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Does Reflux Esophagitis Really Decrease Quality of Life?

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Abstract

Objective: The incidence of reflux esophagitis is increasing due to increased gastric acid output, a decreased *Helicobacter pylori* infection rate, increased interest in diseases, and westernization of lifestyles. Reflux esophagitis has been reported to lower the quality of life (QOL) due to the severity of symptoms. However, assessments of a relationship between reflux esophagitis and QOL have been mostly at the hospital level, and few studies have considered this in health check-ups. Therefore, we examined relationships between reflux esophagitis and gastrointestinal symptoms and QOL in health check-up examinees.

Methods: Our subjects were 366 individuals (207 men and 159 women, aged 33–81 years, mean age 58 ± 11 years) who underwent health check-ups. Relationships between reflux esophagitis and gastrointestinal symptoms and health-related QOL were evaluated using the Gastrointestinal Symptom Rating Scale and Short Form-8 questionnaire, respectively.

Results: Reflux esophagitis was not necessarily associated with gastrointestinal symptoms and there was no clear association with reduced health-related QOL.

Conclusion: It is difficult to predict the presence of reflux esophagitis based solely on subjective symptoms. Therefore, it is necessary to perform endoscopies with the possibility of reflux esophagitis in mind even in patients who do not complain of symptoms.

Keywords reflux esophagitis, health check-up, Gastrointestinal Symptom Rating Scale (GSRS), Short Form-8 (SF-8)

The incidence of reflux esophagitis is increasing and recently it has been found more frequently in patients during health check-ups[1–7]. Factors contributing to the increased incidence of reflux esophagitis are believed to include increased gastric acid output, decreased *Helicobacter pylori* infection rate, increased interest in diseases, and westernization of lifestyles[7].

Analyses of health check-ups examining factors which influenced reflux esophagitis indicated relationships with sex, obesity, and lifestyle habit factors[1–6,8]. An association between reflux esophagitis and hiatal hernia and gastric mucosal atrophy has also been reported[1–9].

Although reflux esophagitis is not a life-threatening disorder, it has been reported to reduce the quality of life (QOL) due to the severity of symptoms[10,11]. However, regarding a relationship between reflux esophagitis and QOL, although there have been many studies on hospital medical examinations for patients with acid reflux symptoms, few studies have focused on health check-ups.

Here, we report on relationships between gastrointestinal symptoms and health-related QOL findings in health check-up examinees with reflux esophagitis.

Subjects and Methods

This study was carried out in accordance with local ethical guidelines and the Declaration of Helsinki recommendations.

It was approved by the Ethics Committee of Sanuki Municipal Hospital (approval date: January 19, 2016; approval number: H27-006) and the Ethics Committee of The TAIJU-KAI Foundation (Social medical corporation) Kaisei General Hospital (approval date: August 19, 2016; approval number: 2016-8).

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This study included 366 subjects (207 men and 159 women, aged 33–81 years, mean age 58 ± 11 years) who received upper gastrointestinal endoscopy during a health check-up at the Sanuki Municipal Hospital (179 beds) from April 2010 to October 2010. Subjects who had malignant tumors, peptic ulcers, or who were post-gastrectomy were excluded.

We obtained consent from all subjects and asked them to fill out questionnaires. The Gastrointestinal Symptom Rating Scale (GSRS) was used for assessing gastrointestinal symptoms and the Short Form-8 (SF-8) survey was used for assessing health-related QOL[12,13]. Endoscopic images were confirmed by two endoscopists (one supervising physician and one specialist). Based on the Los Angeles classification[14], those with Grade A or more, were determined to have reflux esophagitis. A relationship between reflux esophagitis and gastrointestinal symptoms, and a relationship between reflux esophagitis and health-related QOL were investigated.

Values are presented as mean ± standard deviation of the mean. The chi-squared test was used to determine if there was a relationship between reflux esophagitis and gastrointestinal symptoms. The Mann-Whitney U-test was used to examine associations between confirmed reflux esophagitis and GSRS and SF-8 results. The Statcel 12 software program (OMS Publishing Ltd.) was used for statistical analyses.

Results

Subject characteristics are shown in **Table 1**. Although there was some variation in values, no subject was far from the normal range.

Reflux esophagitis was observed in 52 patients (14.2%). The severity was as follows: Grade A in 39 patients (75.0% of total), Grade B in 12 patients (23.1%), and Grade C in 1 patient (1.9%). The rates of reflux esophagitis and other endoscopic findings are shown in **Table 2**.

Reflux esophagitis and gastrointestinal symptoms

Twenty-four patients (6.8%) had GSRS acid reflux scores of 3 or higher. Of the patients with reflux esophagitis, 6 (11.5%) had GSRS acid reflux scores of 3 or higher, indicating that there was no significant difference in this regard between whether subjects had or did not have reflux esophagitis (**Table 3**).

Individual GSRS scores were not significantly different between subjects with and without reflux esophagitis (**Table 4**).

The subject with Grade C had an acid-reflux score of 1 (no difficulty; data not shown).

Reflux esophagitis and health-related QOL

For all categories, SF-8 scores were not significantly different between presence and absence of reflux esophagitis, and were very similar to those in the national standard (**Table 5**).

Table 1. Characteristics of Patients

Gender (persons)	male : 207, female : 159
Age (years)	58 ± 11 (male : 59 ± 11, female : 57 ± 12)
Waist circumference (cm)	83.6 ± 9.4
Drinking (no. of persons)	178
Smoking (no. of persons)	70
Systolic blood pressure (mmHg)	122 ± 18
Fasting plasma glucose (mg/dL)	104 ± 16
Triglycerides (mg/dL)	121 ± 119
HDL-cholesterol (mg/dL)	64 ± 18

Table 2. Endoscopic Findings

Reflux esophagitis :	52 (14.2%)
Grade A :	39
Grade B :	12
Grade C :	1
Grade D :	0
Esophageal hiatus hernia:	174 (47.5%)
Atrophy of gastric mucosa:	227 (62.0%)
Redness:	105 (28.7%)
Flat erosion:	37 (10.1%)
Protruding erosion:	66 (18.0%)
Haemorrhage:	68 (18.6%)
Duodenitis:	49 (13.4%)

Values represent numbers of cases (percentage of total (366)).

Table 3. Reflux Esophagitis and Acid Reflux Symptoms

	Reflux esophagitis	
	Present	None
GSRS 3 or more	6	18
Less than 3	46	295

GSRS: Gastrointestinal Symptom Rating Scale, p=0.1189

Table 4. Reflux Esophagitis and Gastrointestinal Symptoms ; Analysis of GSRS

	Reflux esophagitis	No reflux esophagitis	
Abdominal pain	1.40 ± 0.60	1.40 ± 0.55	ns
Reflux	1.66 ± 1.01	1.43 ± 0.66	ns
Indigestion	1.48 ± 0.63	1.56 ± 0.58	ns
Constipation	1.75 ± 0.95	1.82 ± 0.90	ns
Diarrhoea	1.53 ± 0.75	1.54 ± 0.71	ns

GSRS: Gastrointestinal Symptom Rating Scale, GSRS scores were not significantly different between subjects with and without reflux esophagitis.

Table 5. Reflux Esophagitis and Health-related Quality of Life ; Analysis of SF-8

	National standard	Reflux esophagitis	No reflux esophagitis	
Physical functioning: PF	50.85	50.10 ± 5.53	49.37 ± 7.07	ns
Role physical: RP	50.65	49.76 ± 6.27	50.00 ± 6.49	ns
Bodily pain: BP	51.42	51.90 ± 8.07	51.54 ± 8.07	ns
General health perception: GH	50.99	49.25 ± 5.37	49.12 ± 5.30	ns
Vitality: VT	51.76	51.01 ± 6.17	50.70 ± 6.30	ns
Social functioning: SF	50.09	50.00 ± 7.44	50.40 ± 7.04	ns
Role emotional: RE	50.89	48.95 ± 7.10	49.94 ± 6.64	ns
Mental health: MH	50.96	50.17 ± 5.28	50.53 ± 6.09	ns

SF-8: Short Form-8, There were no differences in scores between patients with and without reflux esophagitis for all SF-8 items.

Discussion

This study revealed that acid reflux symptoms in reflux esophagitis are not always obvious, and few affect QOL.

The prevalence of reflux esophagitis was 14.2% for all health check-up subjects studied, which was similar to past studies. In recent reviews of health check-ups in Japan, the prevalence of reflux esophagitis was reported to be 4-17.9%[1,3,5,6], and 18.6% in an all-male study[4]. Most patients have mild esophagitis, a characteristic finding in Japan[1–7,15]. The prevalence of reflux esophagitis appears to vary by region and race, and a study in Cuba reported that approximately 25% of all people visiting hospitals for examination had reflux esophagitis[16].

In this study, the rate for reflux symptoms was 6.8%, when a GSRS score > 3 was regarded as presence of symptoms. The prevalence of reflux symptoms in Japan was reported to be 6.5–9.5%, which is similar to our finding[17]. In our study, we found no significant relationships between reflux esophagitis discovered in health check-ups, gastrointestinal symptoms, and lowering of QOL. Although it has been reported that reflux esophagitis decreases the QOL due to the severity of symptoms[10,11], we did not find this to be the case in those who had basic health check-ups. Only patients strongly complaining of a decline in QOL due to severe symptoms have more detailed medical examinations at hospitals.

In Japan, the rate of acid reflux symptoms in patients with reflux esophagitis was reported to be 29.5–88.4% in studies involving health check-ups and medical examinations during hospital visits[10,18–20], and 14.7–70.2% in studies involving only health check-ups[1,2,6]. Although symptom rates were higher than in our study, many of the previous studies were conducted at large facilities and background factors may have been different from our study.

Reflux symptoms do not necessarily coincide with endoscopic findings, and it has been reported that the rate of confirmed reflux esophagitis with no patient complaints of symptoms is high in health check-ups[7,15,17,21]. In the single case of Grade C included in our study, no reflux symptoms were noticed, and there was no reduction in QOL. Several studies have reported that the severity and symptoms of reflux esophagitis are not related[15,21]. Grade M, a modified category of the Los Angeles classification, has been adopted in Japan, but it has the problem that evaluation methods and definitions of color changes are not standardized, and the agreement rate among endoscopists is low[22].

Non-erosive reflux disease (NERD) should also be considered when assessing reflux symptoms, but accurate diagnosis of NERD requires pH monitoring. Forty-two % of cases of heartburn without mucosal injury have pathological acid reflux. Other types of heartburn are functional heartburn and reflux hypersensitivity[23]. It is difficult to distinguish functional heartburn and reflux hypersensitivity in studies on health check-up examinees. Therefore, we assessed reflux esophagitis (Grade A to D) with endoscopically evident changes.

Although the etiology of subclinical reflux esophagitis is unknown[7], recent studies have suggested an association between heartburn symptoms and Prostaglandin E1[24], but the relationship between it and factors that cause esophagitis and those that cause heartburn symptoms is far from clear. Further examination of this issue is expected in the future.

It appears that a correlation between reflux symptoms and a decrease in QOL in reflux esophagitis patients is only found when symptoms are severe and they undergo a hospital medical examination. It is still difficult to predict that someone has reflux esophagitis only from findings in health check-ups. Thus, with the possibility of reflux esophagitis in mind, endoscopy should be performed even in patients who have no obvious symptoms, such as those undergoing routine health check-ups. Previous studies have shown that risk factors for reflux esophagitis are: male sex, elderly woman, obesity, dyslipidemia, and hypertension[1–9]. In such cases, special attention is required. However, it has been reported that acid reflux does not coincide with acid reflux symptoms

in diabetic patients[25]. Proton-pump inhibitors (PPI) are known to be highly effective in relieving symptoms of reflux esophagitis. Even patients who do not complain of reflux symptoms could experience other symptom improvement when PPIs are administered[10].

Since the frequency and intensity of reflux symptoms vary with the assessment method, simple comparisons with previous studies are difficult[17]. It was previously reported that reflux symptoms once or twice a week are associated with a decrease in QOL[17], and we believe that any decrease in QOL can be identified in GSRS questionnaires which ask about symptoms. GSRS was used because it allows both reflux symptoms and other digestive symptoms to be evaluated. It has been reported that there is not much difference between GSRS and Quest[26].

In the present study, we were unable to evaluate the use of therapeutic drugs, or the effects of antihypertensive drugs, cardiology drugs, and anti-asthmatic drugs on induction of lower oesophageal sphincter relaxation[5–7,15], and the effects of anti-acid secretory agents are unclear. Although the small number of subjects at a single institution is a limitation of our study, we believe that it is representative of the features of reflux esophagitis found in health check-ups.

Conclusion

Features of reflux esophagitis discovered in health check-ups were examined.

Reflux esophagitis was not necessarily associated with gastrointestinal symptoms and there was no clear association with a decrease in QOL. As it is difficult to predict the presence of reflux esophagitis only based on symptoms, it is necessary to carry out endoscopic examinations to diagnose reflux esophagitis during health check-ups for patients who do not complain of any symptoms.

Conflict of Interest

No author has any conflict of interest in this study.

It has been disclosed to the authors of this study that there was no company involvement that might have created a conflict of interest.

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Original Article *Ningen Dock International* 2020 ; 7 : 8–13

Transabdominal Ultrasound Detection of Pancreatic Cystic Lesions with Reference to Previous Magnetic Resonance Imaging

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Abstract

Objective: Pancreatic cystic lesions (PCLs) should be carefully followed up because they are transabdominal ultrasound (TAUS) findings indicating a high-risk of pancreatic cancer. The aim of this study was to investigate the usefulness of follow-up TAUS for PCL surveillance, with reference to previous magnetic resonance imaging (MRI).

Methods: The hospital database for 781 subjects who underwent a health check-up including MRI was searched. The PCL detection rate and the size of their maximum dimension in follow-up TAUS after MRI were examined. Subjects with and without detected PCLs in follow-up TAUS were statistically compared for clinical characteristics.

Results: The detection rate for PCLs that were invisible in the initial TAUS was 21.9% in follow-up TAUS after MRI and 68.7% of these PCLs were under-measured, with a size difference of −1.8 ± 3.7 mm. Multivariate logistic regression analysis showed that visualization of PCLs by follow-up TAUS was significantly associated with PCL size and the presence of fatty liver (OR, 95% CI, *p*: 1.477, 1.252–1.741, 0.000; 0.252, 0.088–0.725, 0.011). On the other hand, with a detection rate of 97.5% for the visible PCLs in the initial TAUS, the reproducibility of follow-up TAUS was very high, although 51.3% of these PCLs were under-measured, with a size difference of −1.3 ± 2.3 mm.

Conclusions: The PCL detection rate for follow-up TAUS after MRI improved in approximately 20% of subjects with invisible PCLs in the initial TAUS, and high reproducibility was demonstrated for TAUS. It should be noted that PCL size could be under-measured in TAUS, after MRI.

Keywords pancreatic cystic lesion, follow-up transabdominal ultrasonography, magnetic resonance imaging

There are several risk factors for pancreatic cancer, 2 of them family history and diabetes mellitus. Others are chronic pancreatitis and pancreatic cystic lesions (PCLs), including intraductal papillary mucinous neoplasia (IPMN), that should be carefully followed up as premalignant diseases of pancreatic cancer, according to the guidelines for pancreatic cancer issued by the Japan pancreas society in 2013[1]. Although PCLs are often detected incidentally, especially through the widespread use of magnetic resonance imaging (MRI), cysts with invasive carcinoma are rarely found in asymptomatic individuals. Transabdominal ultrasonography (TAUS) is useful in initial screenings as well as in health check-ups, and is also a first choice for pancreatic diseases due to its great convenience, non-invasiveness, and cost effectiveness[2,3]. However, the entire pancreas is difficult to visualize clearly using TAUS because of its deep retroperitoneal location as well disruption of ultrasound transmission due to body habitus and interposed bowel gas[4]. On the other hand, MRI with T2-weighted images and magnetic resonance cholangiopancreatography (MRCP) are considered to be the best imaging modality for detecting PCLs due to their superior contrast resolution and ability to highlight fluid-containing structures[5]. According to the 2015 American Gastroenterological Association institute guideline, MRI is an appropriate surveillance imaging tool for cysts less than 3 cm without a dilated pancreatic duct or a solid component[6]. However, this modality is lengthy, there are people who are contraindicated and it increases medical

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costs when used for follow-up.

Recently, 2 studies regarding the detection rate of TAUS for known PCLs using MR and other correlative images, have been published[7,8]. They concluded that TAUS could be a useful surveillance imaging tool for PCLs because the majority of PCLs were visualized and accurately measured in follow-up TAUS using the correlative images. Therefore, we investigated whether the PCL detection rate was improved by follow-up TAUS with reference to previous MRI findings in our cohort[9]. Its members had been reported to have PCLs based on an optional MRI examination in a health check-up.

Materials and Methods

Subjects

The Institutional Review Board of Keio University Hospital approved this retrospective study and the requirement for informed consent was waived (IRB No. 20160398). We used the same hospital database as the one that had been used for analysis in our previous study[9]. We searched the medical records, including demographics, medical history, the presence of metabolic syndrome, body mass index (BMI), waist circumference (WC), subcutaneous adipose tissue (SAT), visceral adipose tissue (VAT), and blood tests as well as TAUS and MRI reports for consecutive subjects who underwent a health check-up at our facility for the first time between August 2012 and July 2016.

Image acquisition for US, MRI and CT, and image analysis

All the subjects had been fasting overnight when they underwent the screening TAUS examination in the supine or right and left lateral position, not the sitting position, using a Logiq S8 system (GE Healthcare, USA) with 3–6 MHz wide band convex probe. The initial TAUS was performed by an experienced sonographer in the digestive area, who was accredited by the Japan Society of Ultrasonics in Medicine, before the initial MRI examination performed at a maximum of 3 months later, and used color Doppler ultrasonography (US) and a linear probe, if required. In our facility, US was not performed by a method that involved drinking water. Examination time was approximately 10 minutes and the size of the lesion found in TAUS was measured using two dimensions in a magnified image. The TAUS results were available only from the subjects' formal records. They had been confirmed by a radiologist and included the size and the location of the detected pancreatic cyst with the maximum dimension among all detected PCLs. Fatty pancreas was diagnosed when the pancreas was observed to be hyperechoic in comparison with echogenicity in the left lobe of the liver. The PCL detection rate in follow-up TAUS with reference to the initial MRI report was calculated. We also compared the result of follow-up TAUS with that for follow-up MRI carried out within a maximum of 3 months after follow-up TAUS. Thus, this study includes the data from one follow-up TAUS and the subsequent follow-up MRI.

