TITLE :

An initial trial of quantitative evaluation of autoimmune pancreatitis using shear wave elastography and shear wave dispersion in transabdominal ultrasound

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SHORT TITLE:

SWE and SWD measurement in AIP

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ABSTRACT

Background/Objectives: We aimed to examine therapeutic efficacy and prognosis prediction of autoimmune pancreatitis (AIP) using shear wave elastography (SWE) and shear wave dispersion (SWD) in transabdominal ultrasound (US).

Methods: The subjects were 23 patients with diffuse type 1 AIP who underwent SWE and SWD, and 34 controls with a normal pancreas. Elasticity and dispersion were defined as the pancreatic elastic modulus (PEM) and dispersion slope, respectively. PEM and dispersion slope were compared between AIP and control cases, and the short-term therapeutic effect and long-term prognosis were examined.

Results: PEM (30.9 vs. 6.6 kPa, $P<0.001$) and dispersion slope (15.3 vs. 13.0 (m/sec)/kHz, $P=0.011$) were significantly higher in AIP cases than in controls. Among the 17 AIP patients followed-up in two weeks after treatment, these parameters were 12.7 kPa and 10.5 (m/sec)/kHz with median decrease rate of 37.2% and 32.8%, respectively, which were significantly higher than the change in the size of pancreatic parenchyma (14.4%, $P=0.026$). Fourteen of these subjects were followed up for >12 months, during which 2 had relapse; diabetes improved in 5 and worsened in 2; in 60% of cases, the pancreatic parenchyma was atrophied. The % change in PEM after two weeks was tended to be higher in non-atrophy cases.

Conclusion: SWE and SWD measurement in US may be useful for quantitative assessment of AIP and evaluation of short-term treatment efficacy.

INTRODUCTION

Autoimmune pancreatitis (AIP) is pathologically characterized by inflammatory cell infiltration and fibrogenesis, and responds well to steroids [1]. EUS-FNA, CT and MRI are generally used and proposed as the useful diagnostic tools for AIP in the Japanese Clinical Diagnostic Criteria for Autoimmune Pancreatitis 2018 (JPS2018) [2]. However, the use of transabdominal ultrasound (US), which could be a noninvasive and simple examination method for AIP, is not described in JPS2018 and there is no report of quantitative evaluation of AIP using US.

Ultrasound shear wave elastography (SWE) is widely used for diagnosis of tissue stiffness, including for gastrointestinal disorders [3, 4]. SWE assessment is also useful for diagnosis of hepatic tissue stiffness of diffuse liver diseases, including chronic hepatitis, nonalcoholic steatohepatitis (NASH) and liver cirrhosis [5, 6]. The usefulness of SWE as an assessment of fibrosis has also been reported in the pancreas [7, 8]. However, the effectiveness of SWE for assessment of AIP, a diffuse pancreatic disease, has not been examined.

Recently, ultrasound shear wave dispersion (SWD), which is a measure of viscosity using SWE, has become available. In the liver, SWD reflects inflammation and necrosis [9] and clinical application of SWD has been reported [10, 11]. SWD may also reflect fatty changes in normal pancreatic parenchyma [12]. In this study, the primary endpoint was to examine the therapeutic efficacy of steroids and prognosis prediction in subjects with AIP using SWE and SWD of pancreatic parenchyma, and the secondary endpoint was to compare SWE and SWD between AIP cases and controls with normal pancreatic parenchyma.

PATIENTS AND METHODS

The subjects were patients aged ≥20 years who were diagnosed with diffuse type 1 AIP in accordance with the International Consensus Diagnostic Criteria [13] from November 2017 to June 2020, gave consent for the study, and underwent SWE and SWD evaluation using Aplio i900 ultrasound system (Canon Medical Systems Corp.) before steroid treatment. All examinations were performed by one gastroenterologist (SH), who has experience with more than 3,000 transabdominal ultrasounds and is a regular member of the Japanese Society of Ultrasound Medicine. Consecutive control cases with a normal pancreas in which SWE and SWD measurements were performed by SH using the Aplio i900 in the same time period were used for comparison. A normal pancreas was defined as having neither a tumor nor cystic lesion in endoscopic ultrasonography (EUS), contrast-enhanced CT, MRI and US images, no history of diagnosis of pancreatic disease, and no hyperechoic pancreas in US.

