negative direction after partial denture rehabilitation of patients with no more than eight missing teeth. The patient age, number of replaced teeth and pre-test scores were the significant predictor variables for the response shift phenomenon. Future studies are necessary to evaluate whether such response shift phenomenon also occur in different patient populations or by utilising other instruments for measurement of OHRQoL, such as the OHIP.

Conflict of interest

The authors have no conflict of interest.

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Correspondence: Takuo Kuboki, Oral Rehabilitation and Regenerative Medicine, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Okayama 700-8558, Japan. E-mail: kuboki@md.okayama-u.ac.jp

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ORIGINAL ARTICLE

Test–retest reliability of MRI-based disk position diagnosis of the temporomandibular joint

Chiyomi Nagamatsu-Sakaguchi · Kenji Maekawa · Tsuyoshi Ono · Yoshinobu Yanagi · Hajime Minakuchi · Shouichi Miyawaki · Junichi Asaumi · Teruko Takano-Yamamoto · Glenn T. Clark · Takuo Kuboki

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Abstract This study evaluated the test–retest reliability for determining the temporomandibular joint (TMJ) disk position, diagnosed using magnetic resonance imaging (MRI). These assessments were done as a base-line measurement for a prospective cohort study, which examines the risk factors for precipitation and progression of temporomandibular disorders. Fifteen subjects (mean age, 24.2±0.94 years; male/female=8/7) were recruited from the students of Okayama University Dental School. Sagittal MR TMJ images were taken with a 1.5-T MR scanner (Magneton Vision, Siemens) in close and maximal open positions twice at about 1-week (6–11 days) interval. The images were displayed using 200% magnification on a computer screen with a commercially available image software package (OSIRIS, UIN/HCUG). Three calibrated examiners diagnosed the disk positions using the standardized criteria. The disk position of each joint was classified as normal, anterior disk displacement with or without reduction, and others. The first and second disk position diagnoses were compared, and the test–retest reliability level was calculated using the kappa index. The second disk position diagnosis was consistent with the first in 27 out of 30 joints. The calculated kappa value representing the test–retest reliability level between the first and second disk position diagnosis was 0.812. These results indicated that the test–retest reliability of MRI-based diagnosis of TMJ disk positions at about 1-week interval was substantially high, even though they were not completely consistent.

Keywords Temporomandibular disorders (TMD) · Magnetic resonance imaging (MRI) · Temporomandibular joint disk position · Diagnosis · Reliability

C. Nagamatsu-Sakaguchi · K. Maekawa · T. Ono · H. Minakuchi · T. Kuboki (✉)
Department of Oral Rehabilitation and Regenerative Medicine, Okayama University Graduate School Medicine, Dentistry and Pharmaceutical Sciences,
2-5-1 Shikata-cho,
Okayama 700-8525, Japan
e-mail: kuboki@md.okayama-u.ac.jp

Y. Yanagi · J. Asaumi
Department of Oral and Maxillofacial Radiology, Okayama University Graduate School Medicine, Dentistry and Pharmaceutical Sciences,
Okayama, Japan

S. Miyawaki
Department of Orthodontics, Kagoshima University Graduate School of Medical and Dental Sciences,
Kagoshima, Japan

T. Takano-Yamamoto
Division of Orthodontics and Dentofacial Orthopedics, Tohoku University Graduate School of Dentistry,
Sendai, Japan

G. T. Clark
Division of Diagnostic Sciences,
University of Southern California School of Dentistry,
Los Angeles, CA, USA

Introduction

Magnetic resonance imaging (MRI) can accurately depict the temporomandibular joint (TMJ) disk position. One major advantage of MRI over all other radiographic imaging techniques is that it does not expose the patient to radiation. It is also non-invasive, painless, and of minimal risk potential in comparison to other imaging techniques [1–7]. However, the most crucial element is that the image accurately depicts the TMJ disk position and configuration. The validity of MRI in the assessment of the

TMJ disk position has been evaluated using autopsy specimens. Westesson et al. [8] first compared the disk position of sagittal and coronal MR images with corresponding sagittal cryosections using 15 fresh TMJ autopsy specimens. They demonstrated that MRI correctly delineated the position of the disk in 11 (73%) joints [8]. This accuracy rate is slightly lower than has been reported for arthrography [9, 10]. However, there have been substantial improvements in imaging hardware, coupled with several software upgrades. Schwaighofer et al. [11] reported that MR images accurately assess the TMJ disk position at the rate of 86%. In addition, the most recent study using a larger number of samples (55 joints) by Tasaki and Westesson [12] demonstrated that MRI was 95% accurate in the assessment of disk position and disk form and 93% accurate in the assessment of osseous changes. They concluded that MRI should therefore be considered the prime imaging modality for analyzing the soft- and hard-tissue changes of the TMJ.

On the other hand, with regard to the reliability of disk position assessment, some studies evaluated the effect of examiner calibration on inter-examiner agreement levels on disk position assessment. These studies suggested that performing the suitable examiner calibration programs can reduce the examiner variation [13, 14]. Another study evaluated whether the difference of TMJ disk status influences inter-examiner reliability of the disk position assessment. Nebbe et al. [15] reported that the kappa statistics of agreement indicated moderate agreement among all four examiners for both the medial and lateral components of the joints. In addition, they demonstrated that disk displacement without reduction was the category with the greatest agreement among all examiners (kappa= 0.914). Furthermore, the inter-examiner reliability was excellent for diagnosing disk displacements with reduction (kappa=0.78) and for disk displacement without reduction (kappa=0.94), when the image analysis criteria developed by Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) Validation Project was utilized [16].

However, no study has so far attempted to assess the test–retest reliability of plurally MRI-scanned individual joint disk positions. Such information is useful and indispensable, because an MRI-based disk position assessment would be questionable for clinical and research application if the test–retest reliability is not reliable. Therefore, this study investigated the test–retest reliability levels of MRI-based disk position assessment in asymptomatic volunteers. The study subjects underwent MRI scanning of the TMJ twice with the jaws in closed and maximally open positions in a 1-week interval, and the results of the disk position assessment were compared between the initial and second scans. Plural examiners participated to assess the disk positions in order to evaluate the disk position accurately, and an examiner calibration program was performed to standardize the inter-examiner assessment ability before the investigation. In addition, since the three-dimensional assessment using sequential multi-slice images of each joint may possibly diagnose the disk position more accurately, this study detected the disk position using seven sequential images of each joint.

