Research paper

Evaluation of parenchymal vascularity of the thyroid gland with vascularization index by color superb microvascular imaging in patients with Graves' disease

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Abstract

Aim of the study: To determine the parenchymal vascularity of the thyroid gland with color superb microvascular imaging in patients with Graves' disease, and compare the vascularization index values with healthy subjects. **Materials and methods:** The thyroid glands of 37 patients whose laboratory and clinical findings were consistent with Graves' disease, and 40 asymptomatic subjects with normal laboratory values, were examined using color superb microvascular imaging. Measurements of the vascularization index were performed with a free region of interest which was drawn along the outer margin of the gland on the color superb microvascular imaging mode. The vascularization index values obtained in the Graves' disease and control groups were compared. A correlation analysis was performed between the vascularization index values and laboratory and grayscale US parameters. **Results:** The median vascularization index value of the thyroid parenchyma in patients with Graves' disease was significantly higher than in the asymptomatic group [median (min–max); 12 (2.3–32.1) vs 5.04 (1.1–10.8), p <0.001]. When the cutoff value of the vascularization index is determined as 6.3, Graves' disease can be diagnosed with 83.8% sensitivity and 70% specificity. **Conclusions:** The vascularization index obtained with color superb microvascular imaging can be a quantitative indicator of parenchymal vascularity in the diagnosis of Graves' disease, and serve as a supportive tool.

Introduction

Graves' disease (GD) is the most common cause of thyrotoxicosis and the second most common autoimmune thyroid disorder. It is characterized by the presence of circulating thyroid-stimulating hormone receptor autoantibodies responsible for hyperthyroidism. Ultimately, GD causes elevated serum free-thyroxine (fT4) and/or free-triiodothyronine (fT3) levels, and suppressed thyroid-stimulating hormone (TSH) levels. It usually affects middle-aged women[1–3].