This study (registered as UMIN000016497) was conducted after approval from the Ethics Review Committee of Nagoya University Hospital (approval number 2014-0399). Written informed consent was obtained from all subjects after they received a full explanation of the study.

The pancreas was visualized in B-mode imaging and a measurement region-of-interest (ROI) was established in the pancreatic body to avoid blood vessels and the main pancreatic duct, and maximize the pancreatic parenchyma. After establishing the measurement ROI, SWE and SWD measurements were performed at least 5 times. SWE within the measurement ROI was visualized with propagation view and SWD was displayed with color mapping view. The calculation ROI was established to maximize parallel parts with

propagation expression in the measurement ROI (Fig. 1). Measurements were repeated a maximum of 10 times, and if a parallel region was acquired less than five times, the case was regarded as non-evaluable. The median elasticity and dispersion were defined as the pancreatic elastic modulus (PEM) and dispersion slope, respectively.

Phase 1: Comparison of the PEM and dispersion slope with AIP and a normal pancreas

Phase 1 of the study was a comparison of background factors in subjects with AIP and controls with a normal pancreas. The PEM and dispersion slope before treatment for AIP were also compared with these values for a normal pancreas. Background factors included serum IgG and IgG4, diabetes, size of pancreatic parenchyma, and other organ involvement (OOI) at diagnosis. The size of pancreatic parenchyma was determined by measuring the short axis of the pancreatic body using CT. A patient with hemoglobin A1c >6.5% at diagnosis was defined as having diabetes [14].

Phase 2: Assessment of short-term therapeutic effect using SWE and SWD measurement

The short-term therapeutic effect**s** of steroids were evaluated in subjects who underwent SWE and SWD measurement two weeks after the start of steroid treatment. PEM, dispersion slope, size of pancreatic parenchyma, and serum IgG4 were compared with those before treatment, and % changes in these parameters were calculated as (value before treatment – value after treatment)/value before treatment ×100.

Phase 3: Relationship of short-term therapeutic effects with long-term prognosis

The relationships of short-term therapeutic effects with the long-term prognosis were examined. Subjects who had PEM and dispersion slope measurements at two weeks after the start of steroid treatment and were

followed up for >12 months were included in this phase. The relationships of relapse, pancreatic endocrine insufficiency and pancreatic atrophy with PEM and dispersion slope before the start of treatment and % changes in PEM and dispersion slope at 2 weeks after the start of treatment were examined. Relapse was defined as pancreatic enlargement in images or appearance/reappearance of OOI [15]. Diabetes was evaluated as an assessment of pancreatic endocrine insufficiency [16]. Subjects who were receiving insulin or oral antidiabetic agents after steroid treatment at lower or higher doses were defined as having improvement or worsening of diabetes [17]. Pancreatic atrophy was examined in subjects who underwent CT after 12 months of steroid treatment. Subjects with relapse were excluded from this evaluation. The pancreatic parenchyma was measured in CT images and a pancreas with a short-axis diameter of <10 mm was defined as showing atrophy [17].

Statistical Analysis

SPSS (ver.27, SPSS Inc.) was used for statistical analysis. A nonparametric test (Mann-Whitney U test) was used to compare continuous variables and a Fisher exact test was used to examine differences in ratios between two groups. For comparison between paired groups, a Wilcoxon signed rank test was used. A Kruskal-Wallis test was used to examine differences in ratios between three groups. The significance level was set at 0.05. A Spearman rank correlation coefficient (r) was used to examine correlations between indices, and the results are shown as weak (<0.2), mild (0.2 to <0.4), moderate (0.4 to <0.7) and strong (≥0.7).

RESULTS

The subjects were 23 patients (16 men, 7 women) who were diagnosed with diffuse type 1 AIP in our hospital. In all cases, the pancreatic body could be clearly visualized in B-mode imaging, and SWD and SWE could be measured. The background of the patients is shown in Table 1. The median age was 67 (interquartile range [IQR], 11) years. The median serum IgG and IgG4 at diagnosis were 1696 (IQR, 592) mg/dL and 301 (IQR, 357) mg/dL, respectively. Twelve subjects had diabetes. The median size of pancreatic parenchyma was 22.4 (IQR, 9.0) mm. OOI was present in 7 subjects.