Materials and methods

Subjects

This study was incidentally conducted as a base-line measurement of a prospective cohort study on risk factors for the precipitation and progression of TMD. The study subjects of this large cohort study are the students of Okayama University Dental School. The participants in the current study were recruited from the above larger subject population. In total, 30 subjects (male/female=16/14; mean age, 24.1±2.97) participated in this study, and all of them fulfilled the following subject criteria. The inclusion criteria were (1) willing to participate in the study and (2) less than 30 years old. The exclusion criteria of this study were (1) having claustrophobia and (2) not willing to undergo MR imaging twice. Half of those subjects (male/female=8/7; mean age, 23.9±0.24) were involved in the preliminary examiner calibration program. MR images of their TMJs were taken twice, and the mean interval between the initial and second MRI scanning was 38.4±1.24 (from 31 to 48) days. Another 15 subjects (male/female=8/7; mean age, 24.2±0.24) participated in the main study in this report. They also had MR images of their TMJs taken twice with a mean interval of 7.1±0.3 days (range from 6 to 11 days). This study protocol was approved by the Ethical Committee for Human Research in Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences (No. 13).

Clinical examination

The clinical signs and symptoms of each subject were examined by any of two examiners (C.S-N and T.O) before the MR images were obtained. Both two examiners were TMD specialists, and the calibration was performed before the experiment. The clinical examination involved the mouth opening range measurement and the palpation of the TMJ noise. In addition, the subjects provided information concerning pain in the TMJ and the history of the TMJ noise. This process was also performed twice before each scan was performed, and the examiner was randomly assigned at each examination.

MRI scanning technique

Bilateral sagittal MR images of the TMJs with intercuspal and maximally jaw-opening positions were taken twice in each subject. Scans were performed with a 1.5-T MR imaging system (Magnetom Vision: Siemens, Erlangen, Germany) by the same technical expert (H.Y.). Sagittal proton density-weighted images were taken with a fast spin echo technique (repetition time, 2,400 ms; slice thickness, 3 mm; field of view, 125 mm; matrix, 256×80) and through the use of a unilateral surface coil (127 mm). Each subject's head was placed with the Frankfort plane parallel to the opening of the scanner. The head was fixed in position with adhesive tape on a foam rubber support.

Criteria to interpret the disk status

Continuous multi-slice images (at intervals of 3 mm) were obtained in both the close and open jaw positions. The images were magnified (200%) and displayed on a computer screen using a commercially available imaging software program (OSIRIS, UIN/HCUG, Geneva, Switzerland). First, the individual disk position of the images was examined separately by three examiners (T.K., T.O., and C.N.) All examiners were the TMD and orofacial pain specialists. All examiners were blinded to age, gender, symptoms of each subject, and the results of the disk position assessment by other examiners. The criteria for disk position on the image were in accordance with the IZ (intermediate zone) criteria described by Orsini et al. [17, 18]. These criteria determine the disk position by judging the position in relation to the line where the center of two circles is connected and the posterior and anterior bands [19] (Fig. 1). The position of the disk was considered to be normal if the IZ was located between the anterior-superior aspect of the condyle and the posterior-inferior aspect of the articular eminence in the middle or above a line that joined the centers of two imaginary circles which were fitted to these structures. These circles were positioned to closely approximate the condyle and the eminence outlines [20]. On the other hand, the judgment of the disk position was "anterior disk displacement" when the posterior band was located anterior from the line (Fig. 2). Furthermore, the judgment of the disk position

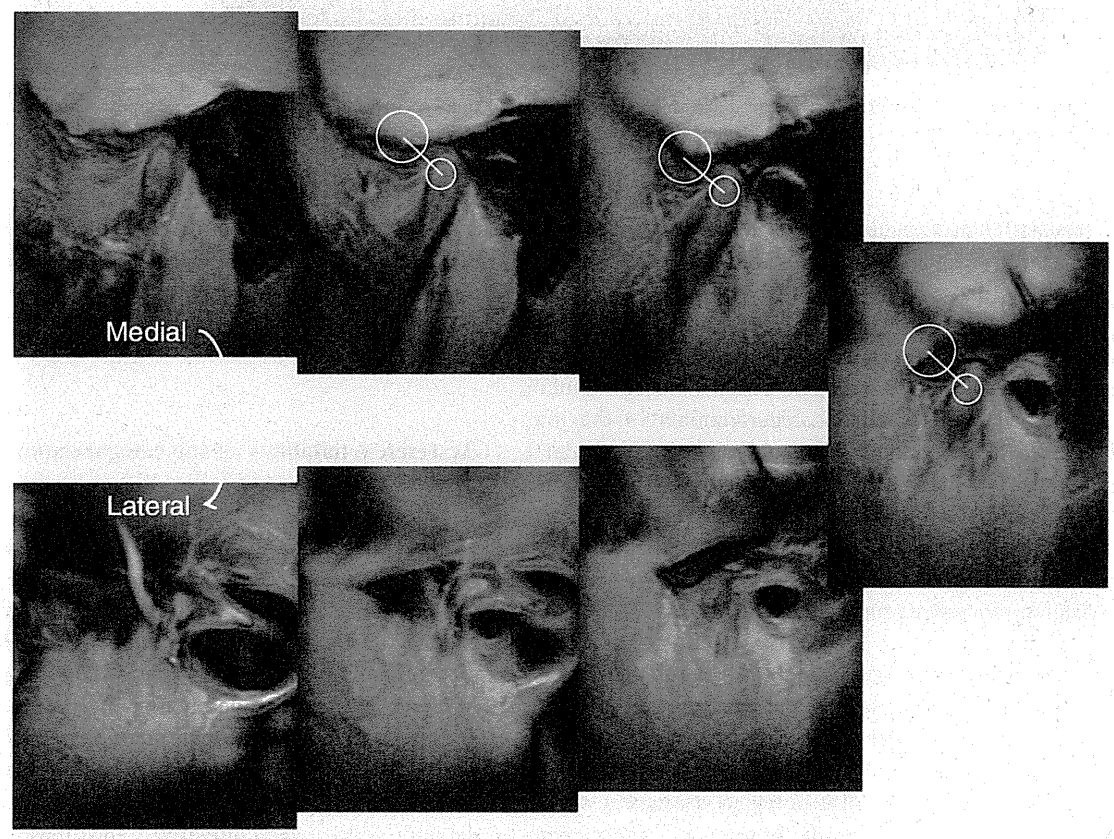

Fig. 1 The images of the subject who was diagnosed as normal disk position using the criteria in this study. The images reveal that the *line*, connecting the center of the two *circles*, is located between the anterior and posterior bands

