Ultrasonographic Detective Flow Imaging for Evaluating Parathyroid Adenoma in Patients with Primary Hyperparathyroidism

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Background: Detective flow imaging (DFI) is a new imaging technology that displays low-velocity blood flow, which is difficult to visualize on conventional color Doppler ultrasonography (CDU). In this study, we compared the usefulness of DFI with that of CDU and methoxy-isobutyl-isonitrile (MIBI) scintigraphy for detecting parathyroid adenoma (PA) in patients with primary hyperparathyroidism (PHPT).

Methods: From March 2021 to March 2023, 87 PHPT patients underwent surgery, and 66 had a single PA. We performed preoperative conventional ultrasonography with CDU, MIBI scintigraphy, and DFI for 42 patients (5 males and 37 females; mean age: 61.6 ± 15.4 years).

Results: MIBI scintigraphy detected PA in 85.7% (36/42) patients, and both CDU and DFI detected PA in all patients. The rates of vascularity in PA detected by CDU and DFI were 71.4% (30/42) and 85.7% (36/42), respectively. Vascularity was detected by DFI in 6 patients who were negative for vascularity on MIBI scintigraphy. Furthermore, DFI detected blood supply in 6 of the 12 patients with undetectable blood supply on CDU. Fisher's exact test revealed that high or low blood flow, as determined by DFI, was significantly associated with detection of feeding vessels in PA by CDU (P < 0.001).

Conclusions: DFI was useful for preoperative detection of PA blood flow.

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Key words: detective flow imaging, parathyroid adenoma, color doppler ultrasonography, superb microvascular imaging, primary hyperparathyroidism

Introduction

Detective flow imaging (DFI) is a new Doppler ultrasonographic imaging technology. Imaging low-velocity blood flow has been difficult, but a new proprietary algorithm allows detailed visualization with greater resolution and sensitivity. Blood flow imaging is advantageous because it can be evaluated without using ultrasonographic contrast-enhancement agents. The ultrasonographic inspection device we use is convenient because it has a DFI mode that is easily accessed by pressing a button. However, only two studies of DFI have been reported: 1 on its use in pancreatic endoscopy¹ and our previous case report on imaging of a parathyroid tumor (PT)². The parathyroid glands, which are responsible for calcium homeostasis through synthesis and release of parathyroid hormone (PTH), are 4 small endocrine glands located in the neck behind the thyroid. Primary hyperparathyroidism (PHPT) is a pathological idiopathic condition that results from persistent PTH hypersecretion independent from serum calcium levels, and is caused by a parathyroid adenoma (PA) (mostly a single adenoma) and multiple hyperplastic parathyroids in approximately

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Fig. 1 Flowchart of patient selection The preoperative diagnosis was primary hyperparathyroidism for all patients. All patients underwent preoperative MIBI scintigraphy, ultrasonographic imaging, and DFI. All postoperative pathological diagnoses of the patients indicated a single PA.

PHPT: primary hyperparathyroidism, MIBI: methoxy-isobutyl-isonitrile scintigraphy, PA: parathyroid adenoma, DFI: detective flow imaging

85% and 15% of cases, respectively. Parathyroid carcinoma is an additional, infrequent cause of PHPT³⁴. When patients are diagnosed with PHPT, an important next step is to detect and localize PT. This study compared the usefulness of DFI with that of conventional modalities, i.e., ultrasonography and methoxy-isobutyl-isonitrile (MIBI) scintigraphy, for preoperative evaluation of PHPT.

Patients and Methods

Patients

In this study, we retrospectively reviewed the ultrasonographic features of PTs in patients who underwent ultrasonography, including DFI, before surgery. Eightyseven patients underwent surgery for PHPT at Nippon Medical School hospital between March 2021 and March 2023. Data from 42 of these patients were analyzed in this study. For these patients the preoperative diagnosis was PHPT; MIBI scintigraphy, ultrasonography, and DFI were all performed preoperatively; and the postoperative pathological diagnosis was a single adenoma (**Fig. 1**). This retrospective study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki, and informed consent was obtained from all patients. The Ethics Committee of Nippon Medical School approved this study (approval no. M-2023-104). All data were analyzed anonymously.

Data Collection

Data on the following variables were obtained from the participants' medical records: age, sex, biochemical data (serum levels of calcium, albumin, and intact PTH), imaging findings (CT images, MIBI scintigraphy, and ultrasonographic findings), and pathological reports.

Ultrasonographic Examination

To evaluate PA preoperatively, ultrasonography was performed on an ARIETTA 750VE device (FUJIFILM Healthcare Corporation, Tokyo, Japan) with an L64 linear probe (5-18 MHz), and DFI data were also obtained. All ultrasonography was performed by a well-trained medical doctor (MM) under the supervision of a boardcertified fellow and senior fellow of thyroidology of the Japan Society of Ultrasonics in Medicine (TJ). Each patient was placed in the supine position with the neck hyperextended, after which transverse and longitudinal views were recorded.