Phase 1: Comparison of the PEM and dispersion slope with AIP and a normal pancreas

A total of 34 control subjects with a normal pancreas underwent SWE/SWD during the study period. The rate of diabetes was significantly lower in the controls compared to the AIP patients ($P<0.001$) (Table 1). The AIP patients had a significantly higher PEM (30.9 (IQR, 15.2) vs. 6.6 (IQR, 2.3) kPa, $P<0.001$) and dispersion slope (15.3 (IQR, 4.2) vs. 13.0 (IQR, 3.4) (m/sec)/kHz), $P=0.011$) compared to controls (Table 1). The relationships of PEM and dispersion slope with serum IgG, IgG4 and size of pancreatic parenchyma at diagnosis in the subjects with AIP are shown in Table 2. A negative correlation was found between PEM and serum IgG. There was no other significant correlation with these parameters or with the rates of diabetes and OOI at diagnosis.

Phase 2: Assessment of short-term therapeutic effect using SWE and SWD

Two weeks after steroid treatment, 17 subjects were evaluated by SWE and SWD. At this time, PEM was

12.7 (IQR, 8.5) kPa and the dispersion slope was 10.5 (IQR, 3.1) (m/sec)/kHz, and both were significantly lower than the values before treatment (both $P<0.001$) (Fig. 2). The median % changes in PEM, dispersion slope and size of pancreatic parenchyma were 37.2%, 32.8% and 14.4%, respectively. The changes in PEM and dispersion slope were significantly higher than the change in the size of pancreatic parenchyma ($P=0.026$) (Fig. 3). The median serum IgG4 after 2 weeks steroid treatment was 217 mg/dL (IQR:169), which was significantly lower than the values before treatment ($P<0.001$). There was no correlation between PEM and dispersion slope after 2 weeks treatment and serum IgG4 after 2 weeks steroid treatment ($P=0.996$, $P=0.807$).

Phase 3: Relationship of short-term therapeutic effects with long-term prognosis

Of the 17 subjects with measurements of PEM and dispersion slope at 2 weeks after the start of treatment, 14 were followed up for >12 months. Of these 14 subjects, 7 had diabetes at diagnosis and 10 underwent CT 12 months later. The median follow-up period was 17.5 (IQR, 10) months. Relapse occurred in 2 (14.2%) subjects. Of the 7 subjects with diabetes at diagnosis, 5 improved and 2 worsened. Due to the small number of cases, statistical analysis was not performed, but there was no specific trend in PEM, dispersion slope, or % change in these parameters between these two groups. Pancreatic parenchyma was atrophied in 6 of the 10 subjects who underwent CT, and the % changes in PEM after 2 weeks of treatment tended to be higher (71.5%) in non-atrophy cases (Table 3).

DISCUSSION

SWE measurement in the gastrointestinal field is commonly used in practice and its efficacy has been shown in many reports. There are many studies of SWE in patients with chronic pancreatitis, but few reports of its use in AIP [8]. In this study, both SWE and SWD were examined. Our previous study suggested that SWD reflected fatty changes in the normal pancreas [12]. In the current study, we found that the dispersion slope in patients with AIP, which involves inflammation and fibrogenesis, was higher than that in a normal pancreas. This suggests that the dispersion slope in patients with AIP reflects inflammation, similarly to liver disease.

SWD measurement using SWE is a novel technique of elastography and there is currently no definition of SWD measurement in the liver field [10]. Sugimoto et al. recommended 10 measurements, similarly to SWE, for diffuse liver disease [10]. The reproducibilities of SWE [7] and SWD [12] in the pancreas have been shown to be high over 5 measurements in our previous studies, and at least 5 measurements were performed in the present study bases on these reports. In addition, it is recommended to use the IQR/median to improve the accuracy of SWE measurements [6]. The IQR/median of dispersion slope for normal pancreatic parenchyma in our previous study was 0.28, which indicates that our assessment of pancreas by SWD was valid [12].

Contrast-enhanced US is useful for discrimination of pancreatic cancer and AIP, and for evaluation of the efficacy of steroid treatment [18, 19]. The EFSUMB Guidelines and Recommendations do not describe SWE, but suggest EUS-elastography (EUS-EG) to be useful for AIP evaluation by showing ubiquitously high hardness [20]. In another study investigating EUS-shear wave measurement (EUS-SWM) for pancreas, the median shear wave velocity of 2.57 m/s in AIP cases was significantly higher than that of 1.89 m/s in normal controls [21]. In a comparison of AIP before and after treatment based on the strain ratio (SR) using EUS-EG, another study

investigating SR was shown after 2 weeks of treatment in all 10 patients evaluated [14]. Since the SR cut-off in EUS-EG varies among studies, evaluation before and after treatment in the same patient may be most appropriate.[14]