The upper abdominal MRI examination was performed on a 1.5 Tesla clinical scanner (Signa HD xt; GE Healthcare, USA) according to the standard department protocol including the following sequences: (1) 3 plane localizer, (2) axial and coronal single-shot fast/turbo spin-echo (SSFSE), (3) Fat-suppressed T2-weighted fast spin echo (FSE), (4) 3D MRCP in rotating coronal oblique orientations. Chemical shift imaging with dual echo T1-weighted gradient-recalled echo in-phase and out-of-phase sequences were also obtained. No intravenous contrast was administered in this cohort. Image analysis was performed on a PACS system (Centricity; GE Healthcare, USA) by 2 independent readers and reviewed in consensus. The MRI results were used as reference standard for the size and location of PCLs in the pancreas.

We reevaluated the image of the pancreas in non-enhanced chest CT performed routinely to screen for chest lesions in order to determine the presence of pancreatic atrophy using a protocol[10], in the absence of information from the TAUS or MRI reports. Pancreatic atrophy was defined as a pancreatic body width of less than 10 mm. Also, routine fat CT was performed at the umbilicus level to measure WC, SAT and VAT, with calculations made using AZE Virtual Place software (AZE Inc., Tokyo, Japan), as previously reported[11].

Statistical analysis

Statistical analyses were performed using SPSS software version 24 (SPSS, Inc., USA). Statistical differences between two groups were determined using the t-test or Mann-Whitney U test for continuous data, and the chi-square test for categorical data, when MRI was considered as the reference standard. Continuous data were presented as the means ± standard deviation. Parameters with a p value of less than 0.05 in the univariate analysis were candidates for the multivariate logistic regression analysis applied to determine factors, which were associated with PCL visualization in TAUS. A p value < 0.05 was considered statistically significant.

Results

Study population and PCL detection rate in follow-up TAUS

The flow chart of the present study is shown in **Fig. 1**. Of the total of 781 subjects enrolled in this study, PCLs were detected in 139 subjects in the initial MRI, including 98 subjects diagnosed as having Intraductal Papillary Mucinous Neoplasm (IPMN), as previously reported[9]. Among them, 56 and 83 subjects, respec-

tively, were diagnosed with PCL and without PCL in the initial TAUS, before the initial MRI[12]. Sixteen and 10 subjects, respectively, were eliminated from these 2 groups, as they had not undergone a follow-up examination within a maximum period of 3 months of each other. Therefore, 40 and 73 subjects in these 2 groups, who had undergone both TAUS and MRI for follow-up, were included in this study. All of them had no history of chronic pancreatitis or other pancreatic diseases. Thirty-nine subjects with visible PCLs and 16 subjects with invisible PCLs in the initial TAUS were diagnosed with PCLs in the follow-up TAUS. **Fig. 2** shows images for a 60-year-old male with IPMN in the pancreatic body. The MRI and MRCP images reveal a cystic mass connected to the main pancreatic duct (A and B). Although the cystic lesion could not be detected in the axial view (C1), or sagittal view (C2) of the initial TAUS, it was successfully detected in follow-up TAUS, with reference to the initial MRI report, in the axial view (D1) and sagittal view (D2). The overall PCL detection rate in the follow-up TAUS was 48.7% (55/113) in contrast to that of 35.4% (40/113) in the initial TAUS. The detection rates by region (head, body and tail) of the pancreas were 64.4 (= 29/29+16)%, 34.1 (= 14/14+27)%, and 44.4 (= 12/12+15)%, respectively, as shown at the bottom of **Table 1**. Only one small cyst (5 mm) found in the initial TAUS could not be detected in the follow-up TAUS, although it was also observed in the follow-up MRI. Thus, the reproducibility of the follow-up TAUS for initially visible PCLs was very high (39/40 = 97.5%), whereas the detection rate in follow-up TAUS after the initial MRI for invisible PCLs in the initial TAUS was just 21.9% (16/73) (**Fig. 1**).

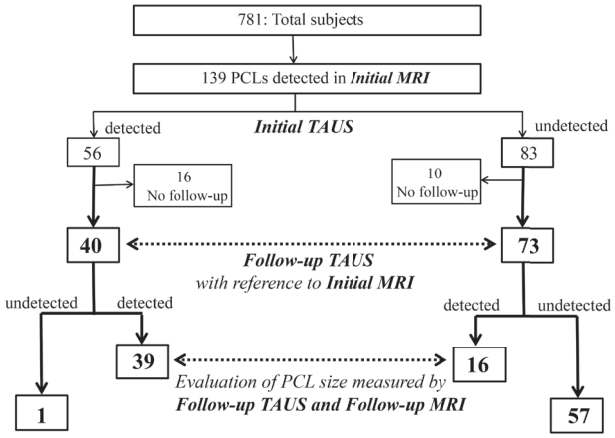

Fig. 1. Flow Chart and Numbers of PCLs Detected by TAUS in Present Study

PCLs: pancreatic cystic lesions, MRI: magnetic resonance imaging, TAUS: transabdominal ultrasonography.

Comparison of clinical characteristics between subjects with detected and undetected PCLs in follow-up TAUS after initial MRI

As shown in **Table 1** and **Table 2**, we compared 55 subjects with PCLs detected by follow-up TAUS and 58 subjects in whom PCLs were not detected. The former group was significantly older (68.2 vs 64.8 years, p = 0.047) and tended to have smaller WC, SAT, and VAT than the latter group, but differences were not significant. The former group had more PCLs in the head of the pancreas (54% vs 28%, p = 0.017), and fatty liver

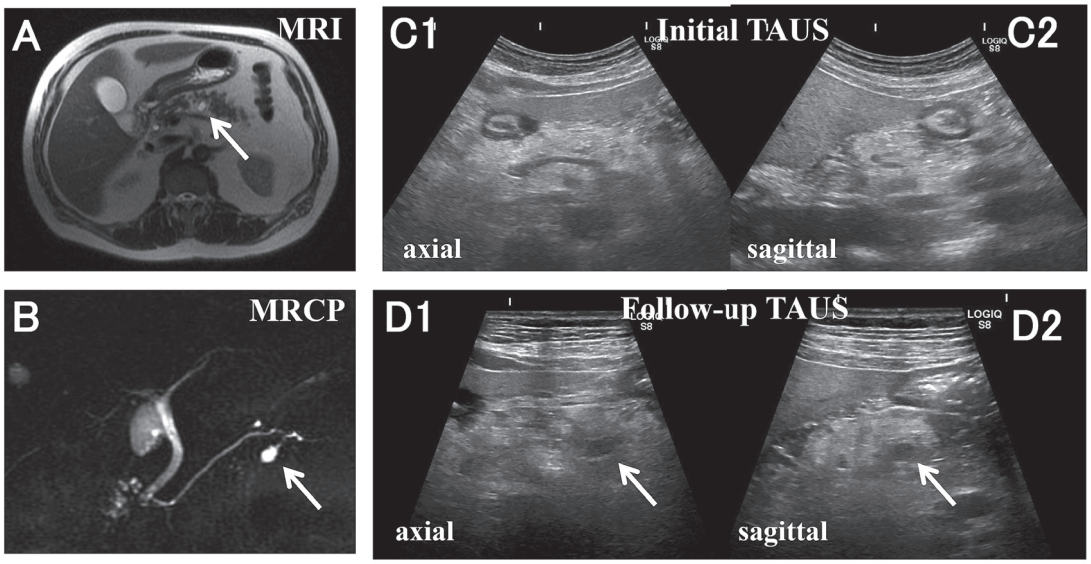

Fig. 2. IPMN Detected in Pancreatic Body of 60-year-old Male

(A) Transverse T2-weighted image in MRI demonstrated a cystic mass in the body of the pancreas. (B) MRCP revealed that this cystic lesion was connected to the main duct of the pancreas. (C1 and C2) The cystic lesion could not be detected in an axial view (C1), or sagittal view (C2) in the initial TAUS. (D1 and D2) With reference to the initial MRI report, the lesion could be detected by follow-up TAUS in an axial view (D1) and a sagittal view (D2).
MRI: magnetic resonance imaging, MRCP: magnetic resonance cholangiopancrea-tography, TAUS: transabdominal ultrasonography, IPMN: Intraductal Papillary Mucinous Neoplasm.

Table 1. Comparison of Clinical Characteristics between Subjects with and without PCLs Detected by Follow-up TAUS after Initial MRI

Characteristics	Subjects with PCLs detected by follow-up TAUS (*n* = 55)	Subjects with no PCLs detected by follow-up TAUS (*n* = 58)	Univariate Analysis *p*	Multivariate Analysis *p* OR (95%CI)
Age, years	68.2 ± 7.6	64.8 ± 10.1	0.047	0.053
Male, *n* (%)	34 (61.8)	44 (75.9)	0.107	
Metabolic synd., *n* (%)	16 (29.1)	15 (25.9)	0.701	
Fatty liver, *n* (%)	16 (29.1)	29 (50.0)	0.023	0.011 0.252 (0.088–0.725)
Fatty pancreas, *n* (%)	13 (23.6)	14 (24.1)	0.950	
Atrophic pancreas, *n* (%)	4 (7.3)	7 (12.1)	0.390	
Body mass index, kg/m^2	22.7 ± 2.9	23.5 ± 2.6	0.127	
WC, cm	81.3 ± 8.0	84.2 ± 8.3	0.055	
SAT, cm^2	144.4 ± 57.3	151.7 ± 55.3	0.496	
VAT, cm^2	101.5 ± 47.6	112.8 ± 45.0	0.198	
PCL size, mm	12.7 ± 6.7	6.2 ± 2.6	0.000	0.000 1.477 (1.252–1.741)
PCL location (Head, Body, Tail), *n* (%)	29, 14, 12 (55, 25, 22)	16, 27, 15 (28, 46, 26)	0.017	0.265

PCL: pancreatic cystic lesion, TAUS: transabdominal ultrasonography, WC: waist circumference, SAT: subcutaneous adipose tissue, VAT: visceral adipose tissue.

Table 2. Numbers (percentages) of Subjects with and without PCLs Detected by Follow-up TAUS after Initial MRI, According to PCL Size

Size (maximum dimension)	Number (%) of subjects with PCLs detected by follow up TAUS (*n* = 55)	Number (%) of subjects without PCLs detected by follow-up TAUS (*n* = 58)	*p*
< 10 mm	25 (45.5)	55 (94.8)	0.000
10 mm ≤	30 (54.5)	3 (5.2)	

PCL: pancreatic cystic lesion, TAUS: transabdominal ultrasonography.

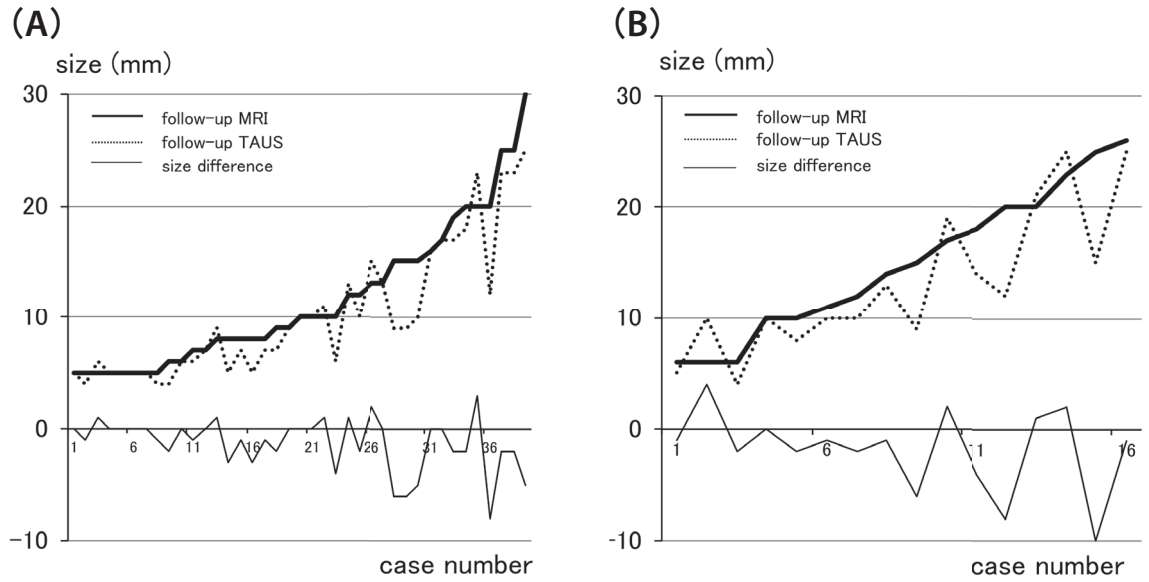

Fig.3. PCL Size Measured in Follow-up MRI and Follow-up TAUS, and Size Difference between the Two Modalities

(A) For 39 PCLs detected in the initial TAUS, the bold line, dotted line and thin line show the sizes measured in follow-up MRI and follow-up TAUS and size difference between the two modalities, respectively.

(B) For 16 PCLs not detected in the initial TAUS, the bold line, dotted line and thin line show the sizes measured in follow-up MRI and follow-up TAUS and size difference between the two modalities, respectively.

MRI: magnetic resonance imaging, PCL: pancreatic cystic lesion, TAUS: transabdominal ultrasonography.

was less frequent than in the latter group (29.1% vs 50%, $p = 0.023$). Additionally, PCLs were not detected by follow-up TAUS if they were smaller (12.7 vs. 6.2 mm, $p = 0.000$; size <10 mm vs. 10 mm ≤ size, $p = 0.000$).

The results of multivariate logistic regression analysis are shown in the far right column of **Table 1**. Presence of fatty liver and PCL size were factors significantly associated with visualization of PCLs in follow-up TAUS (Odds Ratio (OR): 0.252, 95% Confidence Interval (CI): 0.088–0.725, $p = 0.011$; OR: 1.477, 95% CI: 1.252–1.741, $p = 0.000$).

Evaluation of PCL size measured in both TAUS and MRI for follow-up

We also examined the difference in PCL size measured in follow-up TAUS and follow-up MRI for 39 subjects with initially detected PCLs and 16 subjects without them, who underwent both examinations within 3 months of each other (**Fig. 3A**, **3B**). Twenty (51.3%) of the 39 PCLs were under-measured with a size difference of −1.3 ± 2.3 mm (−8 to + 3 mm). In addition, 11 (68.7%) of the 16 PCLs were under-measured with a size difference of −1.8 ± 3.7 mm (−10 to + 4 mm). However, there was no significant difference in PCL size difference between the two groups ($p = 0.524$).

Discussion

This study has 3 main findings. First, the overall PCL detection rate increased from 35.4% (40/113) to 48.7% (55/113) in the follow-up TAUS after MRI, with TAUS showing high reproducibility with respect to the initial TAUS. Our results suggest that undetected PCLs of 10 mm or more in size that were not detected in the initial TAUS could be detected in follow-up TAUS after MRI, and there is the possibility of this increasing when they are located in the pancreatic head. On the other hand, the previous MRI reports probably did not contribute to the detection of PCLs of less than 10 mm, because the detection rate for these PCLs in the initial TAUS was only 30%[12]. Although it seems that TAUS specialists were able to determine the presence of PCLs more confidently using MRI for reference, even when the TAUS image was obscured by adipose tissue and/or intestinal gas, the increase in detection rate in our cohort was much lower than that in the study of Jeon *et al.*[7], which found a significant improvement in detection, from 49.2 to 86.7%. This might be mainly because there was a larger percentage of smaller PCLs in our study than in theirs.

Second, there were no significant associations between PCL visualization in follow-up TAUS and obesity-related factors (BMI, WC, SAT and VAT). However, presence of fatty liver was significantly associated with invisibility of PCLs in follow-up TAUS, which is similar to the result obtained in our recent study[12] and shows that coexisting fatty liver may have lowered PCL detection rates in the initial TAUS.

Third, PCL size was under-measured in the follow-up TAUS for 68.7% of PCLs that were invisible in the initial TAUS. Sun *et al.*[8] conducted a prospective study which showed that under-measurement was slightly more common than over-measurement with TAUS (46 vs. 31%). They also found that the maximum diameter measured by TAUS was smaller by only 0.7 mm on average, compared to that measured by MRI. Also, Kang *et al.*[13] reported that cysts growing faster than 2 mm/year had 3- and 5-year cumulative risks of malignancy of 6.4% and 45.5%, whereas cysts growing less than 2 mm/year had corresponding risks of 1.8 and 1.85%, respectively, in their cohort, which included patients with side-branch IPMN and an initial size of less than 30 mm without main pancreatic duct (MPD) dilatation or mural nodules. In addition, the 2017 revisions of international consensus Fukuoka guidelines[14] recommend surveillance of PCLs depending on the size estimated by an imaging modality. Furthermore, the most recent American College of Gastroenterology (ACG) clinical guideline[15] states that patients with a rapid increase in cyst size of > 3 mm/year should undergo short-interval MRI.

The entire pancreas is indeed difficult to examine using TAUS and the procedure is operator-dependent. Obtaining objective data accurately and reproducibly for cyst dimensions is also difficult with TAUS in the clinical setting. In the present study, there is a high possibility that a considerable number of PCLs were obscured in TAUS and the size may have been under-measured due to overlying gas or adipose tissue. IPMNs are often pleomorphic or clustered, which might cause difficulty in accurate size measurement using an imaging modality. The largest single cyst in a cluster may be measured by TAUS, resulting in under-measurement of size, because it is considered unlikely that all of the individual cysts in a cluster will be fully visualized with TAUS. Thus, accurate evaluation of cyst size during surveillance with a particular imaging modality is important not only for reducing variability in size measurement between modalities but also with regard to risk stratification and clinical decision making.

The limitations of this study include its retrospective design, the fact that it was conducted at a single institution and its relatively small sample size. Also, the use of a linear probe or longer examination time in follow-up TAUS after MRI may have contributed to the higher PCL detection rate. Therefore more prospective research is needed to validate the utility of follow-up TAUS after MRI for detection of known PCLs.