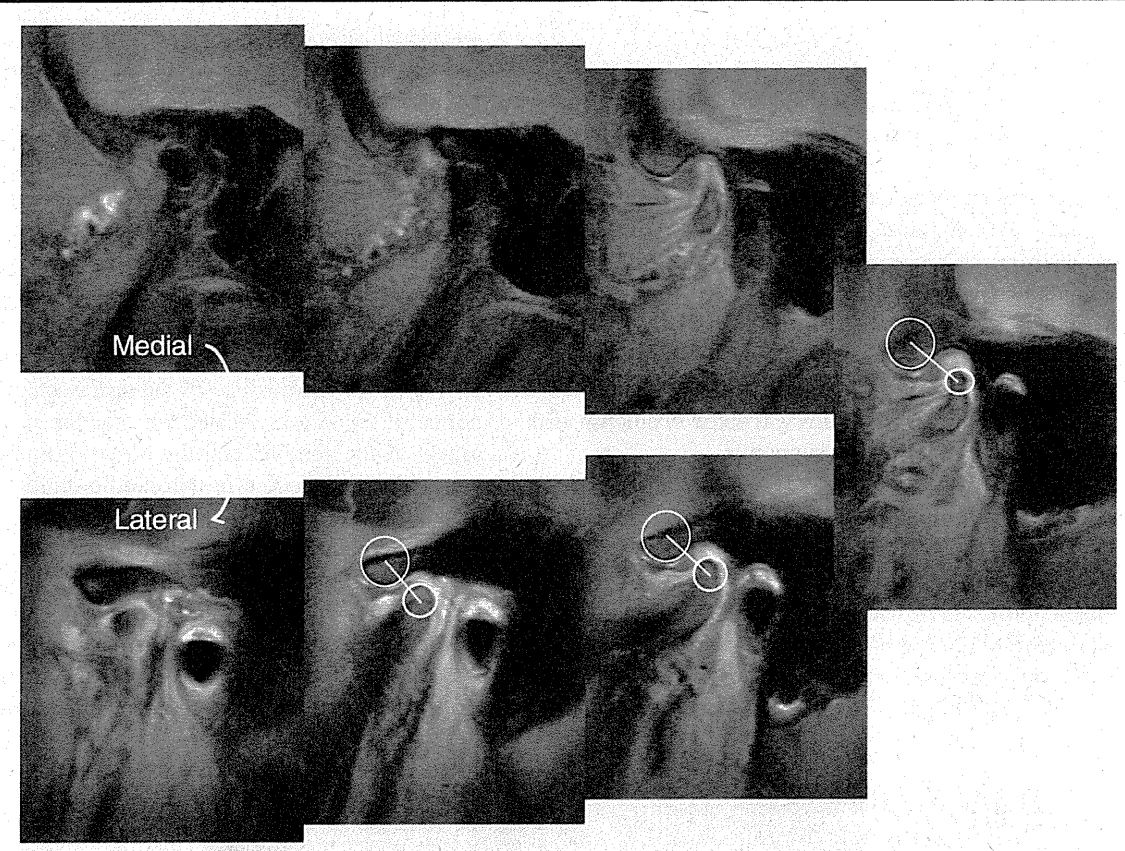

Fig. 2 The images of the subjects who were diagnosed as anterior disk displacement using the criteria in this study. The posterior band was located anterior from the *line*, connecting the center of the two *circles*

was "posterior disk displacement" when the anterior band was located from the line backward, and others were regarded as normal position. The disk position of the joint was considered displaced when at least one of the seven slices in each TMJ was diagnosed as displaced. The disk position, assessed in both the open- and the closed-mouth, was combined, and the final categorization of the joint disk status was formulated for each joint, e.g., normal, anterior disk displacement with or without reduction (ADDwR or ADDwoR), or posterior disk displacement either with or without reduction (PDDwR or PDDwoR).

Calibration procedures for the three examiners

First, the three examiners separately diagnosed the initial set of the 30 MR images with the aforementioned criteria. Then, all examiners discussed the result of their joint disk position assessment, and when disagreement existed, a mutual consensus on the disk position assessment criteria was reached. This calibration discussion took approximately 2 min for each joint disk position. Therefore, 1 h was necessary to assess 30 joints. Next, the three examiners diagnosed the second set of the 30 joints' MR images. The inter-examiner agreement before and after calibration were calculated by using a kappa index. Those indices were calculated between the examiners (A, B, and C) two by two (AB, AC, and BC).

Test–retest reliability of the categorization of TMJ disk status

The three calibrated examiners next assessed another 30 TMJ disk status (15 subjects) using the MR images scanned twice at a week interval (mean interval, 7.1± 0.3 days). This new examination was performed under the same conditions as the previous calibration program. A diagnosis was considered to have been achieved for the final individual joint disk position when at least two of the three examiners agreed on the diagnosis. The results of diagnosed disk position at both the initial and second scans were compared, and these agreements were evaluated using the kappa index calculations (Fig. 3).