This study is the first attempt to evaluate AIP quantitatively using SWE and SWD in US. The results showed that PEM was higher in AIP than in the normal pancreas, similarly to the finding in our previous study using EUS-SWM. Since recent studies suggested that some of the patients with AIP developed into chronic pancreatitis [22-24], it may be favorable to include the patients with conventional chronic pancreatitis as disease controls. However, although we have attempted to evaluate SWD and SWE for the patients with chronic pancreatitis since we introduced SWD in our facility, we were not able to obtain reliable values in these patients because the ROI could not be set to include the sufficient area for measurement due to atrophy and calcification of the pancreatic parenchyma. Therefore, in this study, only a normal pancreas was used as a disease control, which can include the measurement area sufficiently within the ROI to obtain reliable values. This study is also the first trial of comparison of SWE and SWD before and after treatment in the same patients. Similarly to the findings in Ohno et al. and Ishikawa et al [14, 21], PEM at 2 weeks after treatment was significantly lower than that before treatment, indicating an improvement. The dispersion slope after treatment was also significantly lower than that before treatment. These findings suggest that SWE and SWD measurements may be useful for objective evaluation of the disease status before and after treatment.

The only correlation of PEM and dispersion slope with patient background factors was with serum IgG. There was no correlation between PEM or dispersion slope and serum IgG4. Moreover, there was no correlation

between these parameters after 2 weeks of steroid treatment. Therefore, it may be difficult to use PEM and the dispersion slope as absolute values for assessment of AIP activity, but these parameters may be effective for evaluation in the same patient. Ishikawa et al. showed that SR decreased in all 10 patients, and 2 of 10 patients showed a decrease in SR before radiological improvement of pancreatic enlargement on CT, which suggested that elastic changes may occur earlier than morphological changes in AIP [14]. Changes of PEM and dispersion slope 2 weeks after the start of treatment were also significantly higher than the change in the size of pancreatic parenchyma in the current study. This suggests that viscoelastic changes in AIP were larger than imaging changes over a short period after treatment. SWE and SWD measurement in US is simple and less invasive in comparison with other modalities, including CT and MRI, and have an advantage of repeated use during a short period. Thus, SWE and SWD measurement in US is likely to be useful for prediction of the early therapeutic effect on AIP.

Relapse is the major concern in clinical practice for AIP [25]. The short-term prognosis of type 1 AIP is improved by steroid treatment, but the long-term prognosis remains to be clarified [26, 27]. The relapse rate has been reported to be up to 60% and relapse occurs during steroid de-escalation or after discontinuation [27-30]. A multicenter study of the long-term course of type 1 AIP in Japan showed relapse rates of 10% within one year and 25.8% within 3 years [15]. In the current study, the relapse rate of subjects followed up for one year or more was 14.2%, which is similar to the previous findings. Predictors of relapse in clinical practice have been identified in many studies, and include serum IgG4, serum IgE, pancreatic enlargement and OOI [1, 14, 15, 25, 26, 31, 32]. Although it is difficult to draw definitive conclusions regarding predictors of relapse in this study

because of the small number of cases with long-term follow-up and only two cases of relapse, there was no specific trend in PEM, dispersion slope, or % change in these parameters between those with and without relapse.

A second issue in AIP treatment is pancreatic endocrine and exocrine insufficiency, which develop in 40-60% and almost 80% of AIP cases, respectively [33, 34]. Ito et al. found that 78.6% of patients with AIP complicated with diabetes and approximately 63% had no history of diabetes [16]. In this study, 52% of subjects had diabetes at diagnosis of AIP and 71% of 7 subjects during long-term follow-up had a decreased or discontinued insulin dose. Since EUS-SWM is useful to predict decreased pancreatic endocrine and exocrine insufficiency [35], we attempted to examine whether PEM and the dispersion slope could predict improvement in diabetes in patients with AIP, but no tendency for difference was found. Pancreatic atrophy after steroid treatment of AIP may be related to onset of diabetes after steroid treatment [17]. The results of the present study showed that the % PEM change after 2 weeks of treatment tended to be higher in subjects without pancreatic atrophy on CT 12 months after the start of treatment. Therefore, the % PEM change after 2 weeks of treatment may be a predictor of pancreatic atrophy and the incidence of diabetes in the long-term course.