Conclusions

The detection rate for PCLs in follow-up TAUS with

reference to MRI improved in approximately 20% of subjects with invisible PCLs in the initial TAUS and the reproducibility of TAUS with respect to the initial TAUS was very high (97.5%). It should be noted that PCL size can be under-measured by TAUS with reference to MRI.

Conflict of Interest

All authors report that they have no disclosures relevant to this publication to make.

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Original Article

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Importance of Magnetic Resonance Cholangiopancreatography in Diagnosis and Follow-up of Intraductal Papillary Mucinous Neoplasms

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Abstract

Objective: We retrospectively compared the ability of abdominal ultrasound (US) and magnetic resonance cholangiopancreatography (MRCP) to depict intraductal papillary mucinous neoplasms (IPMN), which can be precursors of pancreatic cancer.

Methods: In 170 patients with IPMN, lesion detection by US was examined according to site and size of cysts. Additionally, clinical and imaging features associated with need for surgery during follow-up were determined.

Results: Relative to lesion depiction with MRCP as the standard, cyst detection by US was significantly better in the body of the pancreas than in the head or tail. For small cysts (< 10 mm), US detection was significantly better in the body than in the tail. Among 170 patients, 12 (7.1%) underwent surgical resection during follow-up. A widening main pancreatic duct (MPD; diameter increase ≥ 0.2 mm/year) and greater age (≥ 70 years) were significantly and independently associated with need for surgical resection.

Conclusion: The ability of US to detect cysts in the head and tail of the pancreas is limited, particularly in the latter. Since multiple cysts are relatively frequent in these regions, MRCP should also be performed when a cyst is detected in the body by US. Older individuals and those with relatively rapid widening of the MPD should be considered carefully for surgical resection.

Keywords intraductal papillary mucinous neoplasm (IPMN), magnetic resonance cholangiopancreatography (MRCP), abdominal ultrasound (US)

Intraductal papillary mucinous neoplasms (IPMN) are gaining interest as a risk factor for pancreatic cancer. As many patients with branch-duct IPMN tend to be asymptomatic, cysts representing IPMN are often detected incidentally during abdominal ultrasound (US) performed as part of a routine health check-up or in screening for other diseases. Previous studies have reported 5- and 10-year incidence rates for pancreatic cancer during follow-up of IPMN of 3.0% and 8.8%, respectively[1]. However, factors predicting need for surgical resection in patients with IPMN require further clarification. Through early diagnosis of IPMN and careful follow-up, the need for timely pancreatic surgery can be determined, thereby improving outcomes in pancreatic cancer.

A previous comparison of US and computed tomography (CT) in the diagnosis of IPMN showed that US had significantly higher sensitivity[2]. However, diagnosis requires assessment of the communication between a cystically dilated pancreatic branch duct and the main pancreatic duct (MPD), which is often difficult by US. Magnetic resonance cholangiopancreatography (MRCP) is considered superior to US in this respect, but few studies have compared US and MRCP for diagnosis of IPMN.

This retrospective study compared the abilities of US and MRCP to depict IPMN and sought to identify factors associated with eventual need for surgical resection of IPMN.

Materials and Methods

Patients

Our subjects were 170 follow-up patients with branch duct or mixed-type IPMN who had visited our hospital between January 2007 and December 2016. The definition of IPMN was pancreatic cysts communicating with

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the MPD in MRCP. Follow-up patients were defined as those who underwent MRCP on at least 2 occasions at intervals of at least 6 months. Among them, 85 were male and 85 were female and the mean age at diagnosis was 66 ± 11 years (see statistical analysis section). The mean observation period was 30 ± 19 months. All MR examinations were performed using the same devices. The study was approved by the Institutional Review Board of Fujita Health University and conducted in accordance with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all patients at the time of MRCP.

Clinical features of IPMN

Clinical and imaging features of IPMN considered in this study included diagnostic modality first detecting a lesion, cyst site(s) within the pancreas (head, body, and/or tail), type of cysts (unilocular or multilocular), mode of cyst onset (single or multiple cysts at onset), mean cyst size by site, and increase in diameter of the MPD.

Ability of US to depict IPMN relative to MRCP

Depiction ability was compared between US and MRCP for IPMN that had been depicted by MRCP. Cysts depicted by US were analyzed by site and size.

Surgical resection for IPMN

Clinical features as well as US and MRCP findings were examined for patients who underwent surgical resection. The clinical features included age, gender, duration of follow-up, single vs. multiple lesions at onset, unilocular vs. multilocular cysts, cyst site, cyst growth rate, rate of MPD diameter enlargement, presence of mural nodules, and presence of masses. Comparisons between malignant and non-malignant cases included the features considered in identifying patients who required surgical resection during follow-up. Annual rates of increase in cyst or MPD diameter were calculated by dividing the observed difference in diameter of the cyst or MPD by the time interval (in years) between the start of follow-up (initial diagnosis of IPMN) and the endpoint (date of surgical resection or latest medical follow-up visit prior to December 2016). In investigating the incidence of surgical resection, the above definitions for the beginning and endpoint of follow-up were used. Factors associated with surgical resection were analyzed retrospectively.

Statistical analysis

Categorical data are presented as numbers followed by percentages. Continuous data are presented as the mean± standard deviation (SD) or median (range). Normally distributed variables were compared between groups of patients who underwent and did not undergo surgical resection, such as pancreatectomy, using Student's t test, while non-normally distributed variables were compared using the Mann-Whitney U test. Frequency data were compared using a chi-squared test or Fisher's exact test, as appropriate. Cumulative incidence of surgical resection was calculated using the Kaplan-Meier method. Differences among patients who underwent and did not undergo surgical resection were assessed using the log-rank test. The time frame for surgical resection was defined as beginning at initial diagnosis of IPMN. The Cox proportional hazard model was used for multivariate analyses of factors associated with surgical resection. We determined cutoff values for factors associated with surgical resection using receiver operating characteristic analyses. Statistical analyses were performed using SPSS Statistics 21.0 (IBM SPSS., USA). A p value below 0.05 was considered to indicate statistical significance. Tests were 2-tailed.

Results

Baseline characteristics of enrolled patients

The mean age of the study subjects (85 male and 85 female) was 66 ± 11 years. IPMN were initially detected by US in 110 patients (65%), CT in 40 (24%), MRCP in 11 (6%), and by other methods in 6 (4%), including unknown methods in 3. Cyst numbers by site included 102 in the head, 124 in the body, and 64 in the tail. A single cyst was observed at onset in 43 patients, while multiple cysts were present initially in 127. Mean cyst size was 15.3 ± 8.9 mm in the head, 11.7 ± 6.9 mm in the body, and 9.8 ± 6.5 mm in the tail. Unilocular cysts numbered 93, while 77 cysts were multilocular. The mean MPD diameter was 2.3 ± 1.2 mm (**Table 1**).

Ability of US to detect IPMN relative to MRCP

For all cyst diameters, detection by US relative to MRCP was 60.8% (62/102) for the pancreatic head, 79.8% (99/124) for the body, and 32.8% (21/64) for the tail. Detection by US in the tail was significantly poorer than in the body ($p < 0.005$). US detection of cysts with diameters < 5 mm ($n = 25$) relative to MRCP was 100% (6/6) in the body and 23.1% (3/13) in the tail, again significantly poorer in the tail than in the body ($p < 0.01$). For cysts < 10 mm ($n = 111$), detection by US relative to MRCP was 75.4% (43/57) in the body and 17.2% (5/29) in the tail, representing a significant difference between sites ($p < 0.001$; **Fig. 1**).

Incidence of surgical resection in patients with IPMN

Among the 170 follow-up patients, 12 (7.1%) underwent surgical resection at some point. Their histopathologic tumor diagnoses were typical pancreatic cancer (2 patients), intraductal papillary mucinous carcinoma (IPMC) (3), and intraductal papillary mucinous adenoma (IPMA) (7). Indications for surgical resection were mural nodules (8 patients), cyst enlargement (2), presence of masses (2), and MPD stenosis (2; overlap exists). For the 12 follow-up patients who underwent resection, the mean observation period was 34 ± 29 months, mean cyst size at initial diagnosis was 24.4 ±

Table 1. Characteristics of Patients in Study

Characteristics	Patients
Age (years)	66 ± 10.7
Gender (female/male)	85/85
Mean observation period (months)	30 ± 19
Diagnostic modality	US 110 (65%)/CT 40 (24%)/MRCP 11 (6%)/Others 6 (4%)
Sites and numbers of cysts (head/body/tail)	102/124/64
Mean cyst size (mm; head/body/tail)	15.3 ± 8.9/11.7 ± 6.9/ 9.8 ± 6.5
Unilocular/multilocular	93/77
Single/multiple cyst(s) at onset	43/127
Mean diameter of MPD (mm)	2.3 ± 1.2

US: ultrasonography, CT: computed tomography, MRCP: magnetic resonance cholangiopancreatography, MPD: main pancreatic duct. Data are presented as mean ± SD for continuous variables and n (%) for categorical variables.

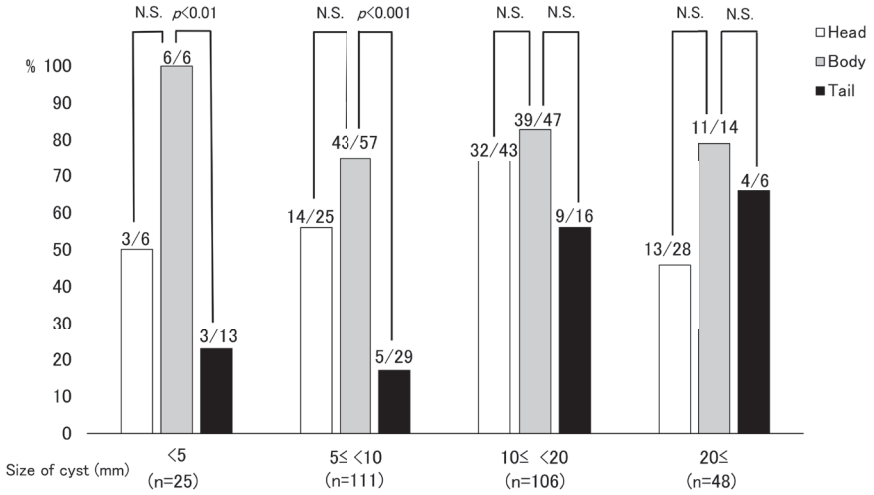

Fig.1. Depiction Ability of US for IPMNs Examined by Site and Size

Relative to Diagnosis of IPMN by MRCP, depiction ability of US for smaller IPMN (less than 5 mm) located in the pancreatic tail was significantly lower than for those located in the body (p<0.01). The depiction ability of US for slightly larger IPMN (more than 5 mm and less than 10 mm) in the tail was also significantly lower than in the body (p<0.001).

Table 2. Clinical and Imaging Findings During Follow-up : Surgical vs. Non-surgical Cases

Characteristics	Surgery (n=12)	No surgery (n=158)	p value
Age (years)	70.0 ± 7.88	66.0 ± 10.8	0.143
Gender (female/male)	8 (67%)/4 (33%)	78 (49%)/80 (51%)	0.248
Follow-up duration (months)	30 ± 19	40 ± 29	0.244
Unilocular/multilocular	7 (58%)/5 (42%)	85 (54%)/73 (46%)	0.761
Single/multiple cysts at onset	1 (8%)/11 (92%)	43 (27%)/115 (73%)	0.145
Sites and numbers of cysts (head and body/tail)	12 (100%)/0 (0%)	150 (95%)/8 (5%)	0.423
Cyst growth rate (mm/year)	0.69 ± 1.09	0.66 ± 1.41	0.944
Rate of increase in MPD diameter (mm/year)	0.41 ± 0.66	0.08 ± 0.31	<0.001
Mural nodules (present/absent)	4 (33%)/8 (67%)	2 (1.3%)/156 (98.7%)	<0.001
Masses (present/absent)	3 (25%)/9 (75%)	0 (0%)/158 (100%)	<0.001

"Surgery" refers to resections involving the pancreas at any time point in the course. MPD: main pancreatic duct. Data are presented as mean ± SD for continuous variables and n (%) for categorical variables.

14.5 mm, preoperative mean cyst size was 30.8 ± 20.3 mm, mean MPD diameter at initial diagnosis was 2.8 ± 1.0 mm, preoperative mean MPD diameter was 3.6 ± 1.9 mm, and preoperative mean size of nodules was 13.8 ± 12.3 mm.

Comparing US and MRCP with regard to the mural nodules found in 8 patients, they were detected by US in 3 patients (37.5%) and MRCP in 6 (75.0%).

Factors associated with surgical resection for IPMN

Among the 170 follow-up patients, 12 were surgery cases. Their characteristics were compared with those of the 158 non-surgery cases (**Table 2**). Significant dif-

ferences were observed between the two groups for rate of change in MPD diameter, presence of nodules, and presence of masses. Surgical resection was more likely in patients with an annual rate of increase in MPD diameter of ≥ 0.2 mm (**Fig.2**). Performing multivariate analysis by Cox proportional hazards regression with factors including age, gender, single vs. multiple cysts at onset, unilocular vs. multilocular cysts, cyst site, cyst growth rate, and rate of change in MPD diameter confirmed increase in MPD diameter by ≥ 0.2 mm/year and age ≥ 70 years to be factors significantly and independently associated with surgical resection in patients with IPMN (**Table 3**).

Discussion

MRCP, endoscopic US, abdominal CT, and abdominal US have been used for the diagnosis and follow-up of IPMN[2]. A previous study comparing US and CT for diagnosis found that US had significantly greater sensitivity than CT (96% vs. 33%)[3]. In another study, IPMN detection rates were approximately 20% for MRCP[4] and 3% for CT[5], demonstrating greater diagnostic ability for MRCP. However, the effectiveness of US vs. MRCP in patients with IPMN has remained an issue. The present study comparing the diagnostic capability of US and MRCP for IPMN demonstrated that US detection of IPMNs with diameters <10 mm in the pancreatic tail was significantly poorer than in the pancreatic body.

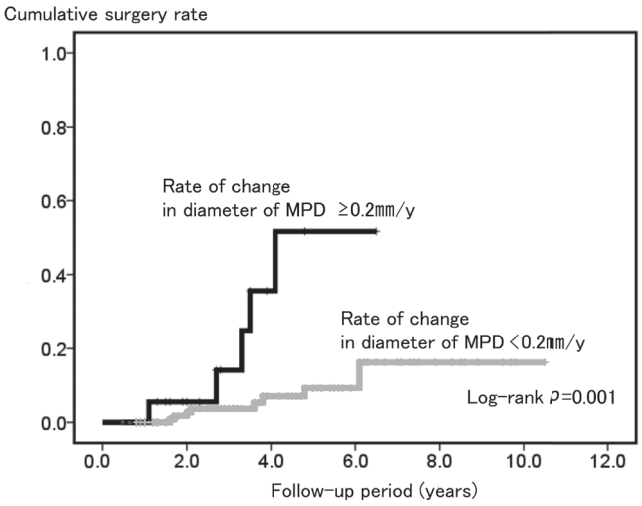

Fig.2. Cumulative Incidence Rates of Surgical Resection According to Rate of Change in the Diameter of MPD
The Maximum Diameter of The Main Pancreatic Duct (MPD) was Measured in Each Patient Using MRCP. The cumulative incidence of surgical resection in patients with higher rates of MPD diameter enlargement (≥ 0.2 mm/year) was significantly higher than that in patients with slower MPD diameter change (< 0.2 mm/year), based on Kaplan-Meier analysis and the log-rank test ($p < 0.001$).

Histopathologic diagnoses of branch-duct IPMNs include hyperplasia, IPMA, and IPMC, with a mean reported incidence for the carcinomas of 31.1% (14.4% to 47.9%)[6–12]. This risk of cancer underscores the importance of identifying factors predicting the need for resection of IPMN. The present study identified an increase in MPD diameter of ≥ 0.2 mm/year and an age of ≥ 70 years as significant independent factors associated with surgical resection in patients with IPMN. Prospective investigations in larger cohorts should provide more definitive evidence.

MRCP is the imaging modality best suited to diagnosis of IPMN. Specifically, MRCP has been advocated as the first choice for detailed examination of IPMN as it can delineate structures such as septa resulting in multiloculation, mural nodules, and communication with the MPD[13]. Among 16 of our surgical cases where mural nodules were observed within cysts, nodules were delineated by MRCP in 10 (62.5%), illustrating the superiority of MRCP.

As US is noninvasive and convenient, it is often used as the initial modality for screening. However, detection ability can be affected by body habitus and presence of gas in the alimentary canal, as well as the skill of the sonographer[14,15]. In particular, cysts in the pancreatic tail are not clearly delineated by US in many cases. This was demonstrated in the present study using MRCP as the standard by the relatively low US detection rate for IPMN in the tail (head: 60.8%, tail: 32.8%). As for CT, it involves radiation exposure and contrast resolution is poorer than with MRCP.

However, MRCP cannot be used for routine assessment in all cases. Disadvantages of MRCP include long examination time and need for considerable patient cooperation, such as having to hold the breath and remain still. In addition, MRCP may be contraindicated in some patients, for instance those with cardiac pacemakers[16].

Performing abdominal US as the first examination can provide valuable information, despite its shortcomings. One study found it highly useful for detecting pancreatic cysts with diameters ≥ 5 mm (sensitivity: 96%; specificity: 94%; diagnostic accuracy: 95%)[2].

Table 3. Factors Associated with Surgery by Cox Proportional Hazard Analysis

Characteristics	Category	Hazard ratio	95% CI	*p* value
Rate of increase in MPD diameter (mm/year)	< 0.2 ≥ 0.2	7.32	2.30–23.36	0.001
Age (years)	< 70 ≥ 70	3.26	1.08–9.85	0.036

CI: confidence interval, MPD: main pancreatic duct.

When cystic lesions detected by US are suspected to be IPMN, depending on cyst size and location, follow-up examination by MRCP can be performed if not contraindicated. (Respiratory triggering of MRCP image acquisition might reduce need for holding the breath in some patients.)

Our retrospective study design imposed some limitations. Not all patients diagnosed with IPMN had undergone both US and MRCP. In addition, examination intervals varied among subjects. Prospective studies involving large numbers of patients with IPMN are needed.