DFI vascularization of PA was classified into 4 grade levels by using the Adler standard level^{5,6}(Fig. 2), as follows: DFI Grade 0, no blood flow in the tumor; DFI Grade 1, a small amount of blood flow, only a few spots of blood flow, or 1 vessel penetrating the nodule (less than half the maximum tumor diameter) in the tumor; and DFI Grade 3, abundant blood flow inside the tumor; with \geq 5 punctate blood flows or 2 long vessels in the tumor. DFI Grade 2 was defined as vascularization between DFI Grade 1 and DFI Grade 3. We then classified DFI vascularization into 2 groups: no or poor blood flow (DFI Grades 0 and 1) and high blood flow (DFI Grades 2 and 3).

Statistical Analysis

The chi-square test and Fisher's exact test were used to analyze categorical variables, and the Mann-Whitney U test was used to analyze continuous variables. A P value of < 0.05 was considered to indicate statistical significance. All statistical analyses were performed in EZR, a modified version of R software (version 1.53; R Foundation for Statistical Computing, Vienna, Austria) with additional biostatistical functions⁷.

Results

The characteristics of the study participants (42 cases) are





(A) DFI Grade 1 with no blood flow by CDU. The insert shows an enlarged image in the bottom left of the DFI image. The arrowhead indicates a small spot of blood flow. Both patients with (B) DFI Grade 2 and (C) DFI Grade 3 exhibited higher blood flow on DFI than on CDU. CDU: color Doppler ultrasonography, DFI: detective flow imaging

summarized in **Table 1**. The number of right-lower, right-upper, left-lower, and left-upper PA locations in these patients were 13, 4, 12, and 13, respectively. Serum calcium levels and intact-PTH values were high, averaging $11.4 \pm 1.0 \text{ mg/mL}$ and $208.0 \pm 176.5 \text{ pg/mL}$, respectively. Preoperative ultrasonographic evaluation showed PA in all patients except for 1 with suspected parathyroid carcinoma. The average tumor size was $17.8 \pm 8.8 \text{ mm}$. All patients were diagnosed with PA by postoperative pathological examination. CT scans of the neck were performed in 17 of the 42 cases, and PT was detected in 64.7% (11/17). MIBI scintigraphy showed MIBI uptake in 85.7% (36/42) of the patients. Ultrasonography, MIBI scintigraphy, and DFI examinations of the patients were performed retrospectively. No ectopic PA was observed.

In all patients, preoperative B-mode ultrasonography identified PA, including in 6 patients who had no detectable blood flow on color Doppler ultrasonography (CDU) and DFI. In the B-mode ultrasonography, 3 patients had irregular tumor shapes and 39 patients had regular tumor shapes. All but 1 patient had rough borders. On internal echo, 22 patients had hypo-, 13 had iso-, and 7 had iso-echoic solid masses. A hyperechoic line on the ventral surface was observed in 16 patients. All patients were examined by CDU, and blood supply from feeding vessels was observed in 71.4% (30/42). DFI was performed in all patients, and the Adler modification grade was 0, 1, 2, and 3 in 6, 18, 7, and 11 patients, respectively (**Fig. 3**). In other words, vascularity in PA was detected by DFI in 85.7% (36/42) of the patients. Of the 12 cases with unde-

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Characteristics	All n=42	DFI Grade 0/1 n=24	DFI Grade 2/3 n=18	P value
Age at surgery, years	61.6±15.4	59.6±17.5	64.4±11.5	0.56
Sex (male/female)	(5/37)	(4/20)	(1 /17)	0.37
Location				
(Rt,L/Rt,U/Lt,L/Lt,U)	(13/4/12/13)	(7/3/6/8)	(6/1/6/5)	0.72
Laboratory data				
Ca (mg/mL)	11.4±1.0	11.2±0.2	11.6±1.0	0.09
Alb (g/dL)	4.4±0.2	4.4±0.2	$4.4{\pm}0.2$	0.78
i-PTH (pg/mL)	208±176.5	180.6 ± 142.8	244.6±207.8	0.10
CT findings (UD/D)	(6/11)	(5/7)	(1/4)	0.60
MIBI scintigraphy findings (UD/D)	(6/36)	(3/21)	(3/15)	1.00
Ultrasonography findings (UD/D)	(0/42)	(0/24)	(0/18)	1.00
Shape (regular/irregular)	(39/3)	(24/0)	(15/3)	0.07
Border (smooth/rough)	(41/1)	(24/0)	(17/1)	0.43
Internal echo (hypo/hypo~iso/iso)	(22/13/7)	(16/5/3)	(6/8/4)	0.11
Hyperechoic line (UD/D)	(26/16)	(14/10)	(12/6)	0.75
Feeding vessels (UD/D)	(12/30)	(12/12)	(0/18)	< 0.001
Tumor size (mm)	17.8±8.8	16.8±8.0	19.2±9.6	0.52

Table 1 Characteristics of the study participants

Rt,L: right lower, Rt,U: right upper, Lt,L: left lower, Lt,U: left upper, Ca: calcium, Alb: albumin, i-PTH: intact parathyroid hormone, CT: computed tomography, MIBI: methoxyisobutylisonitrile, D: detectable, UD: undetectable, DFI: detective flow imaging

tectable vascularity on CDU, vascularity was detectable by DFI in 6. Of these 6 cases with undetectable vascularity by MIBI scintigraphy, vascularity was also undetectable by CDU in 2 but detectable by DFI in all cases.