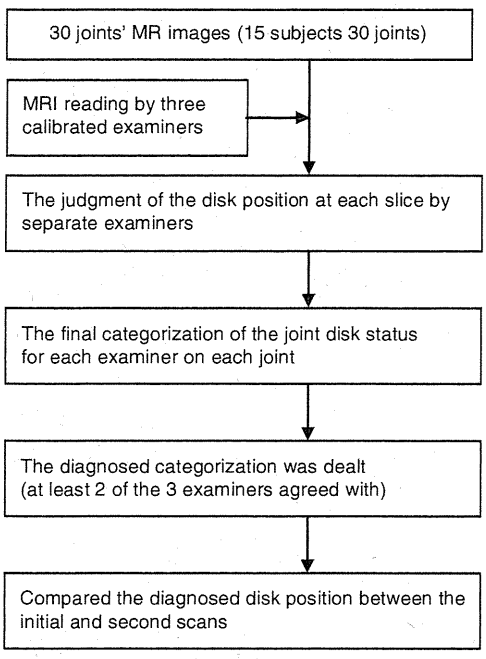

Fig. 3 A flow sheet for the test–retest reliability assessment of the MRI-based diagnosis of the TMJ disk position

Results

Effect of examiner calibration on the TMJ disk status assessment

The comparisons of inter-examiner agreement between before and after calibration are shown in Fig. 4. The mean kappa values among the three examiners increased from κ= 0.377 (before) to κ=0.812 (after) as a result of the calibration program. This kappa value after the calibration program reached almost the perfect level, which was proposed by Landis and Koch [21]. These results clearly suggest that the inter-examiner agreements significantly improved by the examiner calibration utilized in this study.

Test–retest reliability levels of MRI-based assessment of TMJ disk status

Table 1 shows the comparisons of the joint disk status and clinical signs and symptoms between the initial and the second MRI scan in each subject of the main study. Nineteen of 30 joints were diagnosed to be in a normal position, and others were regarded as disk displacement in both the initial and second scans. However, the results of the disk position status of several joints were not consistent between the initial and second scans. While the disk position of 27 joints were consistently diagnosed same positions between initial and latter scans, the disk position of the three joints varied between two scans. The kappa value calculated using the results obtained from two scans was κ=0.812. These results suggest that the test–retest reliability of MRI-based classification of TMJ disk status at 1-week interval was substantially high, even though it was not completely consistent.

A couple of subjects showed a fluctuation between the examinations performed at a 1-week interval. While one of the subjects (subject No. 1) did not show any joint clicking at the first examination (at the initial MRI scanning), it was seen at the second examination (at the second MRI scanning) on the right side TMJ. The joint disk status diagnosed by MRI was also changed from ADDwoR (initial scan) to ADDwR (second scan) in this subject. On the other hand, two subjects showed a fluctuation of joint clicking between the initial and second examination (right side TMJ of subject Nos. 2 and 15). Interestingly, the joint disk statuses of those subjects were both in the normal position and did not change between the initial and the second MRI scanning. In addition, the joint disk statuses of two of the subjects (Nos. 3 and 5) changed from normal to ADDwR between initial and second scanning. However, none of those subjects showed any joint clicking during both the initial and second clinical examination.

Discussion

A review of the literature suggests that MRI is the optimal way to image the hard and soft tissues of the TMJ in patients with signs and symptoms of TMD [22, 23]. It can accurately depict abnormalities of disk position and morphology, and has therefore been used to substantiate the clinically suspected existence of disk displacement. Although a large number of studies reveal the excellent validity of the MRI-based diagnosis of TMJ disk position [11, 12], few studies have tested the reliability. Several

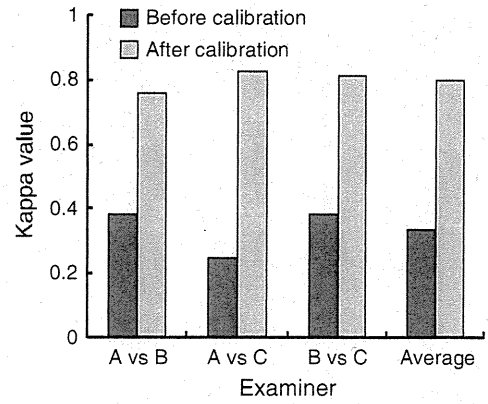

Fig. 4 The comparisons of inter-examiner agreement between before and after the calibration program

Table 1 The comparisons of the joint disk status and clinical signs and symptoms of the second subject group between the initial and second MRI scans

	Gender	Age	Joint disk status				Clicking				History of clicking				TMJ pain during jaw opening					
			Right TMJ		Left TMJ		Right TMJ		Left TMJ		Right TMJ		Left TMJ		Right TMJ		Left TMJ		Maximum range of mouth opening (mm)	
			Initial	Second	Initial	Second	Initial	Second	Initial	Second	Initial	Second	Initial	Second	Initial	Second	Initial	Second	Initial	Second
No. 1	Female	23	ADDwR	ADDwR	ADDwoR[a]	ADDwR[a]	−	−	−[a]	+[a]	−	−	−	−	−	−	−	−	51	52
No. 2	Male	24	Normal	Normal	Normal	Normal	+[a]	−[a]	+	+	−	−	−	−	−	−	−	−	57	56
No. 3	Female	24	Normal	Normal	Normal[a]	ADDwR[a]	−	−	−	−	−	−	−	−	−	−	−	−	40	42
No. 4	Male	23	Normal	Normal	Normal	Normal	−	−	−	−	−	−	−	−	−	−	−	−	64	64
No. 5	Female	23	Normal	Normal	ADDwR[a]	Normal[a]	−	−	−	−	−	−	+	+	−	−	−	−	50	49
No. 6	Male	23	ADDwoR	ADDwoR	ADDwoR	ADDwoR	−	−	+	+	−	−	−	−	−	−	−	−	57	54
No. 7	Female	24	Normal	Normal	Normal	Normal	−	−	−	−	−	−	−	−	−	−	−	−	53	55
No. 8	Female	25	Normal	Normal	ADDwoR	ADDwoR	−	−	+	+	−	−	−	−	+	+	−	−	45	49
No. 9	Male	25	Normal	Normal	Normal	Normal	+	+	+	+	−	−	−	−	−	−	−	−	50	48
No. 10	Male	25	ADDwoR	ADDwoR	ADDwR	ADDwR	+	+	−	−	−	−	−	−	−	−	−	−	44	41
No. 11	Female	24	Normal	Normal	Normal	Normal	−	−	−	−	−	−	−	−	−	−	−	−	43	42
No. 12	Male	25	Normal	Normal	Normal	Normal	−	−	−	−	−	−	−	−	−	−	−	−	48	47
No. 13	Female	24	ADDwoR	ADDwoR	ADDwR	ADDwR	−	−	+	+	−	−	−	−	−	−	−	−	55	51
No. 14	Male	25	Normal	Normal	Normal	Normal	−	−	−	−	−	−	−	−	−	−	−	−	65	64
No. 15	Male	24	Normal	Normal	ADDwR	ADDwR	−[a]	+[a]	+	+	−	−	−	−	−	−	−	−	66	66