Conclusion

In the pancreatic tail, US was less able to depict small cysts than MRCP. As multiple lesions are common with IPMN, US detection of cysts in the pancreatic head or body should be followed by MRCP when possible, particularly for detection of any cysts in the tail that might otherwise be missed. Patients with relatively rapid increases in MPD diameter and older individuals must be monitored closely, as they may require surgical resection.

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Original Article

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Clinical Influence of Hepatitis C Virus Eradication by Direct-acting Antivirals on Lipid Levels and "Ningen Dock" Health Check-up Categories in Patients with Chronic Hepatitis C Virus Infection

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Abstract

Background and Aims: Lipid pathways play a crucial role in multiple aspects of the hepatitis C virus (HCV) life cycle. As treatment for HCV infection, direct-acting antivirals (DAAs) can achieve a high rate for sustained virological response (SVR). The aim of this study was to compare lipid marker changes between SVR and non-SVR patients.

Methods: We compared clinical and lipid markers as well as changes in Japanese "Ningen Dock" health check-up categories.

Patients: This study enrolled 340 patients (154 men, median age: 71 years) who had received DAAs for comparisons of clinical and lipid markers between 333 SVR (97.9%) and 7 non-SVR (2.1%) patients.

Results: Baseline clinical markers were comparable between the SVR and non-SVR groups apart from platelet count ($p = 0.049$). SVR patients exhibited significant decreases in AST, ALT, and AFP and increases in platelet count and albumin (ALB) (all $p < 0.001$) under DAA treatment, while non-SVR patients did not. The SVR group also had significant increases in TC, LDL-C, HDL-C, and non-HDL-C lipid markers (all $p < 0.001$). Regarding Ningen Dock criteria, the proportion of patients in category D-low (Medical care needed) for LDL-C and non-HDL-C decreased significantly, while that of patients in category B (Slightly abnormal), C (Requires follow-up), and D-high for LDL-C and non-HDL-C increased significantly in SVR patients. In addition, the proportion in category C and D-low for HDL-C dropped significantly.

Conclusion: HCV eradication by DAAs can produce significant changes in both lipid profiles and Ningen Dock categories. Clinicians should consider HCV eradication history for patients with abnormal lipid profiles. Further studies are needed on the long-term effect of lipid changes after achieving an SVR for HCV.

Keywords direct-acting antivirals (DAAs), hepatitis C virus, lipids, Ningen Dock

With an estimated 130–170 million people chronically infected worldwide, including 1.5 million in Japan, hepatitis C virus (HCV) infection is a global health concern. Chronic HCV infection eventually results in severe liver disease manifesting as advanced fibrosis, cirrhosis, and hepatocellular carcinoma (HCC)[1–4]. HCV eradication is the most effective treatment for halting disease progression. Since replacing interferon (IFN) and combinations of IFN or pegylated IFN and ribavirin (RBV) eradication treatment, direct-acting antivirals (DAAs) have revolutionized HCV therapy by targeting specific steps within the HCV lifecycle[5], resulting in sustained virological response (SVR) rates of over 95% according to real-world data[6], despite the fact that past history of HCC has been reported to be an independent risk factor for DAA treatment failure[7].

It is well known that lipid pathways play a crucial role in multiple aspects of HCV progression[8]. In a large-scale community-based study, chronic HCV infection was associated with decreased serum cholesterol and low-density lipoprotein cholesterol (LDL-C)

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levels, which implied that the influence of HCV figured prominently in the serum lipid profiles of HCV patients[9]. The resulting hypolipidemia can be resolved with successful hepatitis C treatment but persists in non-responders[10].

In Japan, "Ningen Dock" is a complete health check-up and screening system for the prevention, early detection, and treatment of adult lifestyle-related diseases and maintenance of general health. Ningen Dock includes several tests related to lipid levels. Based on a large body of individual data[11], the results of these tests are mainly divided into the 5 categories described at https://www.ningen-dock.jp/wp/wp-content/uploads/2018/06/Criteria-category.pdf as: A, Normal; B, Slightly abnormal; C, Requires follow-up (including life improvement and re-examination); D, Medical care needed; and E, On treatment.

It had been unknown whether HCV eradication through DAA treatment could lead to Ningen Dock category changes in lipid levels. Accordingly, this study assessed the clinical influence of HCV eradication by DAAs on lipid levels and Ningen Dock categories in patients with chronic HCV infection.

Patients and Methods

Patients

This study was a retrospective, multi-center, cohort analysis across Nagano Prefecture, Japan. For it, a total of 1,291 patients with chronic HCV infection who underwent DAA therapy at Shinshu University Hospital (Matsumoto, Japan) or its affiliated institutions between April 2015 and December 2018 and completed observation periods of 12 weeks after commencing DAA treatment (SVR12) were initially considered. An SVR, which was defined as undetectable HCV RNA at SVR12, was achieved in 1,235/1,291 patients (95.7%). After excluding patients having insufficient clinical data for analysis, 340 patients with chronic HCV infection were ultimately enrolled. The racial background of all patients was Japanese. In accordance with previously reported criteria, diagnosis of chronic hepatitis C was based on presence of serum HCV antibodies and detectable HCV RNA[12]. Presence of chronic HCV infection was defined as detectable HCV RNA in the real-time polymerase chain reaction at initiation of therapy.

This study was reviewed and approved by the Institutional Review Board of Shinshu University School of Medicine (approval number: 3244) and its affiliated hospitals. Written informed consent was obtained from all participating subjects. The study was conducted according to the principals of the Declaration of Helsinki.

Study design

Details of age, gender, history of IFN treatment, history of HCC, and comorbidities such as hypertension, diabetes mellitus, and dyslipidemia were registered for all patients in this cohort upon commencing DAAs.

The patients were treated with DAA regimens that included daclatasvir+asunaprevir (DCV+ASV), ledipasvir/sofosbuvir (LDV/SOF), ombitasvir/paritaprevir/ritonavir (OBV/PTV/r), and elbasvir+grazoprevir (EBR+GZR) for HCV genotype 1, SOF+RBV for genotype 2, and glecaprevir/pibrentasvir (GLE/PIB) for genotype 1, 2, and others based on guidelines issued by the Japan Society of Hepatology[13].

Laboratory testing

All laboratory data, including platelet count, albumin (ALB), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alpha fetoprotein (AFP), total cholesterol (TC), LDL-C, high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) were determined using standard methods at the respective institutions. Non-HDL-C was calculated as: TC – HDL-C.

Ningen Dock lipid level categories

Below are the category ranges for LDL-C, non-HDL-C, and HDL-C as defined in Ningen Dock criteria (https://www.ningen-dock.jp/wp/wp-content/uploads/2018/06/Criteria-category.pdf).

LDL-C: A (Normal) 60–119 mg/dL, B (Slightly abnormal) 120–139 mg/dL, C (Requires follow-up) 140–179 mg/dL, and D (Medical care needed) 59 mg/dL or less (D-low) or 180 mg/dL or greater (D-high).

Non-HDL-C: A (Normal) 90–149 mg/dL, B (Slightly abnormal) 150–169 mg/dL, C (Requires follow-up) 170–209 mg/dL, and D (Medical care needed) 89 mg/dL or less (D-low) or 210 mg/dL or greater (D-high).

HDL-C: A (Normal) 40 mg/dL or greater, C (Requires follow-up) 35–39 mg/dL, and D (Medical care needed) 34 mg/dL or less.

Statistical analysis

Statistical analysis and data visualization were carried out using StatFlex ver. 7.0.7 (Artech Co., Ltd., Osaka, Japan). Continuous baseline data were expressed as the median ± interquartile range and statistically evaluated by means of the Mann-Whitney U test. Categorical variables were presented as the frequency (percentage) and analyzed using the chi-square test. Ordinal data was tested by the Wilcoxon signed-rank test. All statistical tests were two-sided and evaluated at the 0.05 level of significance.

Results

Baseline clinical characteristics

The baseline clinical characteristics in this study are summarized in **Table 1**. Of the 340 enrolled patients, 154 (45.3%) were male and 186 (54.7%) were female. Median age was 71 years. Roughly a quarter of all participants had received previous IFN treatment. Approximately 41% of patients had hypertension as a complication, with almost all cases under medical treatment.

The complications of diabetes mellitus (15.9%) and dyslipidemia (8.8%) were observed as well. Since there are cautions regarding the coadministration of most 3-hydroxy-3-methylglutaryl coenzyme-A reductase inhibitors (i.e., statins) in Japan, all subjects in this study had discontinued statins at least several weeks before commencing HCV eradication. The numbers of patients who were treated with DCV+ASV, OBV/PTV/r, LDV/SOF, EBV+GRZ, GLE/PIB, and SOF+RBV were 43, 29, 98, 47, 73, and 50, respectively. The overall SVR rate was 97.9% (333/340 patients) in the present cohort.

Changes in hepatitis clinical markers and lipid markers

Overall, AST, ALT, and AFP were significantly decreased at SVR12 as compared with before DAA treatment (Pre) (all $p < 0.001$) and platelet count and ALB were significantly increased (both $p < 0.001$). TC, LDL-C, HDL-C, and non-HDL-C were significantly higher at SVR12 as compared with baseline (Pre) levels (all $p < 0.001$) (**Fig. 1**).

Baseline clinical comparisons between SVR and non-SVR patients

The baseline clinical characteristics of the SVR and non-SVR groups are compared in **Table 2**. There were no remarkable differences in clinical markers apart from platelet count ($p = 0.049$).

Hepatitis clinical marker and lipid marker comparisons between SVR and non-SVR patients

AST, ALT, and AFP in the SVR group were significantly decreased at SVR12 as compared with at Pre (all $p < 0.001$) but remained similar in the non-SVR group. Platelet count and ALB were significantly higher at SVR12 versus at Pre (both $p < 0.001$) in the SVR group only. TC, LDL-C, HDL-C, and non-HDL-C were significantly increased at SVR12 as compared with at Pre in SVR patients (all $p < 0.001$) (**Fig. 2**).

Patient proportion changes in lipid level categories

In the SVR group, for LDL-C and non-HDL-C, the proportion of patients in category D-low was significantly decreased, while that in category B, C, and D-high was significantly increased at SVR12 as compared with at Pre ($p < 0.001$, respectively). The proportion of patients in category C and D-low for HDL-C was significantly decreased at SVR12 versus at Pre ($p < 0.001$) (**Fig. 3**).

Discussion

This study identified two important clinical features of lipid changes in long-term HCV eradication therapy using DAAs: 1) lipid levels changed dramatically under DAA treatment, and 2) treatment with DAAs resulted in changes in Ningen Dock lipid level categories. These findings have important real-world implications in pa-

Table 1. Baseline Characteristics in This Study

	Median	(IQR or %)
Age (yrs)	71	(63–76)
Male	154	(45.3%)
HCV genotype 1/2/other	264/73/3	
IFN past history	87	(25.6%)
DAA past history	9	(0.3%)
HCC past history	27	(7.9%)
Hypertension	139	(40.9%)
Hypertension with medication	133	(39.1%)
Diabetes mellitus	54	(15.9%)
Diabetes mellitus with medication	40	(11.8%)
Dyslipidemia	30	(8.8%)
Dyslipidemia with medication*	20	(5.9%)
Laboratory data		
Platelet count (x10^4/μL)	15.8	(12.0–19.8)
ALB (mg/dL)	4.1	(3.8–4.3)
AST (U/L)	37	(27–53)
ALT (U/L)	33	(23–56)
AFP (ng/mL)	4.2	(2.5–7.0)
HCV RNA (Log IU/mL)	6.2	(5.6–6.6)
DAA regimens		
DCV/ASV, OBV/PTV/r, LDV/SOF	43, 29, 98	
EBR+GRZ, GLE/PIB, SOF+RBV	47, 73, 50	
Clinical outcome		
SVR	333	(97.9%)

*: All patients halted medication several weeks before DAA treatment in accordance with drug usage directions.
Abbreviations: IQR, interquartile range; HCV, hepatitis C virus; IFN, interferon; DAA, direct-acting antiviral; HCC, hepatocellular carcinoma; ALB, albumin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; AFP, alpha fetoprotein; DCV+ASV, daclatasvir+asunaprevir; OBV/PTV/r, ombitasvir/paritaprevir/ritonavir; LDV/SOF, ledipasvir/sofosbuvir; EBR+GZR, elbasvir+grazoprevir; GLE/PIB, glecaprevir/pibrentasvir; SOF+RBV, sofosbuvir+ribavirin; SVR, sustained virological response

Table 2. Clinical Comparisons between SVR and non-SVR Groups

	SVR (*N* = 333)	Non-SVR (*N* = 7)	*p*-value
Age (yrs)	71	69	0.672
Male	150 (45.0%)	4 (57.1%)	0.706
HCV genotype 1/2/other	259/71/3	5/2/0	0.013
IFN past history	83 (24.9%)	4 (57.1%)	0.074
DAA past history	9 (2.7%)	0 (0%)	1.000
HCC past history	9 (2.7%)	0 (0%)	0.100
Hypertension	135 (40.5%)	4 (57.1%)	0.450
Diabetes mellitus	52 (15.6%)	2 (28.6%)	0.308
Dyslipidemia*	30 (9.0%)	0 (0%)	1.000
Laboratory data			
Platelet count (x10^4/μL)	19.8	15.8	0.049
ALB (mg/dL)	4.1	3.9	0.121
AST (U/L)	36	56	0.197
ALT (U/L)	33	47	0.297
AFP (ng/mL)	4.1	7.5	0.110
HCV RNA (Log IU/mL)	6.1	6.4	0.122
DAA regimens			
DCV/ASV, OBV/PTV/r, LDV/SOF	42, 29, 96	1, 0, 2	0.518
EBR+GRZ, GLE/PIB, SOF+RBV	45, 73, 48	2, 0, 2	

*: All patients halted medication several weeks before DAA treatment in accordance with drug usage directions.
Abbreviations: IQR, interquartile range; HCV, hepatitis C virus; IFN, interferon; DAA, direct-acting antiviral; HCC, hepatocellular carcinoma; ALB, albumin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; AFP, alpha fetoprotein; DCV+ASV, daclatasvir+asunaprevir; OBV/PTV/r, ombitasvir/paritaprevir/ritonavir; LDV/SOF, ledipasvir/sofosbuvir; EBR+GZR, elbasvir+grazoprevir; GLE/PIB, glecaprevir/pibrentasvir; SOF+RBV, sofosbuvir+ribavirin

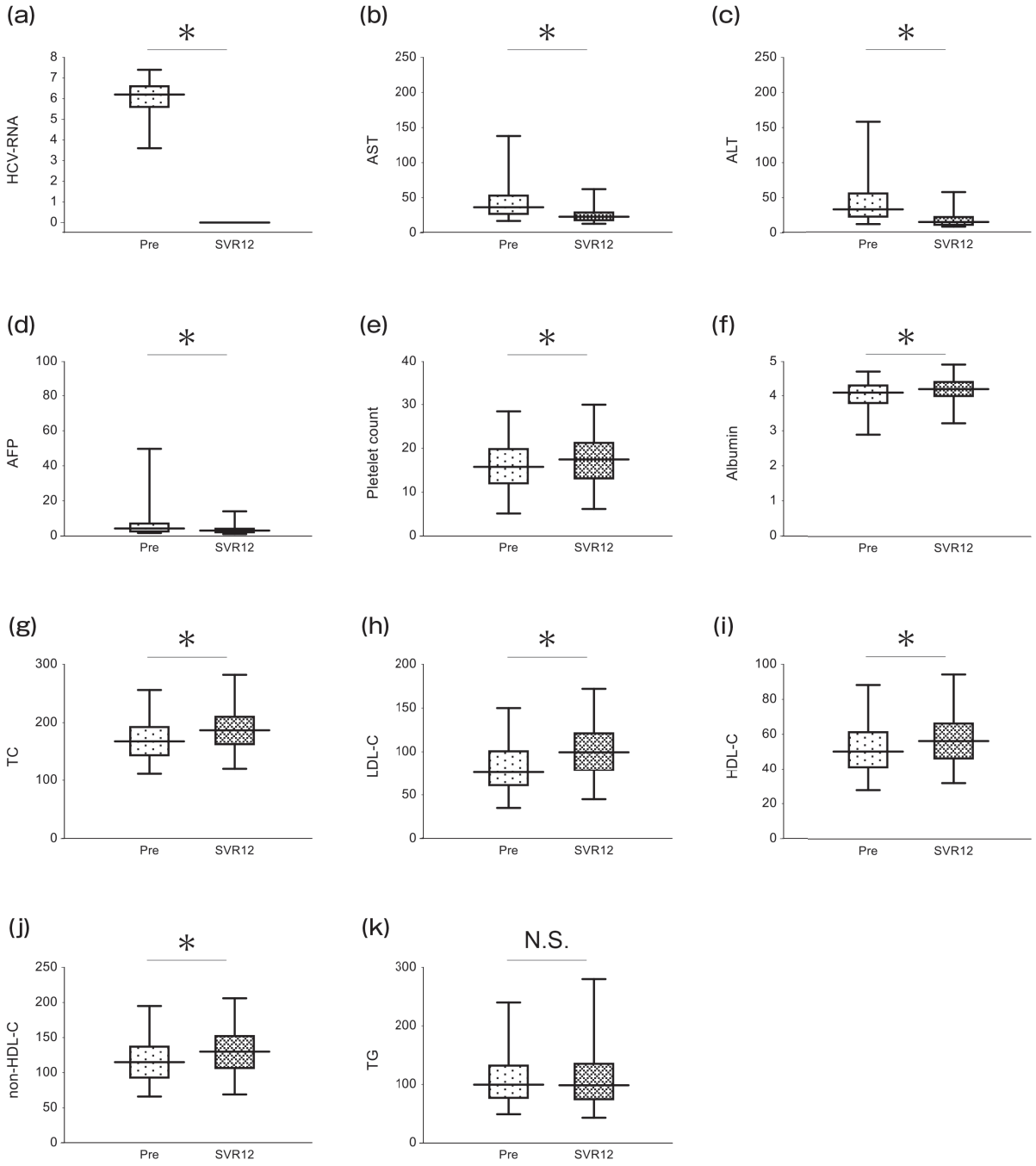

Fig.1. Changes in hepatitis clinical markers (a) HCV-RNA, (b) AST, (c) ALT, (d) AFP, (e) platelet count, and (f) albumin and lipid markers (g) TC, (h) LDL-C, (i) HDL-C, (j) non-HDL-C, and (k) TG, pre treatment with DAAs (Pre) and 12 weeks after commencing DAA treatment (SVR12) (*n* = 340)

*: p <0.001. HCV, hepatitis C virus; AST, aspartate aminotransferase; ALT, alanine aminotransferase; AFP, alpha fetoprotein; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; DAA, direct-acting antiviral; N.S., not significant.

tient treatment during health check-ups.