This study has several limitations, including the retrospective single-center design, the relatively small number of subjects, and the short-term observation period. Further studies are needed to accumulate cases and evaluate PEM and dispersion slope in several-year long-term follow-up to draw conclusions about long-term prognosis. Within these limitations, our results suggest that SWE and SWD in US may be valuable for quantitative assessment of AIP and evaluation of short-term treatment efficacy.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest. This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. But, the Department of Gastroenterology and Hepatology, Nagoya University Graduate School of Medicine received consigned research expenses from Canon Medial Systems Corp. Canon Medial Systems Corp. had no role in the design, practice, or analysis of this study

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FIGURE LEGEND

Figure. 1

Measurement example of shear wave elastography and shear wave dispersion in autoimmune pancreatitis. The color mapping display of dispersion is on the left. The propagation display of elasticity is on the right. In the propagation view, the part where the width of the contour line is constant and is displayed in parallel could be evaluated.

Figure. 2

a Box plot of pancreatic elastic modulus (PEM) in autoimmune pancreatitis (AIP) before treatment and after two weeks of steroid treatment.

b Box plot of dispersion slope in AIP before treatment and after two weeks of steroid treatment. PEM was 12.7 kPa and the dispersion slope was 10.5 (m/sec)/kHz, and both were significantly lower than the values before treatment (both $P<0.001$).

Figure. 3

Box plot of decrease rate after two weeks of steroid treatment in pancreatic elastic modulus (PEM), dispersion slope and the size of pancreatic parenchyma. These parameters were 37.2%, 32.8% and 14.4% respectively. Decrease rate in PEM and dispersion slope were significantly higher than the size of pancreatic parenchyma

(P=0.026).

Table 1. Patients' characteristics

	Autoimmune pancreatitis (n=23)	Normal pancreas (n=34)	*P* -value
Age, median (IQR)	67 (11)	64 (26)	0.320
Gender, n male : female	16 : 7	15 : 19	0.103
Serum IgG, median (IQR), mg/dL	1696 (592)		
Serum IgG4, median (IQR), mg/dL	301 (357)		
Diabetes mellitus at diagnosis, n (%)	12 (52.2)	3 (8.8)	< 0.001
Size of the pancreatic parenchyma, median (IQR), mm	22.5 (9.0)		
Other organ involvement, n (%)	7 (30.4)		
Final diagnosis, n definitive type 1	23		
PEM (kPa), median (IQR)	30.9 (15.2)	6.6 (2.3)	< 0.001
Dispersion slope ((m/sec)/kHz), median (IQR)	15.3 (4.2)	13.0 (3.4)	0.011

IQR, interquartile range PEM, pancreatic elastic modulus

Table 2. Correlations of pancreatic elastic modulus and dispersion slope before steroid treatment with autoimmune pancreatitis patients' characteristics

	PEM		Dispersion slope	
	r_s	*P* -value	r_s	*P* -value
Serum IgG	-0.438	0.037	-0.076	0.730
Serum IgG4	-0.362	0.090	0.072	0.745
Size of the pancreatic parenchyma	0.177	0.420	0.146	0.506
	PEM (kPa), median (IQR)	*P* -value	Dispersion slope ((m/sec)/kHz), median (IQR)	*P* -value
Diabetes mellitus at diagnosis				
No	50.3 (15.2)	0.151	20.5 (3.8)	0.079
Yes	24.0 (15.0)		14.5 (4.3)	
Other organ involvement				
No	35.5 (16.4)	0.492	16.4 (4.2)	0.492
Yes	23.1 (4.4)		14.1 (3.8)	

PEM, pancreatic elastic modulus IQR, interquartile range

Table 3. Comparison of pancreatic elastic modulus, dispersion slope before steroid treatment, and decrease rate

Relapse and non-relapse cases	Relapse cases (n=2)	Non-relapse cases (n=12)
Before treatment		
PEM (kPa), median	24.4	35.1
Dispersion slope ((m/sec)/kHz), median	25.5	14.5
Decrease rate (%)		
PEM	45.6	37.2
Dispersion slope	49.9	29.6
Improved and aggravated cases of diabetes mellitus	Improved cases (n=5)	Aggravated cases (n=2)
Before treatment		
PEM (kPa), median	30.9	23.1
Dispersion slope ((m/sec)/kHz), median	14.9	14.1
Decrease rate (%)		
PEM	40.8	61.0
Dispersion slope	31.5	41.1
Pancreatic atrophy and non-atrophy cases	Atrophy cases (n=6)	Non-atrophy cases (n=4)
Before treatment		
PEM (kPa), median	16.5	40.4
Dispersion slope ((m/sec)/kHz), median	15.5	14.0
Decrease rate (%)		
PEM	16.8	71.5
Dispersion slope	10.5	30.1