ADDwR anterior disk displacement with reduction, *ADDwoR* anterior disk displacement without reduction

[a] Different findings were observed between two examinations or MRI scans

studies have evaluated the inter-examiner reliability of reading MR images of TMJ disk position and morphology [13–15], and reported that inter-examiner agreement is high when an examiner calibration program is performed [14] or a quantification technique is used to interpret MR images. Indeed, the current study also evaluated the effect of an examiner calibration program on the inter-examiner reliability of detecting the TMJ disk position and demonstrated that only one calibration training session substantially improved the inter-examiner reliability levels. However, the test–retest reliability levels of plurally MRI-scanned individual joint disk position have not yet been assessed. The current study is the first report to evaluate the test–retest agreement level of the TMJ disk position using two separate MR images. The results showed that 90% of TMJ disk position diagnosis was consistent between both initial and second images, which were scanned at a week interval. These results provided new evidence that the reliability level of the MRI-based diagnosis of TMJ disk positions at 1-week interval is substantially high. In addition, this reconfirmed that it is sufficiently valuable to apply TMJ disk position diagnosis in clinical and academic settings. In addition to the highly efficient capability of MRI for depicting the TMJ disk, other factors possibly elevated the reliability levels. This study employed sequential multi-slice images of each joint for the detection of the TMJ disk position. This was different from previous studies, which applied a few representative slices from all the images. Therefore, employing an increased number of the slice images might affect the reliability levels for detecting the disk position. However, this study did not evaluate the reliability level of the TMJ disk position using a few selected representative slices from all the images. Future studies which evaluate the influence of the number of the sliced images for detecting the disk position are therefore expected to clarify this point.

On the other hand, this study also demonstrated that a mismatch was observed in three of 30 joints between two scans, and a perfect match was not obtained. One of the possible reasons for these results is that the different detections of the disk position between initial and second MRI scan were due to the examiners' failure. Another possible reason is that the TMJ disk position in some of the participants may have changed within a 1-week interval. Since previous studies reported that existence of TMJ sound fluctuates [24], a positional fluctuation is also a possibility, especially if a patient has an intermittent locking disorder [25, 26]. Indeed, while one of the subjects in this study (No. 1) did not show joint clicking at the initial examination, which was performed prior to the initial MRI scanning, this subject did show joint clicking at the second examination. The joint disk status of this subject actually indicated the changes from ADDwoR to ADDwR. These findings strongly suggested that the disk position of this subject changed within a 1-week interval.

However, the clinical signs and symptoms of two other subjects (Nos. 3 and 5), whose TMJ disk status was different between two scans, did not show obvious changes at a 1-week interval. Although neither subject showed TMJ clicking at both the initial and second clinical examination, the TMJ disk status was diagnosed as ADDwR at either MRI scan. Of course, this might be due to the examiners' failure, but the absence of joint clicking for ADDwR individuals is not a rare finding [27]. In addition, the ADDwR condition has been speculated to develop from an intermittent joint displacement [28]. Therefore, either possibility may explain the difference of disk position status between two scanning. Future studies with larger samples are therefore desirable to clarify this point.

In conclusion, this study indicated the test–retest reliability of MRI-based diagnosis of TMJ disk positions by well-calibrated plural examiners at a 1-week interval and found a substantially high agreement. The reliability level suggested the possibility that MRI-based TMJ disk position diagnosis by the examiners in this study is sufficiently reliable and employs MRI image evaluation in an ongoing prospective cohort study on risk factors of the precipitation and progression of TMDs.

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Conflict of interest The authors declare that they have no conflict of interest.

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Videoendoscopic assessment of swallowing function to predict the future incidence of pneumonia of the elderly

N. TAKAHASHI*†, T. KIKUTANI*‡, F. TAMURA*, M. GROHER§ & T. KUBOKI† *Rehabilitation Clinic for Speech and Swallowing Disorders, The Nippon Dental University School of Life Dentistry at Tokyo, Dental Hospital, Tokyo, †Department of Oral Rehabilitation and Regenerative Medicine, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, ‡Division of Oral Rehabilitation, The Nippon Dental University Graduate School of Life Dentistry, Tokyo, Japan and §Department of Communicative Disorders, University of Redlands, Redlands, CA, USA

SUMMARY **The purpose of the present study was to examine what dysphagic signs identified by videoendoscopy (VE) could predict the incidence of pneumonia and body weight loss in elderly patients living in nursing homes. This study was performed at six nursing care facilities in Japan from March 2007 to February 2009. The 148 subjects (85·1 ± 8·0 years, male/female: 43/105) were evaluated for their feeding and swallowing movements by clinical and VE examinations during the consumption of a regular meal. The VE examination items included the existence/absence of pharyngeal residue, laryngeal penetration, and aspiration of food and saliva. The patients were followed-up for 3 months with individualized feeding therapy based on the results of the clinical/VE examination at baseline, and the incidence of pneumonia was examined as the primary outcome. In patients without pneumonia, the body weight change was also measured as a secondary outcome. The risk factors for pneumonia and body weight loss (of 3% or more) were identified among the clinical/VE examination items by a Cox proportional hazard analysis. Even with elaborative feeding therapy, 12 (8·1%) of the 148 patients developed pneumonia during the 3 months follow-up period. The existence of signs of 'silent aspiration of saliva' or 'aspiration of saliva' detected by VE examination was a significant risk factor for both pneumonia and a body weight loss of 3% or more. This study shows that 'aspiration of saliva' detected by VE is a significant risk factor for both pneumonia and body weight loss in elderly patients living in nursing homes.**

KEYWORDS: **videoendoscopy, aspiration-related pneumonia, dysphagia, aspiration of saliva, body weight loss**

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Introduction

Dependent elderly patients are at high risk for feeding and swallowing disorders as a consequence of disease and/or aging (1–3). Studies done in long-term care facilities have shown a prevalence of such disorders ranging from 60% to 87% (4, 5). Among the various disorders, special attention has been given to dysphagia because it may lead to malnutrition with immune system compromise, dehydration, asphyxiation, or even aspiration pneumonia (1–3). Moreover, a previous follow-up study of patients with dysphagia in such care facilities revealed an incidence of pneumonia of 43% and a mortality rate of 45% at 1 year following the detection of their swallowing disorder (6). Therefore, clinicians should be able to identify dysphagia in order to predict those patients at risk of developing complications secondary to dysphagia, as well as to develop and implement a rehabilitation plan stressing prevention and compensation.