The lipid profiles for TC, LDL-C, HDL-C, and non-HDL-C all changed remarkably during DAA therapy in this study, which is consistent with previous studies on IFN-free treatment[10,14]. Moreover, Ningen Dock category distributions were significantly altered in SVR patients, indicating that HCV replication has a direct effect on lipid homeostasis. In this regard, it has been found that attachment of HCV particles to LDL receptors (LDL-R) on hepatocytes is needed for viral replication[8]. In addition HCV was observed to stimulate LDL-R expression in both HCV-infected Huh7 cells and liver tissue samples from chronic hepatitis C patients[15]. Therefore, from the viewpoint of molecular mechanisms in the liver, we can speculate that HCV eradication reduces LDL-R expression to elevate LDL-C. Further studies are

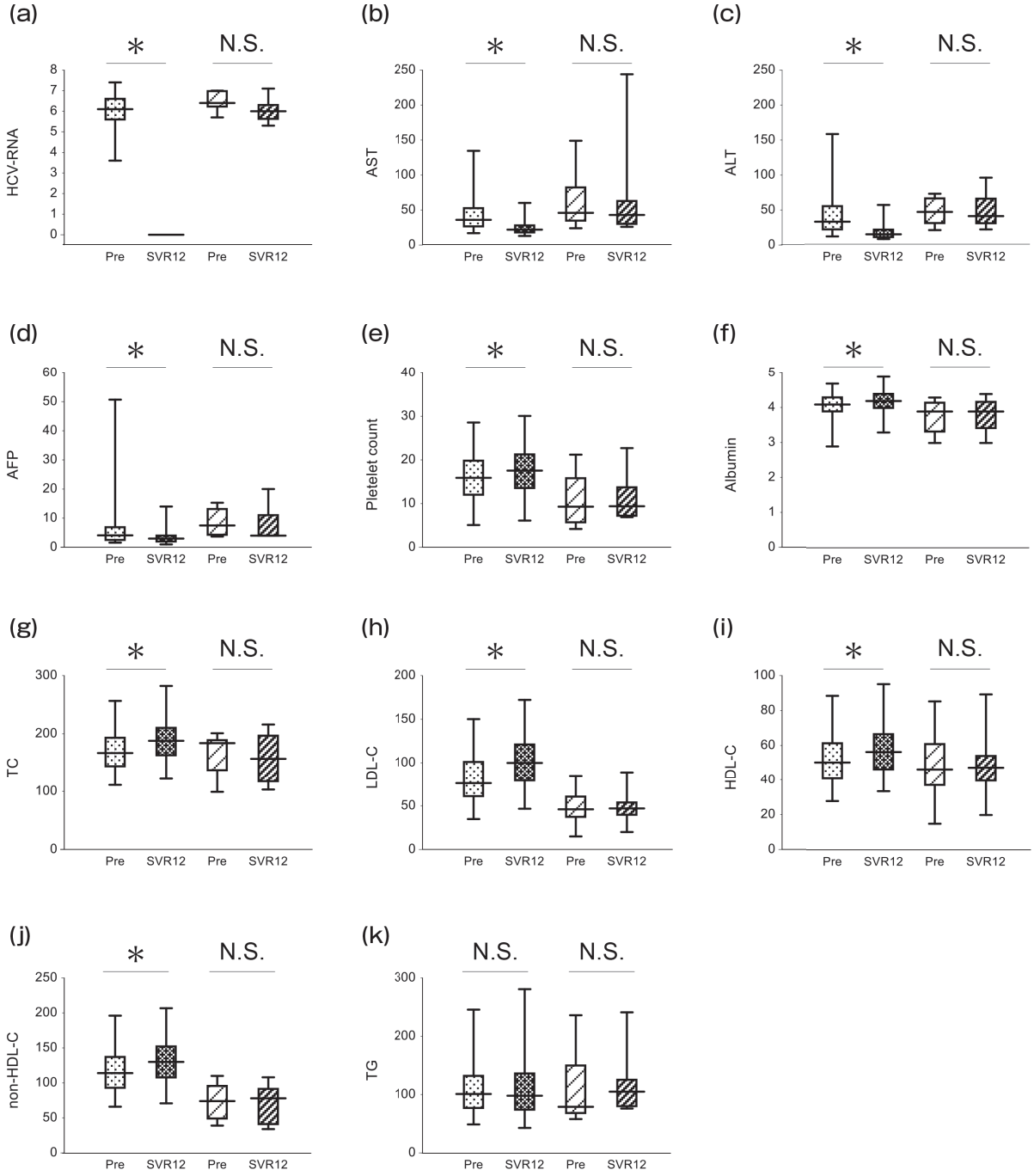

Fig.2. Changes in hepatitis clinical markers (a) HCV-RNA, (b) AST, (c) ALT, (d) AFP, (e) platelet count, and (f) albumin and lipid markers (g) TC, (h) LDL-C, (i) HDL-C, (j) non-HDL-C, and (k) TG pre treatment with DAAs (Pre) and 12 weeks after commencing DAA treatment (SVR12) in SVR (*n* = 333) and non-SVR (*n* = 7) patients

*: p <0.001. HCV, hepatitis C virus; AST, aspartate aminotransferase; ALT, alanine aminotransferase; AFP, alpha fetoprotein; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; DAA, direct-acting antiviral; N.S., not significant

therefore required on additional clinical effects of HCV eradication on lipid and other pathways.

We observed significant lipid level changes under DAA treatment in SVR patients, but not in non-SVR patients. Chida *et al.* reported that apolipoprotein (Apo) A-I, Apo B, Apo C-II, and Apo C-III increased and that Apo A-II and Apo E decreased significantly and rapidly after commencing DAA therapy[10]. They also noted correlations between LDL-C and Apo B differences and between HDL-C and Apo A-I differences before DAAs and at 4 weeks after starting them[10]. In addition, Molina *et al.* reported that Apo C-III in chronically infected HCV patients was lower than in resolved acute HCV infection and HCV-negative patients[16]. Furthermore, circulating HCV has been observed to be complexed with very low-density lipoprotein (VLDL) as lipoviroparticles

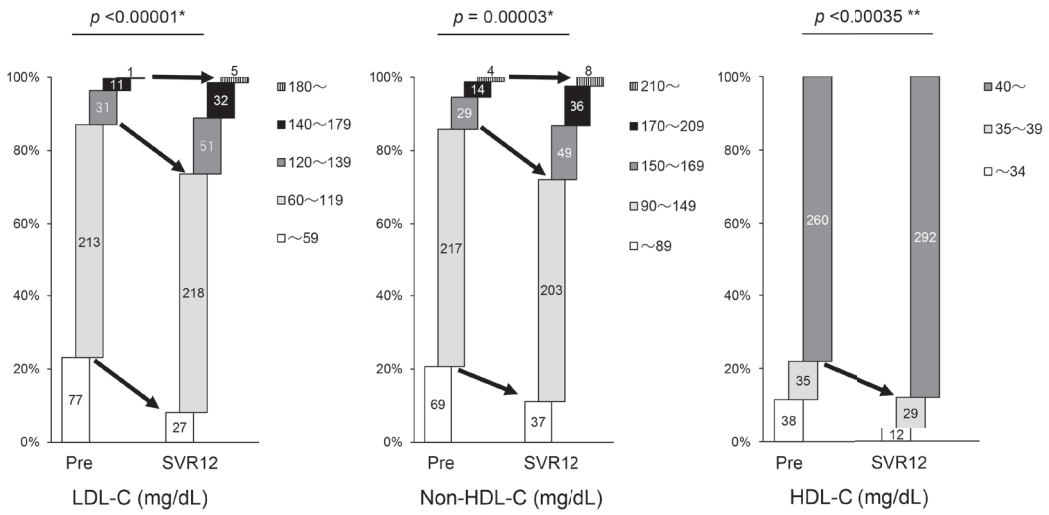

Fig.3. Patient Proportion Changes in Ningen Dock Lipid Level Categories for SVR Patients (*n* = 333)
Categories are based on the definitions described at: https://www.ningen-dock.jp/wp/wp-content/uploads/2018/06/Criteria-category.pdf
*: P values were calculated by 2x5 Chi-squared test. **: P values were calculated by 2x3 Chi-squared test.
LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol

containing host Apo, which play an important role in lipid metabolism during the formation and stabilization of HCV particles[17]. Therefore, the long-term physiological effects of the release of lipids bound to HCV on lipid metabolism need monitoring in our cohort.

It remains debatable whether HCV eradication by DAAs can produce secondary benefits, such as mitigation of atherosclerosis. Previously, HCV eradication by DAAs improved carotid intima-media thickness (IMT) measurements in patients with severe liver fibrosis in an Italian cohort[18]. However, a recent study in Japan noted deterioration in IMT as well as an increase in small dense LDL after a year of DAA treatment[19]. Therefore, future consideration of HCV eradication should include liver status as well as systemic conditions.

Our study had several limitations in addition to its retrospective design. First, it included only a small number of non-SVR patients so larger cohorts are needed. Second, more than half of the potential subjects were excluded due to a lack of lipid data since clinicians, specifically hepatologists, were possibly less concerned about lipid profiles because they felt that they had no direct influence on patients and were trying to keep medical insurance expenses under control. However, based on our findings and those of previous studies, lipid changes also need to be addressed during and after DAA treatment to predict the long-term outcomes of HCV eradication in humans. Third, it will be necessary to determine the compatibility of the Ningen Dock category criteria with other established systems worldwide to validate the findings of this study.

Conclusions

HCV eradication by DAA therapy can achieve significant lipid profile changes as well as those in Ningen Dock lipid measurement categories. Clinicians should consider HCV eradication history for patients with abnormal lipid profiles. Further studies are needed on the long-term effects of lipid changes after achieving an SVR.

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Compliance with ethical standards

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Original Article

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Transitions in Blood Hemoglobin Levels and Platelet Counts in 32–65-year-old Female Examinees Undergoing Periodic Health Check-ups

Atsushi Hioki, Rie Kitayama, Hisakazu Kawai, Makoto Hayashi

Abstract

Objective: Cross-sectional surveys have shown blood hemoglobin (Hb) levels to be low in women in their 30s and 40s. This study investigated secular transitions in blood Hb levels and relevant laboratory data in women aged in their 30s to mid-60s.

Methods: We included the data of 1,370 women who underwent at least six periodic health check-ups, including those for blood Hb level, mean corpuscular volume (MCV), and platelet count. The transitions in and mutual relationships of these data were investigated.

Results: In women who did not receive anemia treatment at any health check-up, blood Hb levels began to decrease when they were in their mid-30s, remained low during their 40s, and increased again in their 50s. This tendency was stronger in women with anemia history than in those without anemia history. MCV decreased and platelet count increased in women in their 40s, but returned to previous levels in their 50s. The average age of menopause during the study period was 50.9 ± 3.1 (SD) years. Platelet count exceeded the reference value in 17.1% of women with blood Hb levels ≤ 11.0 g/dL. A strong negative correlation was observed between individual blood Hb level and platelet count over time, especially with blood Hb level fluctuations ≥ 3 g/dL.

Conclusions: The blood Hb level of women decreased when the women were in their 40s and recovered during their 50s. These changes were small in those without previous anemia history. As the blood Hb level decreased, the proportion of women with platelet counts exceeding the reference value slightly increased.

Keywords female, hemoglobin, platelet, transition

The annual reports of the National Health and Nutrition Survey[1] from 1977 to 2017, and an epidemiological study on health check-up records of healthy women in different age groups[2] showed that blood hemoglobin (Hb) levels were low in Japanese women in their 30s and 40s. This was not observed in men in the same age groups. The mean corpuscular volume (MCV) was low in women in these age groups primarily because of iron deficiency due to menstruation and menorrhagia[2].

Individuals in their 40s and 50s account for a large number of the health check-up examinees in Ningen Dock[3], and it is often necessary to provide proper instruction on anemia prevention or give treatment[4,5]. It is also useful to know the transitions in anemia indicators in these age groups. In addition, since platelet counts increase in patients with iron deficiency anemia[6–8], the present study aimed to clarify the frequency and extent of platelet count increases.

We investigated the secular transitions in anemia-related indicators in the current generation of examinees using time-series data from individuals who continually underwent health check-ups.

Subjects and Methods

Subjects

The study initially enrolled 1,379 women who underwent health check-ups including measurement of Hb, MCV, and platelet count at Ningen Dock and Medical Examination Center, Matsunami Medical Clinic, between April 2008 and March 2019. We included subjects who underwent at least six health check-ups because only 241 subjects underwent all 11 check-ups. Nine women who had previously undergone gastrectomy were excluded from the analysis because it was not possible to confirm whether it was total gastrectomy or not. Those

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undergoing dialysis for chronic renal failure, those receiving anticancer treatment and patients with severe infections or thalassemia had also been excluded. Therefore, the final number of women enrolled was 1,370 and the average number of health check-ups undergone was 8.7 ± 1.7 (SD). The initial mean age of these women at the first check-up was 47.6 ± 6.9 (SD) years.

Methods

Blood Hb level, MCV, platelet count, menstrual condition, and current history of anemia treatment at each check-up were recorded along with the age of each subject and medical history of anemia, uterine leiomyomas (fibroids), endometriosis, and other gynecological diseases. The medical history taken during the interview did not distinguish between renal anemia and other anemia and thus renal anemia may have been included. While most examinees underwent health check-ups at regular intervals, the check-up date sometimes varied between before and after the subject's birthday. Therefore, we defined the age at the first health check-up as the initial age and considered each subject to be 1 year older at the check-up in each year after that. The age-based transitions in blood test values for each subject were determined. Women receiving treatment for anemia during the health check-ups were analyzed separately.

Since serum iron or unsaturated iron-binding capacity (UIBC) measurements had been made for few subjects, we calculated the average values by age group for all examinees in whom they had been measured at our facility between April 2014 and March 2019 to assess the nature of anemia.

We first calculated the mean values of blood Hb level, MCV, and platelet count and the proportion of women with an Hb level < 10 g/dL for each age group of the respective subjects. Among subjects who reported menopause during the study period, we compared blood Hb levels, MCV, and platelet counts before and after menopause. We next investigated relationships among medical history of anemia, uterine leiomyomas, endometriosis, and other gynecological diseases. Among women who had not received anemia therapy at any health check-up, we compared mean blood Hb level and proportion of women with blood Hb level < 10 g/dL at least once, by with or without history of anemia or gynecological diseases. The ages at the first health check-ups were used to compare age differences by medical history among study subjects.

We calculated the mean, fluctuation range, SD, and coefficient of variation for Hb level, MCV, and platelet count for each subject and each age group. We determined the correlation between Hb levels and MCV to assess the involvement of iron deficiency and also that between Hb level and platelet count. These calculations were performed in Microsoft Office Excel 2007 SP3 (Microsoft, Redmond, WA, USA). We obtained intra-individual correlation coefficients between the time courses of Hb, MCV, and platelet count for each subject, as well as the inter-individual correlation coefficients between the mean Hb level, MCV, and platelet count for all subjects. Categorical variables were compared using chi-square or Fisher's exact tests. Comparisons between two groups were performed using paired or unpaired t-tests, and comparisons among more than two groups were performed using analysis of variance with multiple comparisons using the Tukey test. These analyses were conducted using IBM SPSS Statistics, version 24 (IBM Japan, Tokyo).

Before performing this study, the research methods and ethical considerations were approved by the Matsunami General Hospital Medical Ethics Committee, which is under the same medical corporation as our facility. The study was conducted according to the ethical guidelines for medical and health research involving human subjects in Japan.

Results

Of 1,370 women, 100 (7.3%) had received anemia treatment at a health check-up, 330 (24.1%) had not received treatment for anemia but had a history of anemia, and 940 (68.6%) had no history of anemia. The overall averages (± SD) of individual mean blood Hb level, mean MCV, and mean platelet count during the study period were 12.5 (± 1.0) g/dL, 88.2 (± 5.4) fl, and 24.2 (± 5.4) × 10^4 /μL, respectively. Information on the time of the initial anemia diagnosis among women with a history of anemia was limited.