Ultrasonography and Doppler ultrasonography are widely utilized techniques in the diagnosis and follow-up of diffuse thyroid diseases. Color and power Doppler US are well-known techniques to demonstrate the vascularity of tissues. While Doppler US techniques are cost-effective and useful noninvasive methods to evaluate tissue vascularization, they are inferior in the evaluation of small microvessels with a slow blood flow[4]. Also, artifacts related to motion (e.g. in pediatric patients, caused by breathing) can be an important limitation to using these techniques. Conventional Doppler US techniques utilize a wall filter to remove motion artifacts, resulting in a loss of low-velocity flow. On the other hand, the evaluation of tissue vascularization using these conventional Doppler US techniques remains a qualitative assessment[5–7].
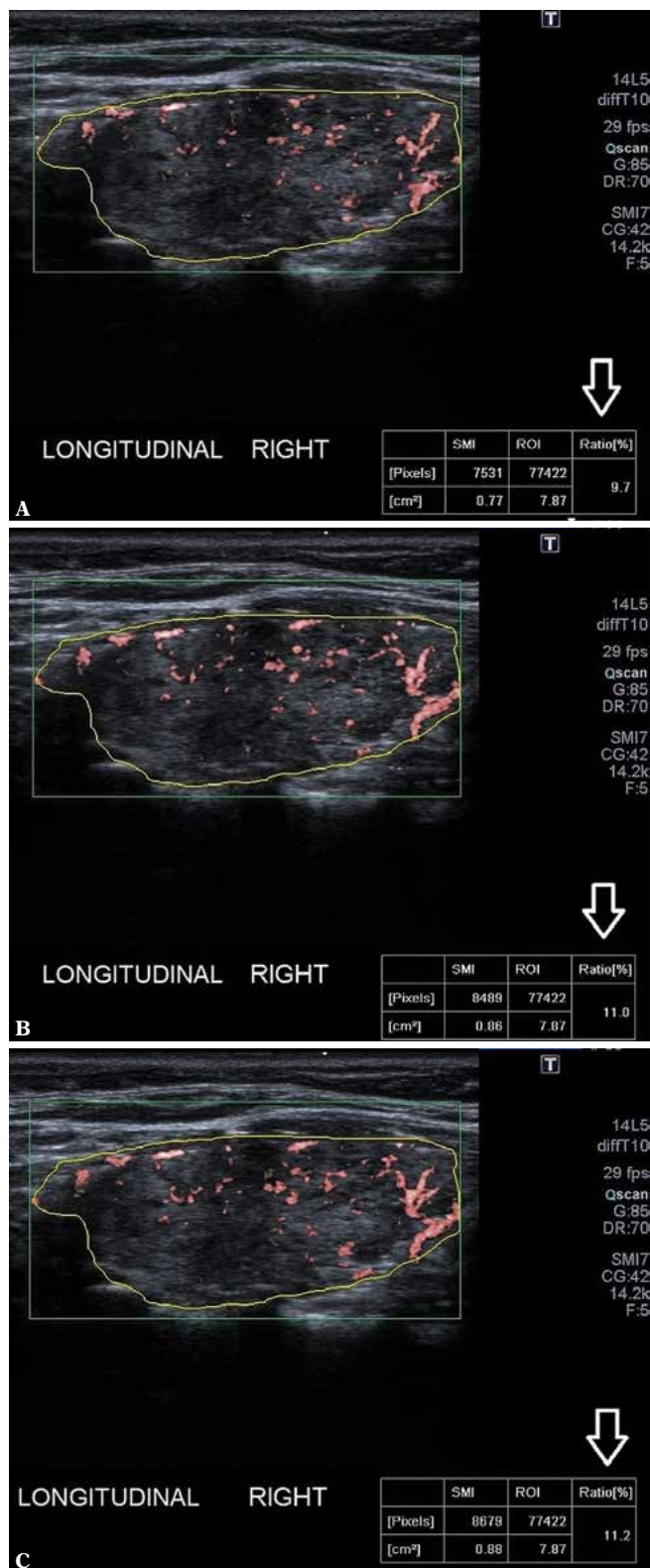
Fig. 1. *A 47-year-old female patient with GD. Quantitative VI values (arrows) were obtained by manually drawing the outer margin of the thyroid gland, on the cSMI mode in the largest longitudinal plane of the right lobe for 5 seconds and the mean of the highest three measurements was calculated. The mean VI value for the right lobe in the longitudinal plane was 10.6% ($\frac{9.7 + 11 + 11.2}{3}$)*

Superb microvascular imaging (SMI) is applied as a novel technique to assess tissue vascularization, with two types being available: monochrome SMI (mSMI) and color superb microvascular imaging (cSMI). The cSMI mode shows simultaneously the traditional grayscale US with color-encoded Doppler signals. The mSMI mode raises the visibility of vascular structures by eliminating the background signals[8,9]. Superb microvascular imaging technique can reduce motion artifacts and shows slow blood flow in microvessels[10,11]. The vascularization index (VI) is a quantitative parameter that can be obtained with cSMI. It indicates the ratio of blood flow within the tissue (a ratio of colored pixels to all of the pixels within the region of interest), and correspond to a percentage[12,13].

Our primary aims were to investigate the VI values of the thyroid parenchyma with cSMI in patients with GD, and compare them with the VI values of healthy participants. Additionally, we performed a correlation analysis between the VI values and laboratory and grayscale US parameters.

Material and methods

The present study was prospectively conducted at our institution between July and December 2019 after the approval of the local Research Ethics Committee. Written informed consent was taken from all of the study participants.