PEM, pancreatic elastic modulus

Figure. 1

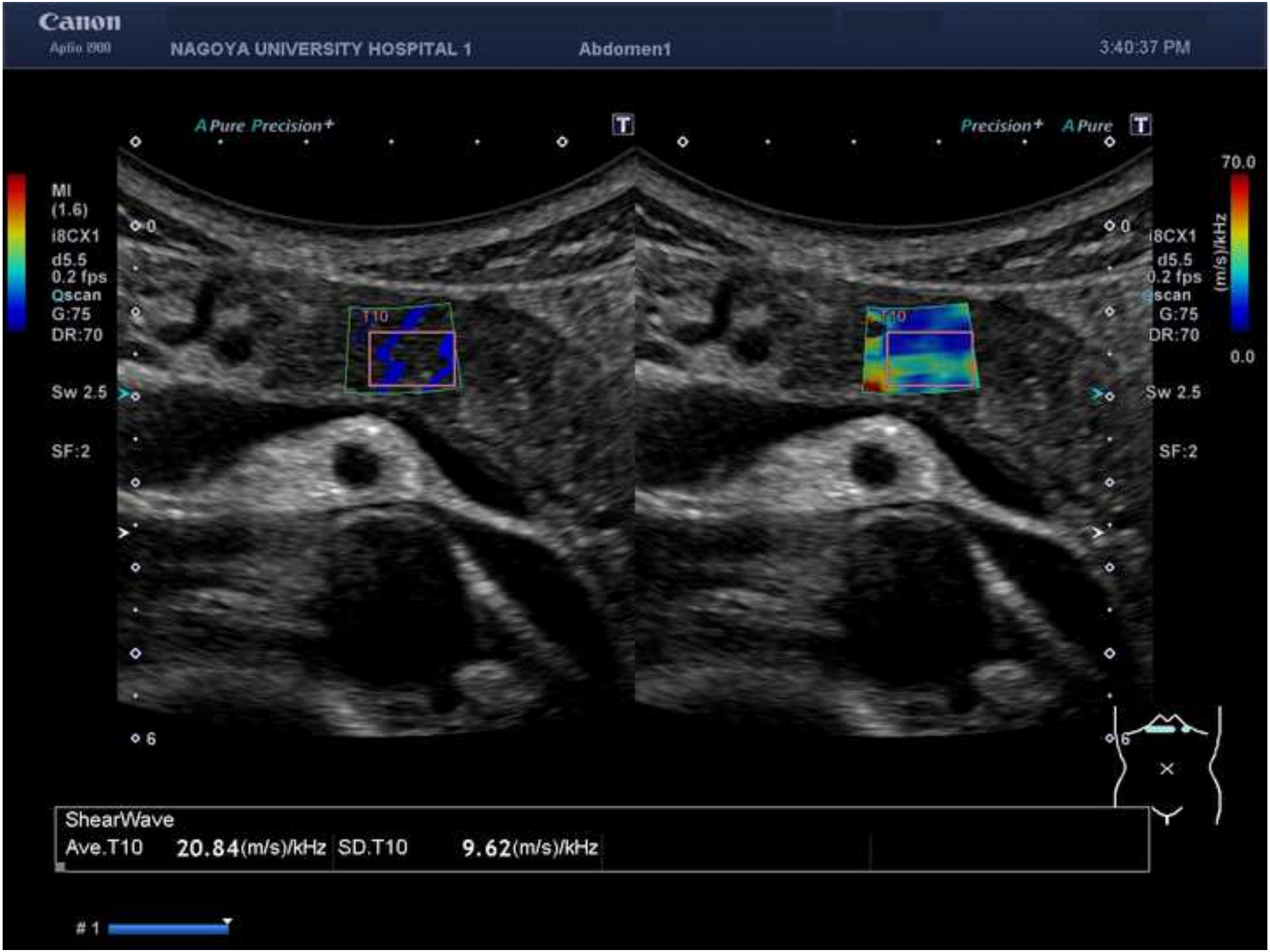

Canon
Aplio i900
NAGOYA UNIVERSITY HOSPITAL 1
Abdomen1
3:40:37 PM
A Pure Precision+
Precision+ A Pure
MI
(1.6)
i8CX1
d5.5
0.2 fps
Qscan
G:75
DR:70
Sw 2.5
SF:2
T10
70.0
0.0
ShearWave
Ave.T10 20.84(m/s)/kHz SD.T10 9.62(m/s)/kHz
1