Fig. 1 shows the transitions in blood Hb levels, MCV, and platelet counts from 32 to 65 years of age. In women not receiving anemia treatment during any health check-up, blood Hb levels began to decrease from the mid-30s, decreased to < 12.4 g/dL during their mid-40s and then increased to 13.0 g/dL in their 50s. The tendencies in these changes were more marked in women with a history of anemia and the magnitude of change was very small in women without a history of anemia. The blood Hb levels of women receiving anemia treatment remained < 11.0 g/dL until they reached their late 40s. In women without anemia treatment, MCV decreased and platelet count increased when they were in their 40s and returned to previous levels in their 50s, in parallel with fluctuations in blood Hb levels. In women without anemia history, the variations in MCV and platelet count were small. The average age at anemia onset was 29.2 ± 11.1 (SD) years in 161 subjects with a history of anemia but not currently treated for anemia and was younger than that of 30.6 ± 12.3 (SD) years in 70 subjects currently treated for anemia

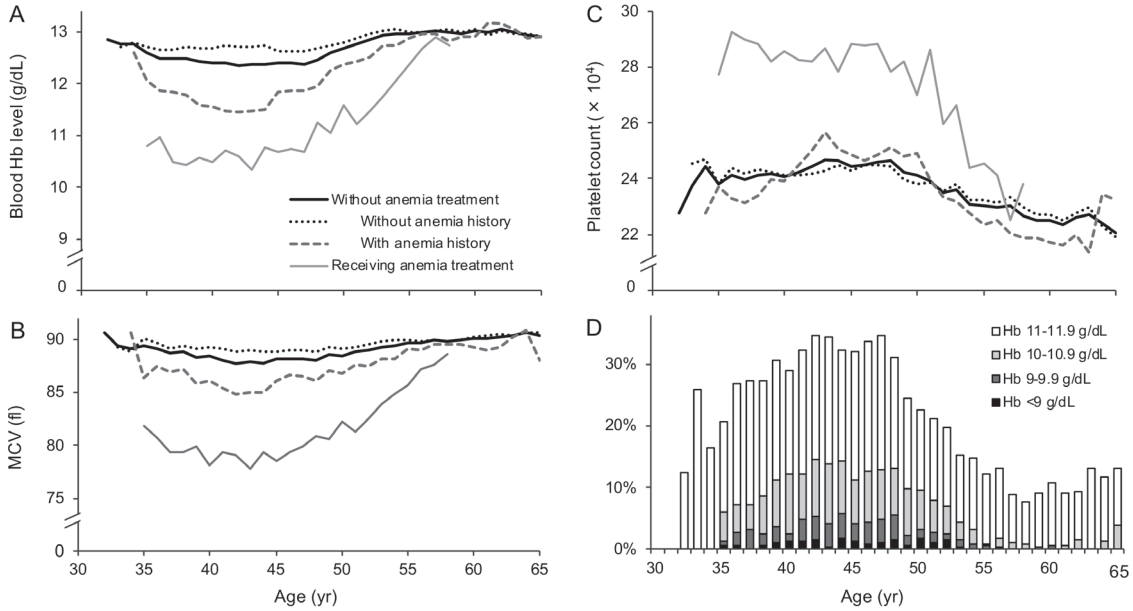

Fig.1. Transitions in blood hemoglobin (Hb) level, mean corpuscular volume (MCV), and platelet count among subjects without anemia treatment at any health check-up (total number = 1,270) and those receiving anemia treatment (total number = 100)
The former was divided into 2 subgroups: those responding that they had no history of anemia (n = 940) and those who had a history of anemia (n = 330). A, blood Hb level; B, MCV; C, platelet count; and D, percentage of subjects with low blood Hb levels among those without anemia treatment.

Table 1. Relationships between Medical Histories of Gynecological Diseases and Anemia

	Number and percentage of subjects without anemia treatment at any health check-up		Number and percentage of subjects with anemia treatment at any health check-up	Total	Chi-square test among groups
	Without medical history of anemia	With medical history of anemia			
Total	940 (68.6%)	330 (24.1%)	100 (7.3%)	1370	
Without history of uterine leiomyoma	750 (71.6%)	244 (23.3%)	54 (5.2%)	1048	$p < 0.001$
With history of uterine leiomyoma	145 (62.0%)	57 (24.4%)	32 (13.7%**)	234	
With history of uterine leiomyoma surgery	45 (51.1%)	29 (33.0%)	14 (15.9%**)	88	
Without history of endometriosis	891 (69.3%)	308 (24.0%)	86 (6.7%)	1285	$p < 0.001$
With history of endometriosis	42 (63.6%)	16 (24.2%)	8 (12.1%)	66	
With history of endometriosis surgery	7 (36.8%)	6 (31.6%)	6 (31.6%**)	19	
Without history of other gynecological diseases	816 (70.4%)	270 (23.3%)	73 (6.3%)	1159	$p = 0.003$
With history of other gynecological diseases	53 (59.6%)	26 (29.2%)	10 (11.2%)	89	
With history of other gynecological surgery	71 (58.2%)	34 (27.9%)	17 (13.9%*)	122	

*$p < 0.01$, **$p < 0.001$ vs. subjects without respective diseases by Fisher's exact test

(p =0.037). The number and mean age of subjects who reported menopause during the study period were 405 and 50.9 ± 3.1 (SD) years, respectively. The mean blood Hb levels increased from 12.7 ± 1.3 (SD) g/dL to 13.0 ± 0.9 (SD) g/dL ($p < 0.001$), while MCV increased from 88.9 ± 5.9 fl to 89.4 ± 4.9 fl ($p < 0.003$) and the platelet count decreased from 23.9 ± 5.5 × 10^4 /μL to 23.1 ± 4.8 × 10^4 /μL ($p < 0.001$) in these women between before and after menopause. The proportion of women with blood Hb levels < 10 g/dL began to increase when the women were in their late 30s, remained high in the 40s and this was followed by a decrease in the early 50s. The highest percentage of women with blood Hb levels < 10 g/dL was 6.1%, at 44 years of age. The highest percentage of women with platelet counts ≥ 40 × 10^4 /μL was 2.0%, at 44 years of age.

The mean (±SD) values of serum iron for all examinees were 111 ± 39, 105 ± 38, 98 ± 47, 105 ± 37, and 108 ± 31 μg/dL for women in their 20s (n = 59), 30s (n = 39), 40s (n = 135), 50s (n = 161), and 60s (n = 156), respectively (not significant). The mean (±SD) UIBC values were 220 ± 24, 219 ± 66, 236 ± 83, 216 ± 63, and 189 ± 49 μg/dL, respectively ($p < 0.001$).

Medical histories of uterine leiomyoma, endometriosis and other gynecological diseases were reported by 23.5%, 6.2%, and 15.4% of the women, respectively. The proportions of women receiving anemia treatment during a health check-up were higher in those with a

medical history of uterine leiomyoma, uterine leiomyoma surgery, endometriosis surgery, or other gynecological surgery (**Table 1**).

In women who had not received anemia treatment, the average individual mean Hb level over time was higher in women without anemia history than in women with anemia history (**Table 2**). The Hb level was higher in women who had undergone uterine leiomyoma surgery. Among them, the mean Hb level of 44 women with confirmed total hysterectomy was 13.1 ± 0.9 (SD) g/dL. There was no difference in the average Hb level between those with and without a medical history of endometriosis or other gynecological diseases. The average Hb level was lower and percentage of subjects with blood Hb levels <10.0 g/dL was higher in women with a history of anemia treatment at a health check-up than in women without treatment history.

The individual mean Hb and MCV values over time were positively correlated in subjects without anemia treatment and overall ($r = 0.544$, $p < 0.001$) (**Fig. 2**). Individual mean platelet counts tended to be high when the mean blood Hb level was low, but overall, there was a weak, negative correlation between the mean blood Hb level and mean platelet count ($r = -0.235$, $p < 0.001$). The percentage of women with a mean platelet count ≥ 33×10^4 /μL was 4.4% overall compared to 17.1% of women with Hb levels ≤ 11.0 g/dL. The number and percentage of women overall with platelet counts exceeding 40×10^4 /μL were 12 and 0.9%, respectively. In women with blood Hb levels ≤ 11 g/dL, the maximum mean platelet count was close to 50×10^4 /μL. The inter-individual coefficient of variation for each mean Hb

Table 2. Relationships between Medical History of Anemia or Gynecological Diseases and Blood Hemoglobin (Hb) Level

	Number of subjects	Average starting age (y.o.)	SD	Average mean Hb level (g/dL)	SD	Number and percentage of women with Hb level <10 g/dL
Total	1370	43.3	6.9	12.5	1.0	207 (15.1%)
Without anemia treatment	1270	43.4	7.0	12.6	0.9	128 (10.1%)
Without medical history of anemia	940	43.5	7.2	12.8	0.8	34 (3.6%)
With medical history of anemia	330	43.2	6.3	12.1**	1.2	94 (28.5%)
Without history of uterine leiomyoma	994	43.1	7.1	12.6	0.9	99 (10.0%)
With history of uterine leiomyoma	202	44.6*	6.3	12.7**	0.9	23 (11.4%)
With history of uterine leiomyoma surgery	74	44.8	5.8	13.0	0.9	6 (8.1%)
Without history of endometriosis	1199	43.5	7.0	12.6	0.9	120 (10.0%)
With history of endometriosis	58	41.6	6.4	12.7	0.9	6 (10.3%)
With history of endometriosis surgery	13	45.2	6.1	12.7	0.9	2 (15.4%)
Without history of other gynecological disease	1086	43.4	7.0	12.6	0.9	103 (9.5%)
With history of other gynecological disease	79	42.7	6.8	12.5	0.9	11 (13.9%)
With history of other gynecological surgery	105	44.1	5.7	12.7	0.9	14 (13.3%)
With anemia treatment	100	41.1**	5.1	11.0**	1.1	79 (79.0%)

*$p < 0.05$, **$p < 0.001$ vs. subjects without respective disease history by t-test or Tukey test

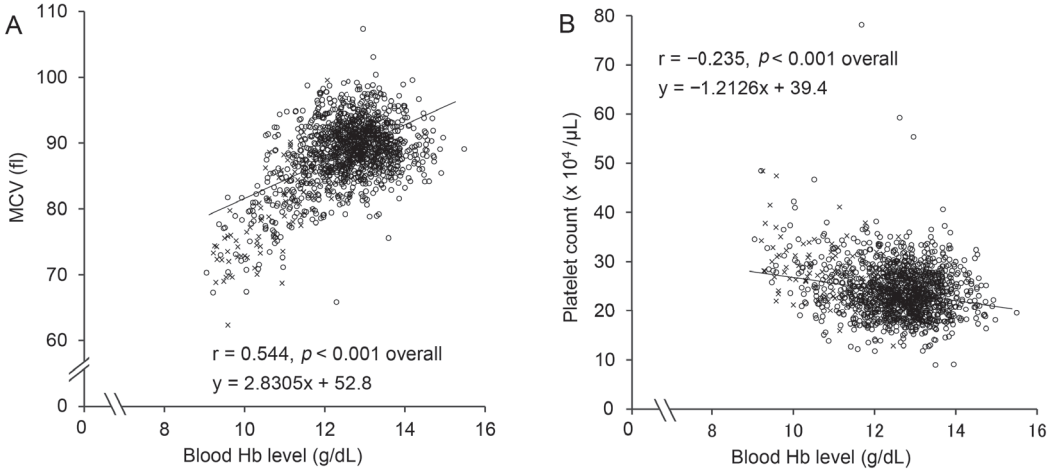

Fig.2. Relationships of individual mean MCV (panel A) or mean platelet count (panel B) with blood Hb level during health check-up period
Circles: subjects without anemia treatment at any health check-up; and crosses: subjects treated for anemia at any health check-up

Table 3. Distribution of Correlation Coefficients between Blood Hb Level and MCV or Platelet Count for Each Subject Over Time by Blood Hb Level Fluctuation Ranges in Women without Anemia Treatment

Fluctuation range of Hb	<2 (*n* = 956)	2 – 3 (*n* = 180)	≥ 3 (*n* = 134)	Total (*n* = 1270)
Correlation coefficient between blood Hb level and MCV				
-1.00 – -0.70	42 (4.4%)	4 (2.2%)	0 (0.0%)	46 (3.6%)
-0.69 – -0.40	155 (16.2%)	15 (8.3%)	1 (0.7%)	171 (13.5%)
-0.39 – 0.39	537 (56.2%)	49 (27.2%)	3 (2.2%)	589 (46.4%)
0.40 – 0.69	156 (16.3%)	31 (17.2%)	7 (5.2%)	194 (15.3%)
0.70 – 1.00	66 (6.9%)	81 (45.0%)	123 (91.8%)	270 (21.3%)
Correlation coefficient between blood Hb level and platelet count				
-1.00 – -0.70	32 (3.3%)	32 (17.8%)	102 (76.1%)	166 (13.1%)
-0.69 – -0.40	116 (12.1%)	52 (28.9%)	29 (21.6%)	197 (15.5%)
-0.39 – 0.39	570 (59.6%)	69 (38.3%)	3 (2.2%)	642 (50.6%)
0.40 – 0.69	181 (18.9%)	20 (11.1%)	0 (0.0%)	201 (15.8%)
0.70 – 1.00	57 (6.0%)	7 (3.9%)	0 (0.0%)	64 (5.0%)

level, MCV, and platelet count in all women were 0.08, 0.06 and 0.22, respectively. In women without treatment for anemia, the blood Hb level and MCV during the health check-up were more positively correlated than in those with blood Hb level fluctuations ≥ 2 g/dL in (**Table 3**). In addition, there were stronger negative correlations between blood Hb level and platelet count in women with larger fluctuation ranges, especially for blood Hb fluctuations of ≥3 g/dL. These correlations became stronger after including women receiving anemia treatment.

Discussion

The blood Hb levels of female examinees who were not treated for anemia decreased most when the women were in their 40s and recovered when they were in their menopausal 50s. This tendency was more pronounced among women with a history of anemia. Over 5% of women in their 40s had Hb values <10 g/dL. The MCV was lower among women in their 40s, likely because of iron deficiency[2]. Our findings of tendencies for reduced serum iron levels and higher UIBC among women in their 40s suggest iron deficiency.

The National Health and Nutrition Survey reported low serum ferritin levels and high total iron-binding capacity among women in their 20s, 30s, and 40s[1]. In addition, Japanese women have high rates of iron deficiency anemia[4,9]. For women with low Hb levels, iron-rich food and supplements should be recommended early when they are in their 30s and 40s[4,10,11]. Furthermore, post-health check-up guidance should be carried out by Ningen Dock facilities. Since it is difficult for women to quantitatively evaluate the amount of bleeding during menstruation[12], it is important to consider this blood loss in subjects with low Hb levels and to perform gynecological examinations and give lifestyle guidance. However, 70% of subjects in their 40s had no history of anemia and small decreases in blood Hb levels.

The mean Hb level was low in women with a medical history of uterine leiomyoma and high in those who had undergone surgery for uterine leiomyoma. Among gynecological diseases, it has been suggested that uterine leiomyoma affects anemia. Abnormal uterine bleeding accounts for 20–30% of the etiology of iron deficiency anemia[13]. However, in the present study, we were unable to assess the frequencies and extent of the effects of gynecological diseases on blood Hb levels because this information was not available for each subject.

The mean platelet count during the health check-up period exceeded the reference range ($14.5–32.9 \times 10^4$ /μL) in 17.1% of women with blood Hb levels meeting the criteria for "medical care needed" of ≤ 11.0 g/dL[14]. In this regard, extreme thrombocytosis (> 100×10^4 /μL) has been reported in patients with iron deficiency anemia[7]. Also, reactive thrombocytosis in iron deficiency is caused by increased erythropoietin, while thrombocytosis in chronic inflammation and cancer is caused by other cytokines such as thrombopoietin and interleukin-6[15–17].

In the present study, the inter-individual correlation coefficients between blood Hb level and platelet count were lower than those between blood Hb level and MCV. The most important factor affecting platelet count increase is a decrease in iron saturation in women with iron deficiency anemia[8]. Also, the inter-individual coefficients of variation in mean platelet count for each subject were larger than those for mean Hb or MCV. This might be due to the effects of factors other than iron deficiency anemia on platelet count[6–8]. Platelet count increases in thrombocythemia and iron deficiency anemia and decreases in aplastic anemia, idiopathic thrombocytopenic purpura, and liver cirrhosis[14]. Among 12 subjects with mean platelet counts exceeding 40×10^4 /μL in the present study, one woman with a mean blood Hb level of 11.7 g/dL was diagnosed with essential thrombocythemia. The other 11 subjects

reported no medical history affecting the platelet count. We could not analyze the effects of factors other than blood Hb levels on platelet count in this study. Interventions to prevent and treat anemia might decrease the percentage of subjects with platelet counts outside of the reference range.

Limitations

Our study subjects were women who underwent detailed health check-ups so they did not represent the general population. Furthermore, the number of women aged < 35 years was insufficient, and it was not possible to determine transitions in Hb level from adolescence. Regarding changes in anemia indicators, the effects of dietary guidance cannot be ruled out for subjects who were identified as having anemia during the observation period. Finally, clinical history and treatment status were self-reported and might have been inaccurate due to recall bias, etc.

Conclusions

Hb levels in women aged 32–65 years decreased most in the 40s and recovered in the 50s. This tendency was small in those without past anemia history. The average age of menopause during the study period was 50.9 ± 3.1 (SD) years. As the blood Hb level decreased, the proportion of subjects in whom the platelet count exceeded the reference value slightly increased.

Conflicts of Interest

The authors have no conflict of interest to declare.

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Original Article

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Quantitative Evaluation of Poor Posture as a Key Factor Related to Physical Fatigue in VDT Workers

Ritsuko Yamada[1,2], Hiroya Kumamaru[1], Ei-ichiro Takebayashi[3], Sei-ichi Yamada[4]

Abstract

Objective: Young workers using visual display terminals (VDTs) commonly suffer from lumbago. During general health check-ups, chest X-ray photographs (Xps) of examinees complaining of lumbago and/or knee pain often show spinal distortion. We therefore quantified this observation for workers using VDTs. Since it is difficult to measure the Cobb angle commonly used in orthopedics solely from routine health check-up data, we measured the distance from the spinous process to the center of the bronchus on chest Xp frontal images, and defined it as an index of spinal distortion. We examined the statistical significance of this index to examine its usefulness as a means of explaining the cause of lumbago in general health check-ups.

Methods: The subjects were 91 VDT (visual display terminal) workers (age 43.6± 11.0 years, 63 men; 28 women). Chest Xps were taken using a CXDI system (Canon, Tokyo). We excluded those with marked aortic sclerosis and aberrant azygous interlobar fissures. Correct posture was achieved by placing both shoulders on the chest Xp board. The deviation from the central bronchus to the spinous process was measured using a function for measuring the distance between two points in DICOM (Digital Imaging and Communications in Medicine) images.

Results: Based on questionnaire responses, subjects with headaches had significantly larger spinal distortion than subjects without headaches ($p < 0.02$), and those with lumbago had a significantly larger spinal distortion than those without lumbago ($p < 0.05$).

Conclusion: Lumbago and headache stemming from physical fatigue in VDT workers could be associated with spinal distortion.

Keywords visual display terminal (VDT) worker, chest X-ray photograph (Xp) frontal view, spinal distortion, lumbago

The occurrence of lumbago in young workers using visual display terminals (VDTs) is increasing. Iwakiri *et al.*'s study[1] on causes of lumbago found that the stiffness and pain in the lower back were mainly related to the sitting posture and the orientation of the wrist when lifted for input on the VDT (visual display terminal).

Empirically, examinees with lumbago and/or knee pain exhibit spinal distortion in chest X-ray photographs (Xps) during general health check-ups, and this is not limited to VDT workers. Our aim was to quantitatively examine the prevalence of this in VDT workers.