All of the subjects were consecutive patients treated at an endocrinology outpatient clinic, including both followed-up patients with the diagnosis of GD and newly diagnosed with GD. GD diagnosis was based on elevated thyroid hormone and autoantibody levels, and clinical evidence of thyrotoxicosis. After determining that the thyroid hormone levels were within normal limits, volunteer individuals were also referred for cSMI examination from the endocrinology outpatient clinic, so that they could be included in the control group. The exclusion criteria of the study were Hashimoto's thyroiditis, multinodular goiter, history of thyroid gland operation, or radioactive iodine treatment. All laboratory tests were done within one week before the cSMI examination. The normal reference ranges of the laboratory parameters were as follows: 2.3–4.4 pg/mL (fT3), 0.89–1.7 ng/dL (fT4), 0.56–5.5 mIU/L (TSH), 0–40 IU/mL (anti-thyroglobulin antibody; TgAbs), and 0–34 IU/mL (anti-thyroid peroxidase antibody; TPOAbs), 1.6–60 ng/mL Tg.

Color superb microvascular imaging technique

All the cSMI examinations in both groups were performed blindly by a radiologist with 14 years of experience in the US, and four years of experience in cSMI, using a 4–14 MHz linear probe (Toshiba Aplio 500, Canon Medical Systems Corporation, Tokyo, Japan). The longest three dimensions of each thyroid lobe were measured to calculate the volume. The total thyroid volume was calculated by summing up volumes of both thyroid lobes. Grayscale US images of the submandibular and thyroid glands were recorded to evaluate the echogenicity.
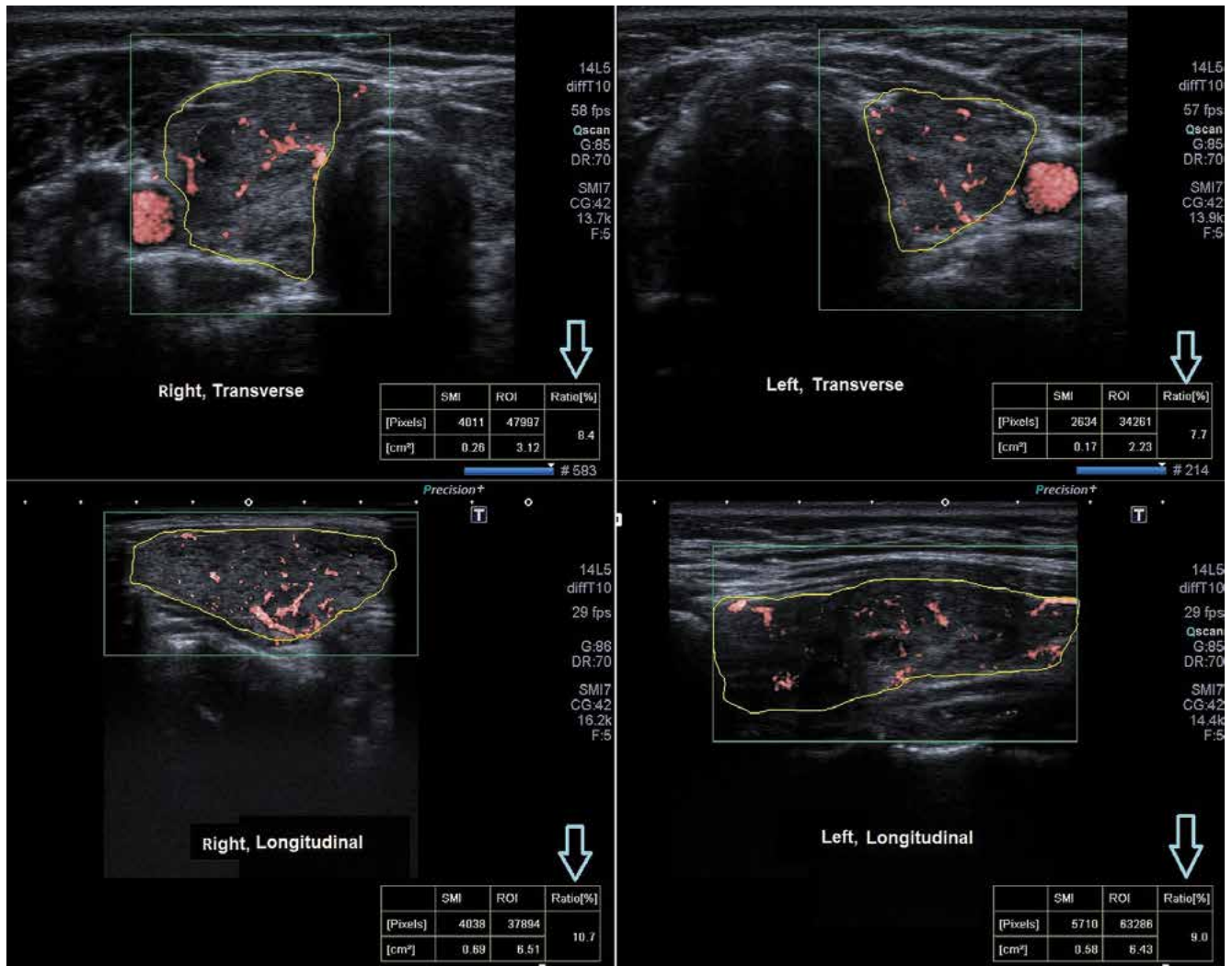
Fig. 2. *A 35-year-old female patient with GD. Quantitative VI values (arrows) were obtained by free ROI on the cSMI mode from both thyroid lobes in the transverse and longitudinal planes as demonstrated*