Videofluorography (VF) has been regarded as the most popular adjunctive instrument for the

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examination of patients with suspected oropharyngeal dysphagia. Previous studies have examined the use of VF as a means to predict those at risk for dysphagia and its complications (7, 8). For instance, Mann *et al.* (7) found that the single best independent predictor for chest infection following an acute stroke was a delayed or absent swallowing response in acute stroke patients. Teraoka *et al.* (8) found that the single best predictor of oral intake in post-stroke patients with dysphagia was the presence of aspiration detected by VF assessment. Nevertheless, one major disadvantage of VF for patients living in long-term care facilities is that the patients need to be transported to a hospital setting, which is sometimes inconvenient or may disorientate the patient because of the sudden change in the environment. Other disadvantages are related to the exposure to x-ray radiation and the risk of aspiration during VF assessment in some patients with severe physical or mental alterations (9).

On the other hand, videoendoscopic (VE) examination of swallowing allows for easy assessment of patients in their usual environment because the instrument is portable and does not require a radiology suite (10). Additionally, although VE is most useful for the examination of the integrity of the upper airway before and after a swallow response, it enables the evaluation of the tongue function during mastication and deglutition, as well as the detection of aspiration by the objective visualization of the airway (11, 12).

Videoendoscopic examination has been shown to successfully estimate the existence of accumulated oropharyngeal secretions, thus resulting in excellent prediction of aspiration (13, 14). In addition, Ota *et al.* (15) reported that the secretion scale based on the VE examination is a useful evaluation tool for predicting not only aspiration, but also pneumonia, in acute-phase dysphagic stroke patients. Furthermore, Link *et al.* (16) reported that there was a relationship between the VE-based pooled hypopharyngeal secretions, laryngeal penetration, aspiration and recurrent pneumonia with neurological disorders in pediatric patients. It is therefore evident that VE is the best tool to examine pooled hypopharyngeal secretions, laryngeal penetration, and aspiration. Therefore, even though the agreement rate between the VF and VE findings on dysphagia was shown to be high (90%) (17), VE examinations are becoming increasingly popular for examining the aspiration of saliva and food at the bedside and in long-term care facilities (17, 18).

In a prospective study with acute stroke patients, Lim *et al.* (19) found a strong association between aspiration detected by VE and the development of aspiration pneumonia. However, the predictors of aspiration pneumonia in dependent elderly patients with dysphagia in long-term care facilities have not been sufficiently investigated using VE. Therefore, the purpose of this prospective cohort study was to investigate whether the dysphagic signs identified by VE were risk factors for pneumonia and body weight loss in patients living in long-term care facilities.

Materials and methods

Subjects

Six hundred and forty-seven inpatients were initially identified from six nursing care facilities in Tokyo, Japan from March 2007 to February 2009 (Fig. 1). All patients, except for 28 subjects who were tube-fed, were screened for dysphagia by a check-list given to the patient's caregiver. The screening check-list contained 11 items: pooling of food, uncomfortable feeling in the throat, previous history of asphyxiation, previous history of aspiration, previous history of pneumonia, increased phlegm production, choking on saliva, choking on food, choking after a meal, prolongation of their eating time, and insufficient intake. The 171 patients who had at least one item checked positively by the caregiver were suspected to have dysphagia and comprised the intended sample population. However, 23 patients were excluded because of cognitive failure or refusal to participate in this study. Consequently, the final study population consisted of 148 patients (male/female: 43/105) with a mean age of 85·1 ± 8·0 years and an age range from 59 to 100 years. The protocol for this study was approved by the Ethics Committee of the Nippon Dental University School of Life Dentistry at Tokyo (#08-10).

Baseline measurements and feeding therapy

At the baseline measurement, a medical doctor assessed the patients' general health condition, and none of the patients fulfilled the Mann's criteria (7) for a diagnosis of pneumonia, that is, the presence of at least three of the following signs and symptoms: fever >38 °C, productive cough with sputum, tachypnea higher than 22 breaths per minute, inspiratory crackles,

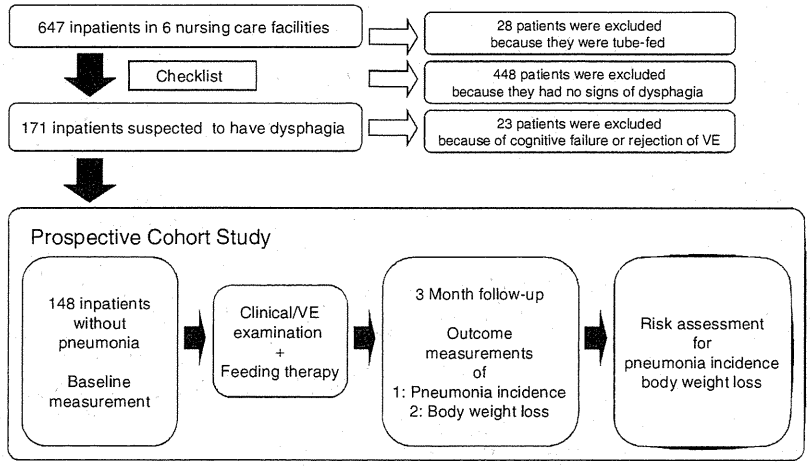

Fig. 1. The sampling process used for this study.

an abnormal chest x-ray, or positive gram staining and cultures.

All included subjects had their eating ability and dysphagic signs and symptoms evaluated clinically according to a clinical examination form regarding the signs and symptoms of dysphagia (spilling food, pooling food, oral food residue after a swallow, inability to open the mouth, choking/coughing, increased phlegm while eating, dyspnea, wet hoarseness, other), the hand and mouth coordination during the meal (feeding posture, prolongation of eating time) and the caregiver's technique used for feeding assistance.