The Cobb angle is commonly used in orthopedics for this purpose but it is difficult to measure solely from routine health check-up data. Therefore, we measured the distance from the center of the bronchus to the spinous process on chest Xp frontal views as a marker of spinal distortion. For this study, we selected young VDT workers as a specific age group due to their similar social backgrounds and work styles.

The purpose of this study was to evaluate whether the distance from a single spinous processes to the center of the bronchus on chest Xp frontal views is a meaningful index of spinal distortion in VDT workers.

Methods

Subjects

In this study we recruited 92 VDT users, consisting of 63 male and 28 female (average age [SD]: 43.6 [11.0] years) subjects. They were workers in work category B, which is defined by the Labor Standards Bureau of the Ministry of Health, Labor and Welfare as a working time of more than 2 hours and less than 4 hours for simple input type or constraint type VDT workers, or

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a working time of more than 4 hours for interactive type, technical type, or monitoring type VDT workers. Examinations were conducted with subjects' approval within the scope of routine examinations. All procedures were in accordance with the ethical standards of the respective committees (institutional and national) on human experimentation and with the 1964 Declaration of Helsinki and later versions.

Methods

Chest Xp examinations were performed using the CXDI system (Canon, Tokyo) according to the following details: in the standing position, from posterior to anterior, putting the back of the hands against the waist, the elbows forward and then irradiating perpendicular to the standing and midline at the lower scapula level. Attention was paid to the subjects' postures by placing both shoulders tightly against the board during Xp imaging. Subjects with signs of aortic sclerosis, aberrant interlobar fissures, or any lesions leading to bronchial deviation were excluded from this study. These used to be performed at the same time as VDT health effect screening. We also investigated daily working time on VDTs and years of using them. Working time was classified as: 1–3 hours, 4–5 hours, 5–8 hours, and 8 hours or more. Tests were conducted within the scope of normal VDT health effect screening associated with general periodic health check-ups.

The distance from the center of the bronchus to the spinous process was measured using the distance measurement function for DICOM (Digital Imaging and Communications in Medicine) images (DICOM software). The bronchus image was obtained from the upper end of the photograph to the second thoracic spine level.

Measurements at 3 or more locations were performed, and the greatest measurement was used as the final spinal distortion value. All subjects also completed a questionnaire regarding physical complaints (**Table 1**).

Statistical analyses were performed using contingency analysis and Student's *t*-test. The sensitivity and specificity were calculated using presence of spinal distortion vs. that of lumbago, neck and shoulder stiffness, or headache as variables.

Results

Out of the 92 subjects, 88 had spinal distortion of 5.45 ± 2.59 mm (**Fig.1**, **2**, **3**). Contingency analysis showed that subjects with spinal distortion had significantly more headaches, shoulder and neck stiffness, and lumbago than those without spinal distortion (**Table 2**).

Subjects with headaches had significantly greater spinal distortion as compared to subjects without headaches ($p < 0.02$), and subjects without lumbago ($p < 0.05$) (**Fig.4**).

Blurred vision was more frequent in subjects with 5-8 VDT working hours than in those with 1–3 hours. Headaches were also more frequent in those with 5–8 working hours. In addition, subjects with 1–3 working hours had less neck and shoulder stiffness, and those with more than 8 hours frequently complained of dull arms (**Table 3**). In subjects with 5–8 hours working hours, vision was frequently blurred, and in subjects with 1–3 hours, it was rarely blurred. Subjects working for more than 8 hours frequently had dull arms (**Table 3**).

Spinal distortion value may be a cause of various complaints in VDT workers because subjects with greater spinal distortion had higher rates for shoulder and neck stiffness, headache, and lumbago as compared to those with less distortion. We examined the accuracy of associations between spinal distortion measurements and lumbago, neck and shoulders stiffness, and headache. The results were 64.8% sensitivity for shoulder & neck stiffness, 73.2% specificity for headache and 70.4% specificity for lumbago (**Table 4**).

Table 1. Physical Complaints in Questionnaire

01	eye fatigue
02	blurred vision
03	hyperemia
04	soring
05	headache
06	shoulder and neck stiffness
07	dull arms
08	fingers hurt
09	backache
10	lumbago
11	heavy legs
12	appetite loss
13	insomnia
14	easily frustrated
15	Tiredness continues to next day

Table 2. Post Hoc Cell Contribution between Spinal Distortion and Shoulder & Neck Stiffness, Lumbago, or Headache

post hoc cell contribution: distortion vs. shoulder and neck stiffness		
	stiffness (–)	stiffness (+)
distortion(–)	5.25*	–5.25
distortion(+)	–5.25	5.25*
post hoc cell contribution: distortion vs. lumbago		
	lumbago (–)	lumbago (+)
distortion(–)	3.06*	–3.06
distortion(+)	–3.06	3.06*
post hoc cell contribution: distortion vs. headache		
	headache (–)	headache (+)
distortion(–)	2.23*	–2.23
distortion(+)	–2.23	2.23*

* : $p < 0.05$ significance

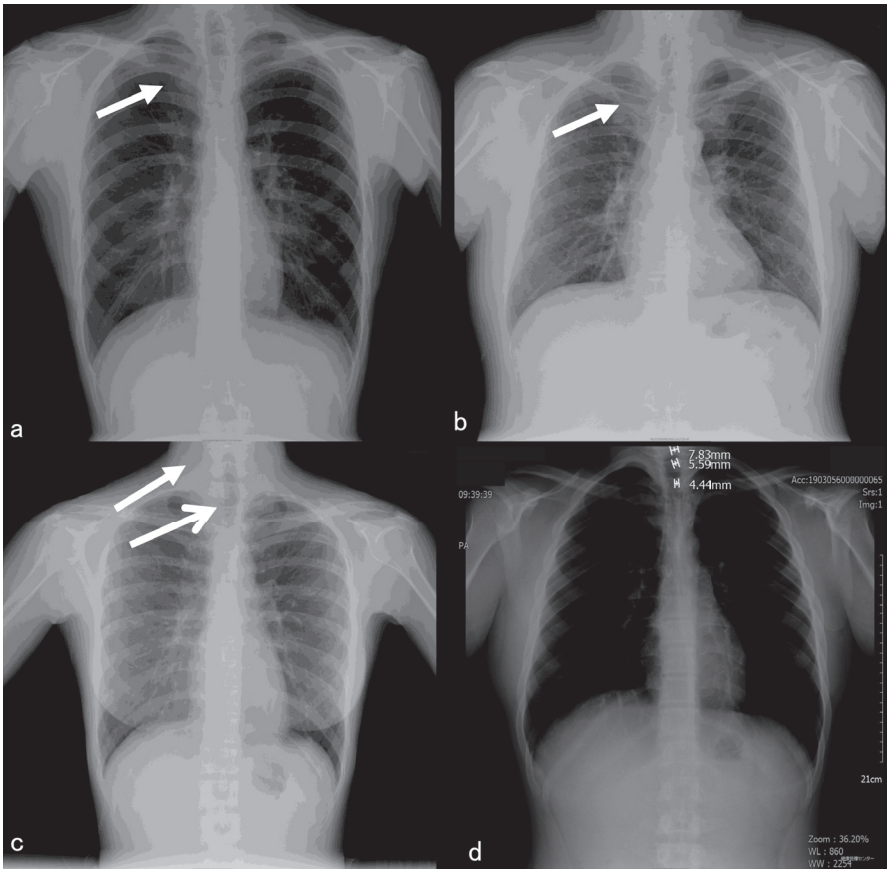

Fig.1. Chest Xp Frontal Images Showing Spinal Distortion 1

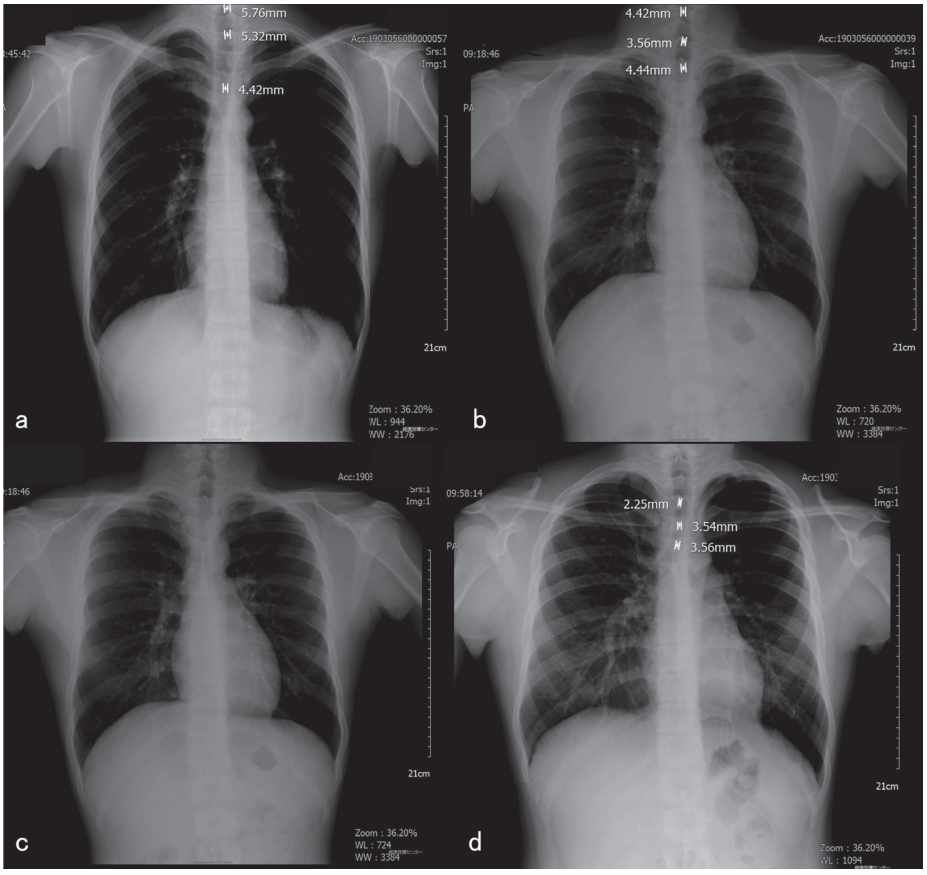

Fig.2. Chest Xp Frontal Images Showing Spinal Distortion 2

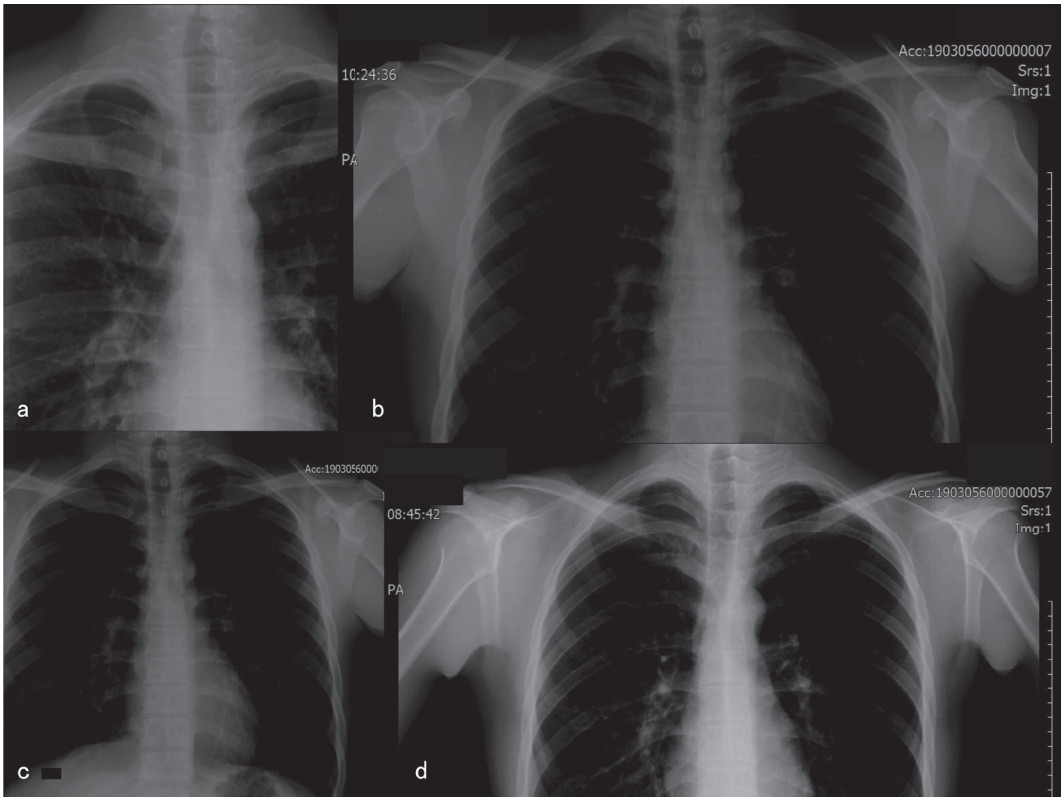

Fig.3. Chest Xp Frontal Images Showing Spinal Distortion 3

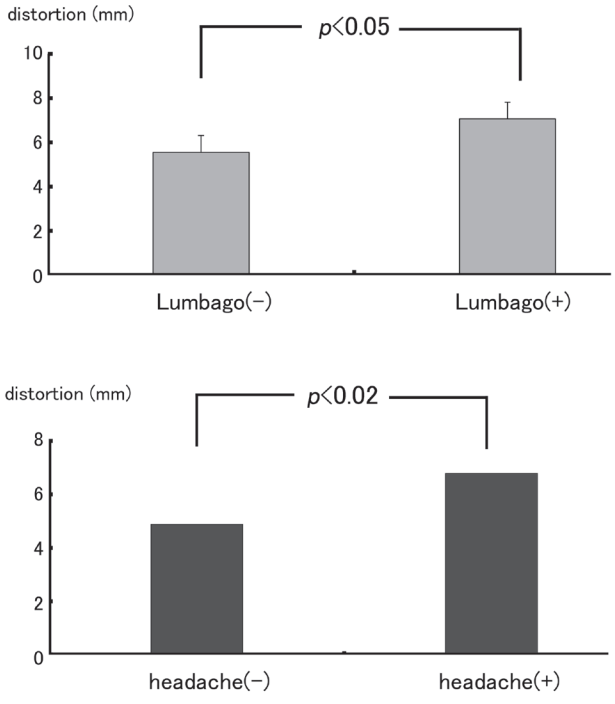

Fig.4. Comparison of Spinal Distortion in Subjects with/without Lumbago or Headache

Table 3. Post Hoc Cell Contribution between Working Time and Blurred Vision, Headache, or Dull Arms

post hoc cell contribution: working time (hr/day) vs. blurred vision		
	blurred (–)	blurred (+)
1-3hr	2.04*	–2.04
3-5hr	0.35	–0.35
5-8hr	–2.14	2.14*
8hr<	–0.04	0.04
post hoc cell contribution: working time (hr/day) vs. headache		
	headache (–)	headache (+)
1-3hr	0.79	–0.79
3-5hr	1.15	–1.15
5-8hr	–1.92	1.92*
8hr<	0.08	–0.08
post hoc cell contribution: working time (hr/day) vs. neck and shoulder stiffness		
	stiffness (–)	stiffness (+)
1-3hr	2.39*	–2.39
3-5hr	–0.83	0.83
5-8hr	–0.83	0.83
8hr<	–0.60	0.60
post hoc cell contribution: working time (hr/day) vs. dull arms		
	dull arms (–)	dull arms (+)
1-3hr	0.76	–0.76
3-5hr	0.96	–0.96
5-8hr	0.96	–0.96
8hr<	–3.26	3.26*

* : $p < 0.05$ significance

Table 4. Sensitivity and Specificity of Spinal Distortion for Headache, Shoulder/Neck Stiffness, and Lumbago

Headache	Sensitivity	26.8%
	Specificity	73.2%
Shoulder & neck stiffness	Sensitivity	64.8%
	Specificity	35.2%
Lumbago	Sensitivity	29.6%
	Specificity	70.4%

Discussion

Orthopedically, lumbago is defined as muscle soreness from overactivity, disk injury including disk tear and herniation, and disk degeneration including degenerative spondylolisthesis, spinal stenosis and scoliosis. However, almost all young patients with lumbago have no conclusive magnetic resonance imaging (MRI) findings. Regarding occupational health aspects, the main factors in the development of lumbago stated by the Japanese Ministry of Health, Labour and Welfare and Industrial Safety and Health Act are as follows: Lifting and handling heavy items, static working posture for long periods (restraint posture), unnatural posture; environmental factors such as temperature variation; floor condition, lighting, workspace/equipment layout, working conditions; personal factors such as age, sex, muscular strength; past or underlying disease, and psychological and social factors.

From the occupational health viewpoint, 3 types of management (work, environment, and health management) and 1 type of education (occupational health education) are important. Additionally, there are various other causes of lumbago and it is necessary to eliminate them sequentially. Since lumbago is correlated with working conditions and workers' conditions, and changes in them, lumbago prevention measures need to be implemented continuously in the workplace.

The targeted VDT works in an office mean inputting, searching, collation, editing and modifying data, programming, and monitoring text and images using VDT equipment consisting of a display and keyboard[2–4]. Additionally, workers were categorized according to their work-type and working hours[5], and it was ensured that occupational health management had been properly carried out for each category. According to the guidelines of the Tokyo Labor Bureau of the Ministry of Health, Labor and Welfare, VDT work is classified as simple input type, restraint type, monitoring type, interactive type, and technical type. The work-time is divided into three parts: less than 2 hrs, from 2 to 4 hrs, and more than 4 hrs. However, depending on the type of business, this may not applicable, so their original questionnaire is being used. They have established standards for lighting, daylight, glare prevention and noise reduction measures to reduce the fatigue of workers and allow them to work without hindrance. Work environment management applicable to VDT work has been implemented. In order to allow workers to perform work with less mental and physical burden, certain standards for working time and work downtime have been established, considering working time management and work volume. Additionally, the VDT equipment and work environments have been inspected and cleaned, and improvement measures have been implemented.

Many preventive measures are being taken, which include reducing work-time, active breaks, measures to improve posture and those applied to input devices, reducing continuous working time, seat surface adjustment, armrest use, cushion adjustment, use of ergonomic keyboards and mice, and external displays. Complaints of lumbago and stiff shoulders from a young age will never end, and will increase unless appropriate measures to reduce bad posture are taken. Chest radiographs of young people often show spinal distortion, which is considered to be one of the main causes of lumbago.