After the initial grayscale US evaluation, all subjects were examined with the cSMI technique using a pulse repetition frequency (PRF) set at 120–180 Hz. During the examination, the patients were asked to breathe normally. To measure the VI, the thyroid gland was examined in the cSMI mode for five seconds, after which the image was frozen. The VI measurements were performed on cSMI images with a free region of interest by manually drawing the margins of the whole thyroid gland. The highest three VI values were noted. Next, the average of the three measurements was calculated (Fig. 1). The VI measurements were performed by the same procedure separately for the right and left lobes on the longitudinal and transverse planes (Fig. 2).

The obtained images were transferred to our picture archiving communication system (PACS). The VI values of both lobes on the longitudinal plane were summed and divided into two to calculate a mean VI value for the longitudinal plane. Transverse plane mean VI values were calculated by the same procedure. In the next stage, the mean longitudinal and transverse plane VI values were summed and divided into two to calculate the VI of the whole gland.

Statistical analysis

The Kolmogorov-Smirnov test was used to determine the normal distribution of continuous variables. Categorical variables were expressed as raw numbers, and numeric variables were expressed as mean ± SD for normalized variables, and median (min–max) for non-normalized variables. Comparisons between the GD and control groups were performed using the Mann-Whitney U test for quantitative variables, and the Chi^2 test for qualitative variables, as appropriate. The VI values according to the lobe and measurement plane were compared with the Wilcoxon test. The Spearman correlation analysis was performed for the laboratory values and the VI values. The receiver operating characteristic (ROC) curve analysis was used to determine the best cutoff value to discriminate patients with GD. A *p* value of less than 0.05 was considered statistically significant. The statistical analysis was performed with the Statistical Package for Social Sciences version 23 (IBM, Armonk, New York) software.