In addition, each patient's swallowing function was examined by VE, which consisted of a flexible endoscope (ENF-V2*) connected to a high-intensity compact light source (CLH-SC*) and a video recorder (OTV-SC*).The endoscope was passed transnasally to the hypopharynx at a vantage point that provided a full view of the laryngeal vestibule, and was kept in place for a period of 10–15 min to assess the patient's eating ability, or saliva swallows when the patient was not consuming a meal. The patients were examined in their usual eating position, that is, the ambulatory patients were seating in the upright position, while the bed-bound patients were sitting on a bed. All swallows were recorded on videotapes for the further analyses by experienced physicians familiar with endoscopic swallowing studies and who were blinded to the intentions of the study. Each patient's video-recording data were reviewed for the presence or absence of pharyngeal residue, and penetration and aspiration of food or saliva. 'Penetration' was defined as a passage of material into the larynx that does not pass below the vocal folds, while 'aspiration' was defined as passage of material below the level of the vocal folds. In cases where the aspiration of food or saliva did not induce a cough, it was defined as 'silent aspiration' according to the criteria proposed by Rosenbek *et al.* (1996) (20). To assess the inter-rater reliability of the swallowing evaluations, the three investigators who were unaware of the original evaluation results, separately reviewed a random 10% sample of these evaluations. The overall agreement rate between investigators was substantial according to the Landis and Koch criteria (21) (kappa coefficient = 0·660).

On the basis of these aforementioned evaluations, the patients received various feeding therapies (22) during the follow-up period, for example, confirmation of feeding conditions [76 patients (51·4%) of 148 patients, multiple answers possible], appropriate feeding assistance [69 patients (46·6%)], food modification [32 patients (21·6%)], modification in feeding posture [19 patients (12·8%)] and modification in food intake [four patients (2·0%)] for 3 months. Food modification involved changing the dietary consistency. We modified the food and liquid texture individually according to the National Dysphagia Diet recommendations (23). Food intake and feeding assistance required modifications to accommodate the individual needs of the patients, such as changes in the rate and amount of the food consumed, appropriate utensils and the

*Olympus Corporation, Tokyo, Japan.

method used for self-feeding (22). Modifications in the feeding posture were applied in order to maximize the physical capabilities and improve swallowing, and involved strategies such as head-turn or chin-tuck maneuvers or whole body-positioning strategies including the patient tilting to the side or back, side-lying, or maintaining an upright posture (22). All patients received oral health care after every meal by the caregiver who was instructed once a week about the oral care procedures by a dental hygienist. Caregivers cleaned each patient's oral cavity using a toothbrush for approximately 5 min after each meal. The brushing was carried out as usual for daily tooth brushing without paste, and included brushing the palatal and mandibular mucosa and tongue dorsum. Dentures were also cleaned with a denture brush every day.

The 3 month follow-up and outcome measurement

The first outcome variable after 3 months of follow-up was the incidence of pneumonia diagnosed according to the same criteria applied at the baseline measurement. Once the patients received a diagnosis of pneumonia, they were sent to a local hospital for treatment, without exception. Consequently, their oral feeding was prohibited to prevent further aspiration pneumonia and their body weight typically decreased as a result (24). The incidence of pneumonia and body weight loss were therefore strongly correlated after the development of pneumonia. Thus, when pneumonia was identified, follow-up measurements of the patient's body weight were terminated.

The second outcome variable during the follow-up period was a change in body weight demonstrated by monthly measurements. Since there is a close relationship between pneumonia and body weight loss, the incidence of body weight loss of 3% or more was examined in patients who had not been diagnosed with pneumonia during the 3 months of follow-up. Once the patients developed a body weight loss of 3% or more, the patients received some form of nutrition therapy, and thus, the follow-up observation was terminated.

Statistical analysis

A survival curve of the patients who had not been diagnosed with pneumonia was drawn for a Kaplan–Meier analysis. According to the presence/absence of pneumonia during the 3 months of follow-up, we divided the final sample population into pneumonia and non-pneumonia sub-groups, and performed a *t*-test, chi-square analysis or Fisher's exact test to analyse the differences between the two groups.

Similarly, a survival curve of those patients who had not lost more than 3% of their body weight was drawn for a Kaplan–Meier analysis (outcome event: the incidence of body weight loss of 3% or more). Differences between the weight gain/no change sub-group (body weight gain, or a small weight loss of no more than 3% of the initial body weight) and the weight loss group (body weight loss of 3% or more (10, 25)) were analysed with the same statistical tests utilized for the incidence of pneumonia.

Additionally, a Cox proportional hazard analysis was performed to identify the risk factors for the incidence of pneumonia and the body weight loss of 3% or more. The analysed predictors were age, self-feeding ability, the Barthel activities of daily living (ADL) index, a body mass index (BMI) lower than 18·5, pharyngeal residue, laryngeal penetration, aspiration of food and aspiration of saliva. Regarding the aspiration of food or saliva, the data were handled as ordinal variables (negative, positive, positive as silent aspiration). The data were analyzed with the Statistical Package for the Social Sciences software program (SPSS version 15.0†). A *P*-value $<0{\cdot}05$ was considered to be statistically significant.

Results

Baseline condition of the patients

Examination of the medical conditions of the initial 148 patients showed the presence of a prior stroke in 83 (comorbidity admitted) (56·1%), dementia in 74 (50·0%), Parkinson's disease in 10 (6·8%), cardiovascular disease in 10 (6·8%), hypertension in 8 (5·4%), previous pneumonia in 5 (3·4%), diabetes mellitus in 3 (2·0%), fractures in 3 (2·0%) and other comorbidities in 14 patients (9·5%).

The clinical examination regarding the eating ability and signs and symptoms of dysphagia before the VE evaluation showed choking/coughing in 110 out of 148 patients (multiple choice admitted), pooling of food in 28, prolongation of the eating time in nine, inability to

†SPSS Japan Inc., Tokyo, Japan.

open the mouth in two, and spilling of food in one patient.

The VE evaluation detected pharyngeal residue in 97 (65·5%) out of the 148 patients, laryngeal penetration in 67 (45·3%), aspiration of food in 41 (27·7%), silent aspiration of food in 19 (12·8%), aspiration of saliva in 8 (5·41%), and silent aspiration of saliva in 10 (6·76%) patients (Table 1).