Figure. 2

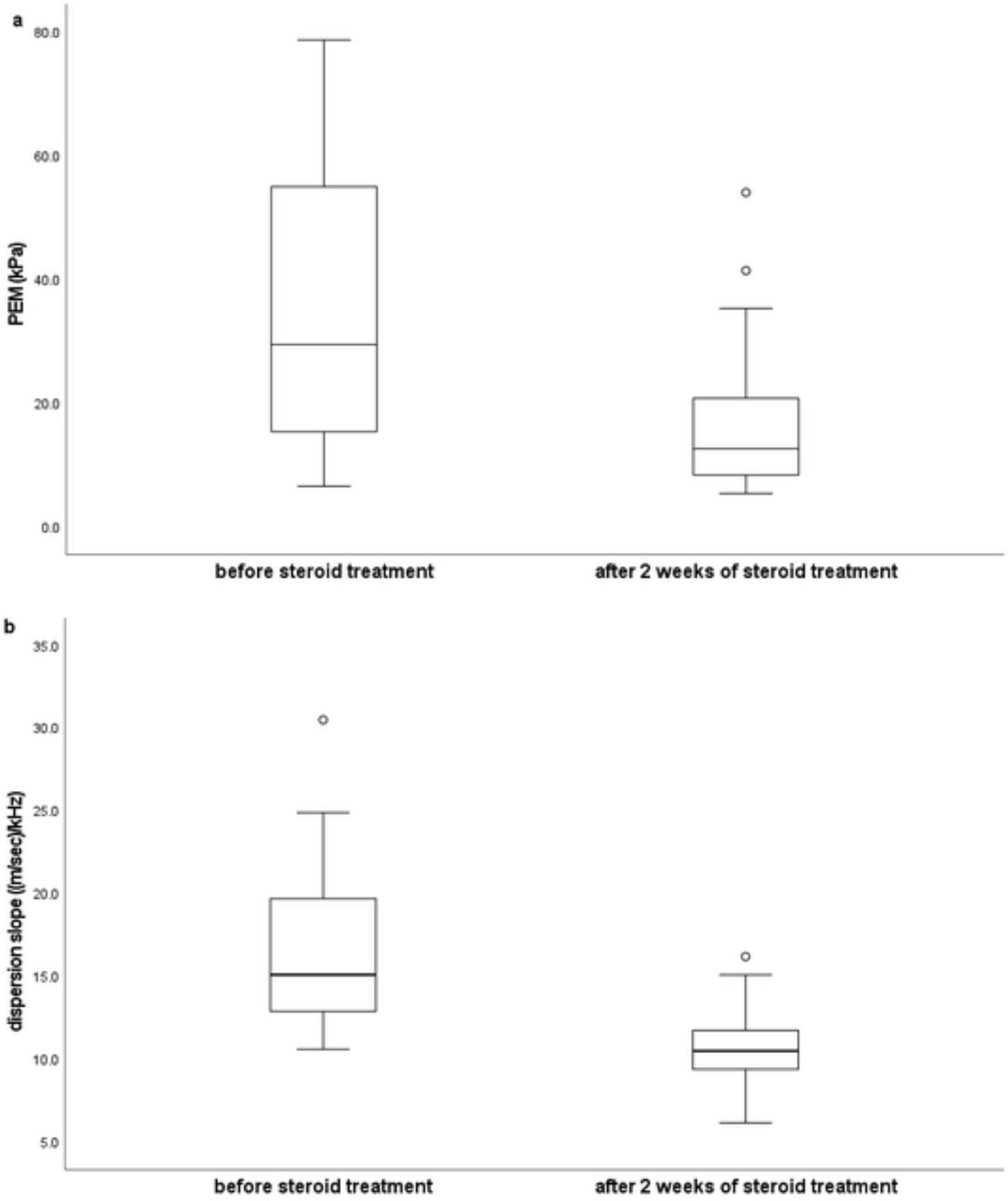
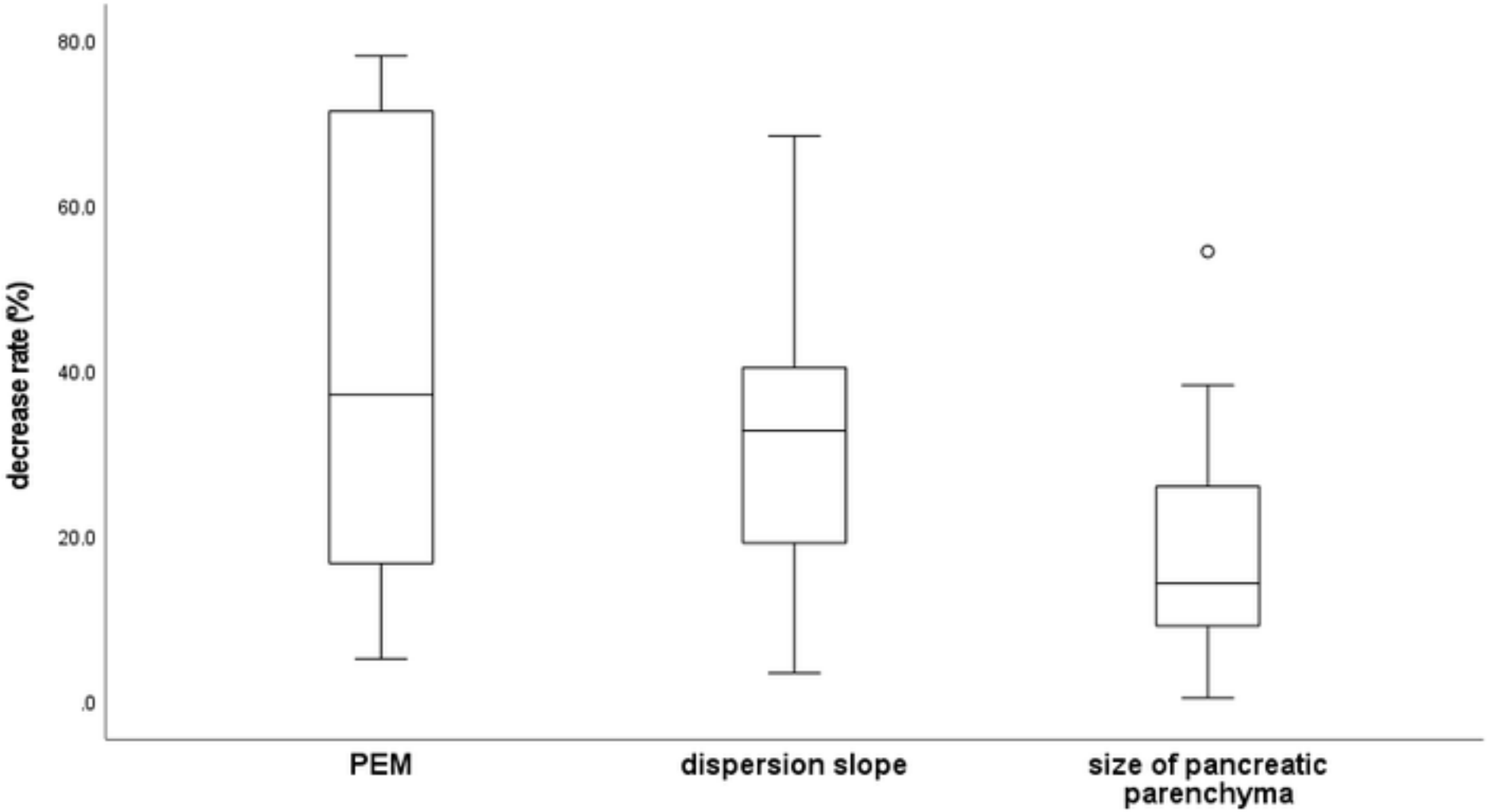

a
80.0
60.0
40.0
20.0
0.0
PEM (kPa)
before steroid treatment
after 2 weeks of steroid treatment
b
35.0
30.0
25.0
20.0
15.0
10.0
5.0
dispersion slope ((m/sec)/kHz)
before steroid treatment
after 2 weeks of steroid treatment

Figure. 3


80.0
60.0
40.0
20.0
.0
decrease rate (%)
PEM
dispersion slope
size of pancreatic parenchyma