Tab. 1. *Characteristics of study population**#*

Variables		Graves disease subgroups		Graves disease (*n*: 37)	Control group (*n*: 40)
		New diagnosis (*n*: 11)	Follow up (*n*: 26)		
Gender		2 M / 9 F	8 M / 18 F	10 M / 27 F	11 M / 29 F
Age (mean ± SD)		37.7 ± 8.7	41.4 ± 10.9	40.3 ± 10.3	40.9 ± 11.5
Isthmus thickness (mm)		4.4 (3–12)	4.2 (1.7–7.8)	4.4 (1.7–12)	3 (1.2–7.3)
Volumes	Right lobe volume (cm³)	12.4 (4.5–31.1)	9 (4.4–32.6)	10.3 (4.4–32.6)	5.8 (2.5–23.4)
	Left lobe volume (cm³)	11.1 (2.2–21.3)	7.3 (3–46.5)	8.5 (2.2–46.5)	5.6 (2.8–17.8)
	Total volume (cm³)	23 (6.7–50.8)	16.2 (7.4–79.1)	19.4 (6.7–79.1)	11.5 (5.3–31.2)
Hormone levels	TSH (mU/L)	0.01 (0.01–0.18)	1.07 (0.01–4.67)	0.12 (0.01–4.67)	2.24 (0.56–4.14)
	fT4 (ng/dL)	2.2 (0.88–7.47)	1.16 (0.89–3.04)	1.23 (0.88–7.47)	3.27 (2.67–4.1)
	fT3 (ng/L)	6.2 (2.76–28.1)	3.37 (2.59–11.2)	3.63 (2.59–28.1)	1.28 (0.9–1.69)
Autoantibodies	TPOAbs (IU/mL)	91.3 (11.7–600)	110 (10–600)	108.4 (10–600)	-
	TgAbs (IU/mL)	47 (21.6–591)	89.2 (10.9–1478)	78.6 (10.9–1478)	-

* While Graves disease and control groups were age and sex-matched groups, thyroid volumes and hormone levels were significantly different between both groups (*p* <0.01)
# Whilst TSH, fT3, and fT4 levels were significantly different between new diagnosis and follow up groups (*p* <0.01), all other provided parameters were similar between these two groups

Tab. 2. *Vascularization index (VI) measured with cSMI of patients with Graves disease and control group**#*

Vascularization index of	Measurement plane/lobe	Graves disease subgroups		Graves disease (*n*:37)	Control group (*n*:40)
		New diagnosis (*n*:11)	Follow up (*n*:26)		
Right lobe (R)	Transverse (T)	15.2 (2.5–30)	13 (2.9–41.2)	13.2 (2.5–41.2)	4.8 (0.7–10.1)
	Longitudinal (L)	13 (1.35–29.2)	11.6 (0.7–32.8)	11.8 (0.7–32.8)	5.8 (1.6–12)
	(T+L)/2	13.3 (3.1–29.6)	12.3 (3–35.05)	12.4 (3–35.05)	5.15 (1.75–9.65)
Left lobe (L)	Transverse	9.5 (4.6–25)	12.1 (1.5–29.1)	12.1 (1.5–29.1)	4.8 (0.8–10)
	Longitudinal	12.6 (4.9–31.3)	9.9 (1.7–29.4)	11.5 (1.7–31.3)	5.4 (0.3–15.6)
	(T+L)/2	11.4 (5.2–28.5)	11.2 (1.6–29.2)	11.4 (1.6–29.2)	5 (0.5–12.8)
Transverse	(R+L)/2	13.05 (4.6–27.5)	13.1 (2.95–35.1)	13.05 (2.95–35.1)	4.8 (0.75–10)
Longitudinal	(R+L)/2	11.2 (4.5–30.2)	12.2 (1.2–29.1)	11.95 (1.2–30.2)	5.05 (1.55–11.7)
Total thyroid	(R+L)/2	11.9 (4.7–28.9)	12.1 (2.3–32.1)	12 (2.3–32.1)	5.04 (1.1–10.8)

* All the VI values were significantly different between the control group and Graves disease, new diagnosis, follow up groups (*p* <0.001).
# All the VI values were similar between new diagnosis and follow up groups (*p* >0.05).
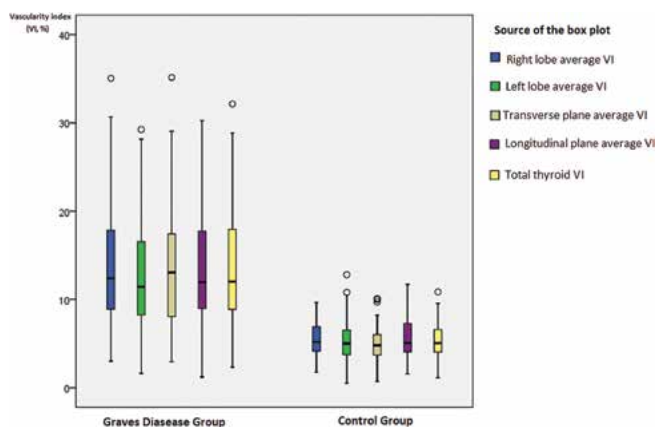
Fig. 3. *Box plot graphs of VI values in GD and control groups*