Fisher's exact test revealed that high or low blood flow on DFI was significantly associated with detection by CDU of feeding vessels in PA (P < 0.001). In all patients, the operation method was parathyroidectomy, and partial thyroidectomy was added for 2 patients with coexisting thyroid benign tumors.

Discussion

To localize PT, we often perform MIBI scintigraphy imaging and B-mode ultrasonography with blood flow evaluation by CDU. In this study, we showed that in 6 cases DFI was able to detect PAs that MIBI scintigraphy failed to detect. This finding demonstrates the usefulness of DFI for evaluating preoperative PT.

A hyperechoic line between the parathyroid and thyroid glands represents the very thin capsules of these glands. This hyperechoic line is histologically produced by reflection of ultrasound waves in the layer between the parathyroid gland and thyroid tissue. Therefore, detection of hypertrophic lines is important in the ultrasonographic diagnosis of PT. Yabuta *et al.*⁸ studied 50 patients with normally located PA and reported detection of a hyperechoic line and feeding vessels in 74% and 70%, respectively. Among our cases, a hyperechoic line was detected in 38.1% (16/42) of patients, and feeding vessels were detected in 71.4% (30/42). The rates of detection of hyperechoic lines differed between the 2 studies but showed a trend similar to that for the feeding vessels. The difference in the proportions of patients with hyperechoic lines may be attributable to differences in the characteristics of the ultrasonography procedure.

CDU is often performed to show blood flow inside tumors but is disadvantageous for some slow-flowing microvessels9. Furthermore, CDU is not sufficiently sensitive to detect small vessels and slow blood flow¹⁰. The usefulness of CDU for detecting PA has been frequently studied, but it has been difficult to detect feeding vessels in small PAs^{11,12}. A comparison of DFI and CDU for preoperative assessment of PA blood flow showed that the detection rate was higher for DFI than for CDU (85.7% vs. 71.4%). This difference indicates that blood flow at lower speeds was better evaluated by DFI than by CDU. Furthermore, Fisher's exact test revealed that the presence of high or low blood flow, as determined by DFI, was significantly associated with detection of feeding vessels in PA by CDU (P < 0.001). The finding that DFI detected PA in 6 of 12 patients with undetectable PA on CDU indicates that DFI is advantageous because it can detect slow blood flows.

Superb microvascular imaging (SMI) (Canon Medical



Fig. 3	Correlation between the results for CDU and DFI.
CDU fai	led to detect blood flow in the 6 patients classified
as DFI C	Grade 1 (box with bold lines).

CDU: color Doppler ultrasonography, DFI: detective flow imaging

Systems Corporation, Tochigi, Japan), which has functions similar to those of DFI, became available earlier than DFI and has been studied in persons with thyroid and breast cancer¹³⁻²³. Zhu *et al.*¹³ conducted a metaanalysis using the combination of SMI and a Thyroid Imaging Reporting & Data System (TI-RADS), which is a guideline created to help develop a reporting system that stratifies the risk of thyroid nodules on the basis of ultrasonographic findings and recommends appropriate management. The meta-analysis included 496 benign and 408 malignant thyroid nodules and suggested that the combination of TI-RADS and SMI resulted in high diagnostic accuracy and was more effective than TI-RADS alone in distinguishing benign from malignant thyroid nodules.

Regarding DFI, Yamashita *et al.*¹ described a new method, named DFI-endoscopic ultrasonography (EUS), to image and detect fine vessels and low-velocity blood

flow without using ultrasonographic contrast agents. DFI-EUS is a novel EUS imaging technique for visualizing microcirculation in pancreatobiliary lesions. Therefore, quantitative analysis of vessels in tumors by DFI-EUS may be useful for differential diagnosis of pancreatic tumors. Similarly, quantitative analysis of vessels in tumors by DFI may be useful for differential diagnosis of PT. We previously described the utility of DFI in diagnosing PT in 2 patients². In 1 patient, PA and a parathyroid cyst were in close proximity. The other case was parathyroid carcinoma. Thus, it is probable that DFI also helps differentiate between adenoma and carcinoma. However, there have been no reports of PT diagnosis by SMI so far.

Limitations

This study had limitations that should be considered when interpreting the results. First, it was a retrospective study with a small sample size. Therefore, additional prospective studies are needed in order to obtain more objective evidence for clinical use. Second, only patients scheduled for surgery were included in this study, and DFI was not performed for all surgical cases of single PA.

Conclusion

Our results suggest that DFI is useful and advantageous for preoperative evaluation of PTs.

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Conflict of Interest: The authors declare no conflicts of interest.

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