Using the bronchus of the chest X-ray frontal image as a reference for the index of spinal distortion is an unconventional method, and may not be ideal because of poor imaging conditions, or bronchial deviations by the vena cava or azygous interlobar fissure. However, since X-rays are an essential examination in general health check-ups and can be performed at the same time as VDT health effect screening the results can be easily acquired.

The subjects of this study were relatively young people with similar social backgrounds, and we obtained the data through the use of appropriate imaging conditions. Patients who complain of lumbago and stiff shoulders often have spinal distortion, and the distance from the spinous process to the center of the bronchus in chest X-ray frontal images, may approximate spinal distortion.

Further studies with a larger sample size and follow-up are now required.

Conclusion

Our findings suggested that headaches and lumbago in VDT workers with physical fatigue might be related to spinal distortion.

Human rights statements and informed consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions.

Informed consent was obtained from all patients in the study.

There are no conflicts of interests to declare.

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Acknowledgments

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The Regulations of the International Society of Ningen Dock

Article 1
Name
The name of the association shall be the International Society of Ningen Dock.

Article 2
Office
The Society has its principal office in Japan Society of Ningen Dock.

Article 3
Aims
The Society, an organization of Japan Society of Ningen Dock for international operations, aims to contribute to global health promotion by enhancing the development of ningen dock as a medical check-up system.

Article 4
Tasks
The Society conducts the following tasks to achieve the aims described in the preceding section.
1. Holds congress (World Congress on Ningen Dock), board meetings, lectures, and committee meetings
2. Publishes journals and news magazines
3. Communicates and cooperates with related academic societies both in Japan and overseas
4. Promotes research activities in ningen dock and related fields
5. Does whatever is necessary to achieve the aims of the Society

Article 5
Membership
1. The Society consists of the following members
   1) Regular member
      A regular member shall be a member of the International Society of Ningen Dock who agrees to the aims of the Society, and has expert knowledge, techniques, or experience in the areas associated with the Society.
   2) Supporting member
      A supporting member shall be a person, a corporation, or a group that agrees to the aims of the Society, and supports its programs.
   3) Honorary member
      An honorary member shall be recommended, from those who have significantly contributed to the areas associated with the Society, by the executive board.
2. Those who want to apply for regular or supporting membership of the Society shall submit the prescribed application form with the membership fee.
3. The board meeting will process applications mentioned in the preceding section, and promptly notify the applicants of its decision.

Article 6
Officials
1. The Society shall appoint the following honorary advisors and officials.

Honorary advisor: Number not decided
Congress president: 1
President: 1
Vice president: 3 (from Japan : 2, overseas: 1)
Board members: up to 25 (from Japan : 15 or less, overseas : 10 or less)
Auditor: 2

Article 7
Honorary advisor
1. An honorary advisor shall be appointed by the president from those who have contributed to the development of the Society for a long period, and approved by the executive board.
2. Honorary advisors shall be eligible to attend the board meeting, and to express opinions; honorary advisors will not have voting rights.

Article 8
Congress president
1. The congress president shall be recommended by the executive board and appointed by the president.
2. The congress president shall represent the Society and host the World Congress on Ningen Dock as a scientific meeting.

Article 9
President
1. The president shall be selected by and from among board members and delegated by the president of Japan Society of Ningen Dock.
2. The president shall preside the Society.

Article 10
Vice president
1. The vice president shall be appointed, from among board members, by the president.
2. The vice president shall assist the president. In the case of accident, one of the vice presidents will be appointed by the president and will temporarily take over the duties.

Article 11
Board members
1. Board members from Japan shall be selected among candidates from regular members at Japan Society of Ningen Dock.
2. Overseas board members shall be selected at the recommendation of the executive board.
3. Board members execute duties for the Society under the orders from the president.
4. Board members, together with the president and the vice president, comprise the executive board.

Article 12
Board meeting
1. The president will call a board meeting on an as-needed basis, and serves as the chairman of the meeting.
2. The board meeting will pass resolutions on important matters of the Society.
3. The board meeting shall have the right to start proceedings if the majority of all the board members (including a letter of proxy) attend the meeting.
4. The board meeting shall pass resolutions with the majority votes of attendances.

Article 13
Auditor
Auditors shall audit accounts of the Society, and report to the board meeting.

Article 14
Commissioner
For the aims of successful programs of the Society, the president will set up committees and divisions through the resolutions of the executive board, and delegate the commissioners to regular members or other members of the Society.

Article 15
Accounting
1. The fiscal year for the Society starts on April 1 every year and ends on March 31 the following year.
2. Expenses required for the Society shall be covered by the following revenues.
   1) Membership fees
   2) Grants
   3) Donations
   4) Others

Article 16
Modification of rules
The rules of the Society can be amended by the resolution of the executive board.

Article 17
Miscellaneous provisions
Detailed regulations necessary for the enforcement of the rules of the Society are defined elsewhere by the president with the approval of the executive board.

Article 18
Additional clause
The Regulations of the International Society of Ningen Dock will come into effect on September 15, 2006.

Detailed Regulations of the International Society of Ningen Dock

Detailed regulations of the International Society of Ningen Dock are defined as follows:

(Detailed regulations on members)

Article 1

1. Members shall pay the following annual membership fee; honorary members will be exempt from membership fee.
   1) Regular member : 2,000 yen
   2) Supporting member : from one unit (unit: 20,000 yen)
2. Annual membership fee paid shall not be refunded for any reason.
3. Members with foreign citizenship shall pay a 3-year membership fee of 50 dollars.

Article 2

Members will be given priority in the following events :

1) Participation in scientific meetings hosted by the Society;
2) Contributions of articles to and receipt of the journal of the Society.

Article 3

Members shall lose their memberships in the event of the following:

1) Withdrawal from membership;
2) Adjudication of incompetence or quasi-incompetence;
3) Death or adjudication of disappearance, or dissolution of the group in the case of a member of a supporting group;
4) Delinquency in payment of membership fee for over three year.

Article 4

Those intending to withdraw from the Society must submit the notice of withdrawal in the prescribed form to be approved by the executive board.

Article 5

The Society can expel a member to whom either of the following would apply, with a resolution of the executive board:

1) Those who violate their duty as members of the Society;
2) Those who damage the honor of members of the Society or act against the aims of the Society.

Article 6

Those who satisfy Sections 1 and 2 of Article 5 of the Regulations of the International Society of Ningen Dock will be accepted as members of the Society.

(Detailed regulations on officials)

Article 7

1. The president will be selected from the board members of Japan Society of Ningen Dock.
2. In principle, the majority of board members from Japan will be selected from among the board members of Japan Society of Ningen Dock.

3. Overseas board members will essentially be selected from Asia, Pacific Rim, North America, or Europe.

Article 8

1. The term of the congress president will be from the end of the congress of which he/she is in charge to the next congress.
2. The term of board members will be six years (two terms of three years).

(Detailed regulations on congress and board meeting)

Article 9

Congress and board meeting will be held as follows :

1) The title of the congress will be World Congress on Ningen Dock.
2) In principle, the congress and the board meeting will be held once every three years; with the resolution of the executive board, however, the congress and the board meeting will be held as needed.
3) The congress and the board meeting will be held at the same time.
4) The name of the congress president and the location of the next congress will be announced.

Article 10

1. Those who want to take part in the congress shall pay the participation fee, which is defined separately.
2. Participation fee for the congress will be defined accordingly by the congress president.
3. Only regular members shall be allowed to present the results of their studies, except those who have been approved by the congress president.

(Enforcement of the detailed regulations)

Article 11

1. The detailed regulations will come into effect on September 15, 2006.

INSTRUCTIONS TO AUTHORS

Ningen Dock International
Official Journal of Japan Society of Ningen Dock

Ningen Dock International is the official journal of Japan Society of Ningen Dock, in which original articles, case reports, and review articles in both Japanese and English are published. Ningen Dock accepts only manuscripts that are original work in the field of ningen dock and related areas not previously published or being considered for publication elsewhere, except as abstracts. The manuscripts published in Ningen Dock will appear on the website of our society.

If the manuscript concerns a clinical study, it must be in accordance with the Declaration of Helsinki of 1964 (subsequent revisions included). Therefore, for a manuscript whose content is epidemiological or clinical research, the approval of the facility's Institutional Review Board (IRB) or the Ethics Committee of Japanese Society of Ningen Dock must have been obtained for the study described. Also, in the text, it should be indicated that informed consent has been obtained from subjects. Additionally, for case reports, it should be stated that adequate care has been taken to ensure the privacy of the subject concerned.

Online submission system

Ningen Dock International uses an online submission system called ScholoarOne Manuscripts.
Please access http://mc.manuscriptcentral.com/ningendock
This site is only in Japanese at this time.

Preparation of manuscript

All manuscripts must be written in English with MS-Word, Excel, PowerPoint and/or a common graphic format. Authors who are not fluent in English must seek the assistance of a colleague who is a native English speaker and is familiar with the field of the manuscript.

The title, abstract, text, acknowledgments, references, tables, and figure legends should begin on separate sheets, with pages numbered, and be typed double-spaced using the 12-point font size in MS-Word.
Files for submission should be prepared in English in a Microsoft Word or other file format that may be uploaded to the online system.

Available formats for files to be uploaded: doc (docx), xls (xlsx) ppt (pptx), jpg, tiff, gif, ai, eps, psd File names must consist of alphanumeric characters and an extension.

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All measurements should be expressed in SI units. Less common abbreviations should be spelled out at first usage and the abbreviated form used thereafter.

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Titles should be concise and informative. Include the full names of authors, names and addresses of affiliations, and name and address of a corresponding author to whom proofs are to be sent, including a fax number, telephone number and e-mail address.

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The abstract should not exceed 250 words, and should be arranged under the following subheadings: Objective, Methods, Results, Conclusions, and have up to 4 keywords.

Types of articles

Original articles: An original article should not exceed 4,000 words, and should be arranged as follows: Abstract, Objective, Methods, Results, Discussion, (Conclusion), (Acknowledgments), and References.

Case reports: A case report should not exceed 3,000 words, and be arranged as follows: Abstract (which should be a brief summary of the content without headings), Introduction, Case report, Discussion, and References.

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References should be numbered consecutively in order of appearance in the text and cited in the text using superscript numbers. For example, according to the study by Sasamori[1]. For journals, the names and initials of the first three authors, followed by "*et al.*" if there are other coauthors, the complete title, abbreviated journal name according to Index Medicus, volume, beginning and end pages, and year should be included. For books, the names and initials of the first three authors, followed by "et al." if there are other coauthors, the complete title, book name, edition number, beginning and end pages, name and city of publisher, and year should be included. Examples of references are given below.

Journal: Ishizaka N, Ishizaka Y, Nagai R, *et al.*: Association between white cell count and carotid arteriosclerosis in Japanese smokers. Atherosclerosis 2004; 175: 95-100.

Book: Kaplan NM: Measurement of blood pressure. In: Kaplan NM(ed), Kaplan's Clinical Hypertension. 7th ed., Lippincott William & Wilkins, Philadelphia, 2002, 25-55.

Tables

Tables should be cited in the text, and numbered sequentially with Arabic numerals. Each table should be given a number and a brief informative title, and should appear on a separate page. Explain in footnotes all abbreviations used.

Figures

Figures should be cited in the text, and numbered sequentially with Arabic numerals. A brief descriptive legend should be provided for each figure. Legends are part of the text, and should be appended to it on a separate page. Color figures can be reproduces if necessary, but the authors will be expected to contribute towards the cost of publication.

Conflict of Interest (COI)

All authors are required to disclose any conflict of interest (COI) on the form designated by the Japan Society of Ningen Dock.

If no author has any COI, this should be indicated in the manuscript.

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Thirty reprints of each paper are free, and additional reprints are available at charge in lots of 10, but for a minimum order of 50. Reprints should be ordered on submission of the manuscript as follows: For example, "I order 100 reprints: 30 (free) + 70."

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Categories of manuscript:

- ☐ Original article (not more than 4,000 words)
- ☐ Case report (not more than 3,000 words)
- ☐ Review article (not more than 5,000 words)

Typing:

- ☐ Manuscript on A4 paper with wide margins
- ☐ Type double space using 12-point

Title page:

- ☐ Title of paper
- ☐ Full names of authors and affiliations without title of MD, PhD, etc
- ☐ Full name and address of a corresponding author including fax number, telephone number and e-mail address.
- ☐ Running title not more than 50 characters.

Abstract:

- ☐ Not more than 250 words.
- ☐ Arranged in the order of Background, Methods, Results, and Conclusion.
- ☐ Up to four key words.

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- ☐ Measurements are expressed in SI units.
- ☐ Abbreviations are spelled out at first usage.

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Abbreviations

1	**1,5-AG**	1,5-anhydroglucitol	61	**hCG**	human chorionic gonadotropin
2	**17-OHCS**	17α-hydroxycorticosteroid	62	**HCV**	hepatitis C virus
3	**95% CI**	95% confidence interval	63	**HDL-C**	high-density lipoprotein cholesterol
4	**α-GI**	α-glucosidase inhibitor	64	**HLA**	histocompatibility [leucocyte] antigen
5	**β_2-MG**	β_2-microglobulin	65	**HPLC**	high-performance liquid chromatography
6	**γ-GTP**	γ-glutamyl transpeptidase	66	**Ht**	hematocrit
7	**A/G ratio**	albumin-globulin ratio	67	**ICD**	International Classification of Disease
8	**ABI**	ankle-brachial index	68	**ICU**	intensive care unit
9	**ACTH**	adrenocorticotropic hormone	69	**IFG**	impaired fasting glucose
10	**ADL**	activities of daily living	70	**IGT**	impaired glucose tolerance
11	**AFP**	α-fetoprotein	71	**IMT**	intima-media thickness
12	**ALP**	alkaline phosphatase	72	**LAP**	leucine aminopeptidase
13	**ALT**	alanine aminotransferase	73	**LDH**	lactate dehydrogenase
14	**Apo (a)**	apolipoprotein (a)	74	**LDL-C**	low-density lipoprotein cholesterol
15	**APTT**	activated partial thromboplastin time	75	**Lp(a)**	lipoprotein (a)
16	**AST**	aspartate aminotransferase	76	**LPL**	lipoprotein lipase
17	**BMI**	body-mass index	77	**MCH**	mean corpuscular hemoglobin
18	**CA125**	carbohydrate antigen 125	78	**MCHC**	mean corpuscular hemoglobin concentration
19	**CA19-9**	carbohydrate antigen 19-9	79	**MCV**	mean corpuscular volume
20	**cAMP**	cyclic adenosine 3', 5'-monophosphate	80	**METs**	meatbolic equivalent
21	**CAPD**	continuous ambulatory peritoneal dialysis	81	**MetS**	metabolic syndrome
22	**CBC**	complete blood cell count	82	**MMG**	mammography
23	**Ccr**	creatinine clearance	83	**MRA**	magnetic resonance angiography
24	**cDNA**	complementary deoxyribonucleic acid	84	**MRI**	magnetic resonance imaging
25	**CEA**	carcinoembryonic antigen	85	**mRNA**	messenger RNA
26	**cGMP**	cyclic guanosine 3', 5'-monophosphate	86	**MRSA**	methicillin-resistant *Staphylococcus aureus*
27	**ChE**	cholinesterase	87	**MSW**	medical social worker
28	**CKD**	chronic kidney disease	88	**NMR**	nuclear magnetic resonance
29	**COI**	conflict of interest	89	**PET**	positron emission tomography
30	**COPD**	chronic obstructive pulmonary disease	90	**PSA**	prostate-specific antigen
31	**CK**	creatinine kinase	91	**PTH**	parathyroid hormone
32	**CRP**	c-reactive protein	92	**PWV**	pulse wave velocity
33	**CT**	computed tomography	93	**QOL**	quality of life
34	**CVA**	cerebrovascular accident	94	**RBC**	red blood cell
35	**D-Bil**	direct bilirubin	95	**RF**	rheumatoid factor
36	**DBP**	diastolic blood pressure	96	**RI**	radioactive isotope
37	**DNA**	deoxyribonucleic acid	97	**RIA**	radioimmunoassay
38	**DRG**	diagnosis-related group	98	**RNA**	ribonucleic acid
39	**dsDNA**	double stranded deoxyribonucleic acid	99	**SBP**	systolic blood pressure
40	**EBM**	evidence-based medicine	100	**SD**	standard deviation
41	**ECG**	electrocardiogram	101	**SEM**	standard error of the mean
42	**eGFR**	estimated glomerular filtration rate	102	**STD**	sexually transmitted disease
43	**EIA**	enzyme immunoassay	103	**T-Bil**	total bilirubin
44	**ELISA**	enzyme-linked immunosorbent assay	104	**T_3**	triiodothyronine
45	**EPO**	erythropoietin	105	**T_4**	thyroxine
46	**ESR**	erythrocyte sedimentation rate	106	**TC**	total cholesterol
47	**FBG**	fasting blood glucose	107	**TG**	triglyceride
48	**FDA**	Food and Drug Administration	108	**TIA**	transient (cerebral) ischemic attack
49	**FEV**	forced expiratory volume	109	**TIBC**	total iron binding capacity
50	**FEV_1**	forced expiratory volume in one second	110	**tPA**	tissue plasminogen activator
51	**FEV_1%**	forced expiratory volume % in one second	111	**TPHA**	*Treponema pallidum* hemagglutination assay
52	**FPG**	fasting plasma glucose	112	**TSH**	thyroid stimulating hormone
53	**FSH**	follicle stimulating hormone	113	**TTT**	thymol turbidity test
54	**FT3**	free triiodothyronine	114	**UCG**	ultrasonic echocardiography
55	**FT4**	free thyroxine	115	**UIBC**	unsaturated iron binding capacity
56	**FVC**	forced vital capacity	116	**UN**	urea nitrogen
57	**GFR**	glomerular filtration rate	117	**VLDL**	very-low-density lipoprotein
58	**GH**	growth hormone	118	**WBC**	white blood cell
59	**Hb**	hemoglobin	119	**WHO**	World Health Organization
60	**HbA1c**	hemoglobin A1c	120	**ZTT**	zinc sulfate (turbidity) test

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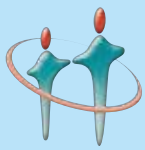
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