Results

The GD group included 37 patients (27 F, 10 M), and the control group consisted of 40 patients (29 F, 11 M). The two groups were age and sex-matched (*p* >0.05). The thyroid volume, hormone levels, and autoantibody values of the study population are listed in Tab. 1 for both groups with GD subgroups: new diagnosis (*n* = 11) and follow-up (*n* = 26). The median follow-up duration was 11 (range: 2–41) months. The followed-up patients with the diagnosis of GD used thyromazol tablets in different doses ranging from 2.5 mg to 40 mg.

The median of the thyroid volume values obtained in the GD group was significantly higher than those in the control group (*p* <0.01). While the TSH and fT4 values of the GD group were significantly lower from the control group's values, the fT3 values were significantly higher (*p* <0.01).

In the GD group, the VI values were significantly higher than in the control group (median values for total thyroid 12 vs 5.04, respectively; *p* <0.001) as shown in Tab. 2 and Fig. 3. On the other hand, all the VI values were similar between the new diagnosis and follow-up subgroups (*p* >0.05). Vascularization indices of the same participants were compared as dependent variables with the Wilcoxon test (Tab. 3). These further analyses found that the VIs of an individual showed no significant differences depending on the lobe (right vs left) or the measurement plane (transverse vs longitudinal).

Tab. 3. *Comparison of VI values of the study population according to the average values and measurement planes*

Comparison of VI values		P*
Right transverse	Right longitudinal	0.61
Left transverse	Left longitudinal	0.96
Right transverse	Left transverse	0.28
Right longitudinal	Left longitudinal	0.25
Right average	Total thyroid	0.14
Left average	Total thyroid	0.13
Right average	Left average	0.14
Transverse average	Longitudinal average	0.67
Transverse average	Total thyroid	0.6
Longitudinal average	Total thyroid	0.67
* Wilcoxon test		

Tab. 4. *Correlation analysis between total thyroid VI and laboratory values, isthmus thickness, and total thyroid volume*

Correlation analysis between		p	Spearman's rho
Total thyroid vascularization index (VI) and	TSH	0.001*	−0.426
	fT4	0.018*	−0.270
	fT3	0.001*	0.67
	TPOAbs	0.28	0.179
	TgAbs	0.36	−0.155
	İsthmus thickness	0.004*	0.327
	Total volume	0.001*	0.466
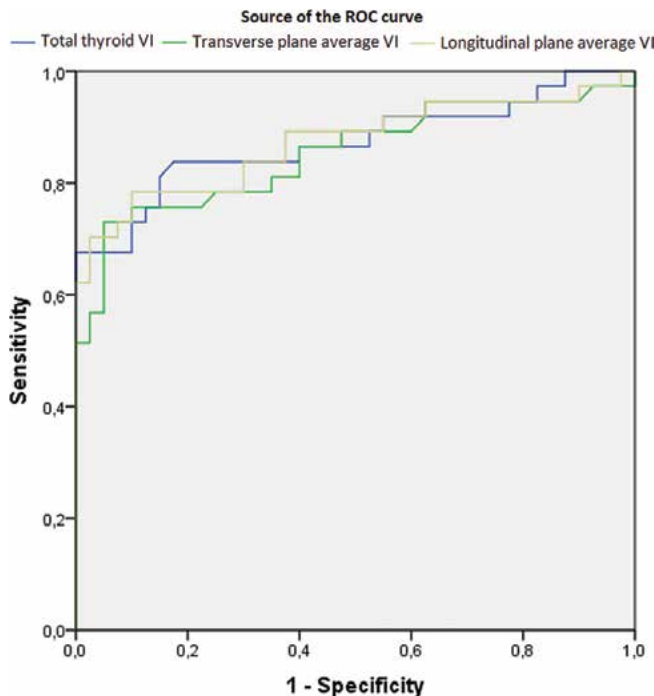
Fig. 4. *The ROC curves of VI values to discriminate patients with GD*

