thus, documentation of a venous gradient in Tg levels in patients with DTC is a new investigational topic.

Serum Tg levels are generally undetectable in patients without residual tumor during the postsurgical follow-up of DTC. However, in some cases, serum Tg level may be detectable or elevated without evidence of persistent or recurrent disease. In those patients, simultaneous venipuncture of the jugular and peripheral veins may allow focused work-up and selection of imaging studies.

In the previous published data, it has been shown that preoperative selective venous sampling for proteins secreted by endocrine tumors is beneficial to localize tumors which cannot be detected by conventional imaging studies [4–7, 10–13]. However, the role of venous sampling for Tg in patients with DTC is not clearly known. In a recent study, Kebebew and Reiff showed that 15 patients who underwent thyroidectomy and/or lymph node dissection for primary and persistent or recurrent DTC had a venous gradient in Tg levels, and also they suggested that venous sampling for Tg may be used to localize DTC in patients who have high or increasing Tg levels but negative imaging studies [9]. Similarly, according to the results of this study, there is a significant venous gradient between the Tg levels of venous samples adjacent to primary tumor and distant circulation in patients with DTC.

In the presented study, the venipuncture of the internal jugular vein was performed during the surgical procedure by an open neck and direct accesss to the internal jugular vein. We also think that the venous sampling process for this diagnostic method in Tg positive and scan negative patients can be performed with USG guided transcutaneous internal jugular vein venipuncture. The revealed venous gradient will then be a reason for neck dissection.

Approximately 20% of patients with DTC have positive anti-Tg antibodies during the posttreatment follow-up. Some investigators reported that positive serum anti-Tg antibodies frequently prevent to measure the serum Tg level correctly [1]. Therefore, they suggested to measure the serum Tg messenger RNA level to overcome of this matter [3, 14]. However, it has not been yet used routinely to detect persistent or recurrent DTC. The serum anti-Tg antibody levels were high in two of 26 patients in this study. One of these patients had a serum Tg gradient of 2.6-fold.

Although the half-life of Tg is longer (range, 6-96 hours) than the other proteins secreted by endocrin tumors and is influenced by liver function, Tg levels were significantly higher in the venous samples adjacent to primary tumor than the peripheral venous circulation in 23 patients [15]. However, the other three patients had a higher Tg level in the peripheral veins. Nevertheless, there is a quite limited difference in Tg levels between two venous samplings in those patients and also there is no venous gradient in Tg levels. Moreover, none of the patients had distant metastases.

It is not completely clear that how the normal thyroid tissue influence the serum Tg levels and Tg gradient. However, some investigators report that the patients who have normal thyroid tissue do not have any gradient in venous Tg levels. On the contrary differentiated thyroid cancers directly secrete thyroglobuline [1, 16–18].

In conclusion, the results of this study suggest that the venous sampling for Tg may be a useful tool to localize recurrent or perhaps persistent DTC in the neck for patients who have no detectable disease on radioiodine scans or other imaging studies. However, larger studies are required to confirm the results of this study.

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