The Spearman correlation analysis between the total thyroid VI values and laboratory tests is listed in Tab. 4. While there was a negative correlation between the VI values and TSH, fT4 levels (*p* <0.05), positive correlations were found between the VI values and the fT3 level, isthmus thickness, and total thyroid volume (*p* <0.01). No significant

Tab. 5. *Median VI values of total thyroid according to the echogenicity of the thyroid parenchyma in the GD group. The echogenicity of the thyroid parenchyma was not correlated with VI values (p = 0.26)*

Echogenicity of thyroid parenchyma	GD group (*n*:37)	VI values of total thyroid Median (min–max)
Hyperechoic	7 (18.9%)	12.26 (5.7–32.1)
Isoechoic	20 (54.1%)	10.75 (2.3–22.8)
Hypoechoic	10 (27%)	16.77 (4.5–28.9)

correlation was revealed between the VI values and TgAbs, TPOAbs levels.

The echogenicity of the thyroid gland was compared with the echogenicity of the submandibular gland in patients with GD, and classified as either hypoechoic, isoechoic or hyperechoic. The echogenicity of the thyroid gland was not correlated with the VI values in the GD group (Tab. 5).

ROC curves of the VI values were obtained to discriminate patients with GD (Fig. 4). The cutoff values of the VI suggestive of GD are shown in Tab. 6 with appropriate sensitivity, specificity, AUC, and 95% confidence interval values. A cutoff value of 6.3 for the total thyroid VI was distinguishing GD patients with 83.8% sensitivity and 70% specificity.

Discussion

The cSMI technique can be a complementary tool in the diagnosis of GD, demonstrating the quantitative blood flow via the VI. A cutoff value of 6.3 for the total thyroid VI could discriminate GD patients with 83.8% sensitivity and 70% specificity. There was no significant difference between the VI values of different measurement planes (transverse vs longitudinal) and lobes (right vs left). According to these results, one can reliably reduce the duration of VI measurement by cSMI. Instead of obtaining a few measurements to calculate an average VI value for the whole thyroid gland, only one VI value obtained from the longitudinal or transverse plane of a single lobe may be utilized in the diagnosis of GD in the daily routine. Also, we showed that VIs were not significantly different between newly diagnosed patients and GD patients under follow-up. Furthermore, we reported the VI values of the thyroid gland in healthy subjects [median (min–max); 5.04 (1.1–10.8)].

Superb microvascular imaging technique can be utilized to evaluate the vascularity of various organs such as the testis, parotid gland, palatine tonsil, breast, liver, peripheral arteries, and lymph nodes beside the thyroid gland[5,8,9,14–19]. Although SMI is largely studied to assess the vascularization of the previously mentioned organs, the VI is utilized in a minority of these studies. In the literature, there are five papers evaluating thyroid gland vascularity based on the VI by cSMI[12,13,20–22]. Bayramoğlu *et al*.[20] studied the VI determined by cSMI in 70 pediatric patients with Hashimoto thyroiditis. The authors reported that the median VI of the thyroid gland was 7.95 (5.98–9.7) in asymptomatic volunteers, and 13.5 (8.7–18) in children with Hashimoto thyroiditis (*p* <0.001). Durmaz *et al*.[13] studied the VI

Tab. 6. *Best cutoff values according to the ROC analysis of VI values of the thyroid gland*

VI values	Cutoff value	Sensitivity, %	Specificity, %	AUC	95% Confidence interval	
					Lower bound	Upper bound
Transverse average	6.3	83.8	82.5	0.872	0.786	0.958
Longitudinal average	7.25	78.4	75	0.852	0.761	0.944
Total thyroid	6.3	83.8	70	0.872	0.785	0.958

measured by cSMI in children with Hashimoto thyroiditis. They reported a mean VI value of the thyroid gland of 12.45 ± 5.87 in the Hashimoto thyroiditis group, and 4.74 ± 1.96 in the control group (p <0.001). Bayramoğlu *et al.*[21] evaluated the VI by cSMI in pediatric patients with GD (n = 34) and Hashimoto thyroiditis (n = 37) in another study. Their results for median VI levels of the control, GD, and Hashimoto thyroiditis groups were given separately for the right and left lobes, and were equal to: 8 and 8; 11 and 13; and 25 and 26, respectively. Another study, reported by Adaletli *et al.*[22], utilized the VI determined by cSMI in pediatric patients with thyroid dyshormonogenesis. The reported median VI of the thyroid gland was 11 (6.5–46) in the thyroid dyshormonogenesis group, and 7.42 (3–10) in the control group (p = 0.008). Lastly, a recent study reported on the VI values of the thyroid gland in healthy children[12]. The common point of the above-listed studies using the VI determined by cSMI to quantitate the vascularization in diffuse thyroid diseases was that all of them were conducted in the pediatric age group. To the best of our knowledge, the present study is the first analysis which utilized the VI measured by cSMI in the assessment of thyroid vascularization in adult patients with diffuse thyroid disease. Other studies applying SMI to the thyroid gland in adults focused on thyroid nodules and malignancies[6,7,23–28].

The VI measurements by cSMI were different in the mentioned studies. Bayramoğlu *et al.* obtained their VI measurements from the upper, middle, and inferior sections of both lobes at the transverse plane[20]. In two studies, the measurement of the transverse plane VI included both lobes as well as the isthmus[12,13]. Our measurement technique is different, as described in the methodology (selecting the largest area in the longitudinal and transverse planes for each lobe). Although the VI measurements in the longitudinal plane were the same in the present study and in the report by Durmaz *et al.*, we did not assess the vascularity of the isthmus. Also, the selected PRF values can alter the VI values. While the PRF values were set at 120-180 Hz in our study, in previous studies the PRF values were 150-180 Hz[13,20,21]. Researchers should pay attention to the PRF value because it can automatically change with the size of the cSMI window.

Whilst no significant correlation was revealed between the VI and autoantibody levels in our study, Bayramoglu *et al.* reported a positive correlation between them[20]. We found a negative correlation between the VI and fT4, TSH. However, a positive correlation was revealed between the VI and fT3 levels. We also showed positive correlations between the VI values and isthmus thickness, total thyroid volume. Additionally, no significant correlation was identified between the echogenicity of the thyroid gland and the VI values in the present study. Durmaz *et al.* reported a negative correlation between the VI and echogenicity of the thyroid in children with Hashimoto thyroiditis[13].

The present study has some limitations. First of all, the study population is relatively small. The diagnosis of GD was based on laboratory parameters and clinical findings instead of tissue sampling. We did not compare SMI and conventional Doppler US techniques to evaluate the vascularization of the thyroid gland. Autoantibody levels were not measured in the asymptomatic group. However, the grayscale US evaluation of the thyroid parenchyma was normal in the participants with normal thyroid hormone levels. As a final limitation, the evaluation of the parenchymal echogenicity of the thyroid gland by comparison with the submandibular gland echogenicity could be influenced by diseases of the salivary gland.

Conclusions

As a conclusion, patients with GD had quantitatively higher VI values than the control group. Utilizing cSMI can be a promising non-invasive diagnostic tool with high sensitivity and specificity rates to identify patients with GD.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organizations which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

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