Risk factors for pneumonia and body weight loss

Even with elaborative feeding therapy, during the 3 months of follow-up after the baseline measurement, 12 (8·1%) of the 148 patients developed pneumonia (Fig. 2). In addition, among the non-pneumonia patients, 90 (66·2%) of them presented with weight gain, no change or weight loss of 3% or less (weight gain/no change group), while 46 patients (33·8%) lost 3% or more of their body weight (weight loss group) (Fig. 3).

The differences between the pneumonia and non-pneumonia groups concerning the clinical/demographic data and the dysphagic signs detected by VE are shown in Table 1. The unpaired *t*-test showed that there were no significant differences in the patient age ($P = 0·505$), gender ($P = 0·244$), self-feeding ability ($P = 0·419$), number of patients with a BMI lower than 18·5 ($P = 0·190$), and the Barthel Index ($P = 0·060$) between the subjects with and without pneumonia. On the other hand, there was a significant difference in the frequency of 'aspiration of saliva' between the pneumonia and non-pneumonia patients ($P = 0·026$). In contrast, a comparison between the body weight gain/no change and body weight loss groups showed that there were no significant differences concerning any of the analysed variables (Table 2).

The results of the Cox proportional hazard analysis revealed that a sign of the 'aspiration of saliva' detected by VE was a significant risk factor for pneumonia (Table 3) and for a body weight loss of 3% or more (Table 4).

Discussions

The presence of aspiration-related pneumonia is known to be associated with a high mortality rate in the elderly. Patients in nursing homes may have a higher incidence of pneumonia because of their multiple underlying diseases, which may lead to immunosuppression, excessive use of medications, generalized decreased functional status, as well as factors related to malfunctioning of the masticatory and orophraryngeal systems and inadequate oral care. In particular, dysphagia is known to be strongly associated with aspiration pneumonia. Teramoto *et al.* (26). reported

Table 1. The relationship between the clinical/VE signs and the incidence of pneumonia

	Total subjects	No pneumonia ($n = 136$)	Pneumonia ($n = 12$)	*P*-value
Age (mean ± s.d.)	148	85·0 ± 8·1	86·8 ± 5·4	0·505†
Male/female	148	38/98	5/7	0·244††
Self-feeding (yes/no)	148	47/89	5/7	0·419††
Barthel Index (mean ± s.d.)	116*	13·1 ± 18·1	7·2 ± 7·12	0·060†
BMI < 18·5**	118**	43/110 (39·1%)	5/8 (62·5%)	0·190††
Pharyngeal residue	148	88 (64·7%)	9 (75·0%)	0·354††
Laryngeal penetration	148	62 (45·6%)	5 (41·7%)	0·519††
Aspiration of food	148			0·326††
Silent aspiration	19	19	0	
Aspiration	41	38	3	
NA	88	79	9	
Aspiration of saliva	148			0·026††
Silent aspiration	10	7	3	
Aspiration	8	7	1	
NA	130	122	8	

*Of 116 patients, 107 were in the no pneumonia group and nine were in the pneumonia group.
**Of 118 patients, 110 were in the no pneumonia group and eight were in the pneumonia group.
†*T*-test.
††Chi-square test.

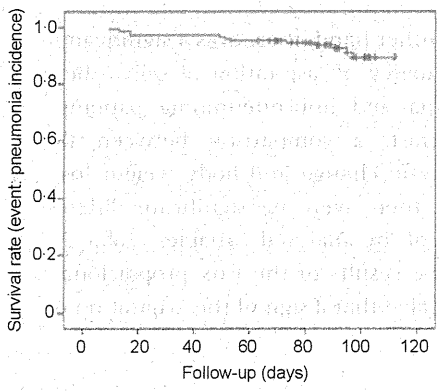

Fig. 2. The survival curve of the patients who did not suffer from pneumonia. The survival curve was drawn for a Kaplan–Meier analysis (outcome event: incidence of pneumonia).

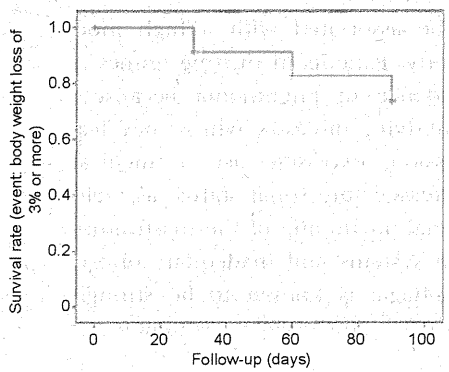

Fig. 3. The survival curve of the patients who did not suffer from a body weight loss of 3% or more. The survival curve was drawn for a Kaplan–Meier analysis (outcome event: incidence of body weight loss of 3% or more).

that 70% of the pneumonia in the elderly occurred due to aspiration, and Yamaya *et al.* (27). reported a high prevalence of silent aspiration in older persons leading to the deterioration of swallowing function due to cerebrovascular disease. In a previous study, Doggett *et al.* (28) estimated that approximately 43–54% of stroke patients have dysphagia and aspiration of food or saliva, and that approximately 37% of these patients would develop aspiration-related pneumonia.

In this present study, penetration and aspiration (apparent or silent) was observed in 67 subjects (45·2%) and 60 subjects (40·5%), respectively. The prevalence of aspiration found in this investigation was relatively high compared to previous studies utilizing VE examination (29%) (29), but was similar to the range observed in a previous review article where it was reported to occur in 15–39% of subacute dysphagic stroke patients (30). According to this review, the exact prevalence of aspiration remains unknown because of the differences in the size and methodology used in the existing studies.

The incidence of pneumonia was 12 (8·1%) among the 148 subjects (Table 1), which is in accordance with the study by Lim *et al.* (19), who reported that five patients (10%) developed pneumonia during their inpatient stay, and that all of them were at risk of aspiration of saliva or food as determined by a VE examination. On the other hand, Croghan *et al.* (6) reported that 55% of their nursing home patients presented with aspiration on VF examination, and 43% developed pneumonia.

One possible reason for such a discrepancy in the association of pneumonia and aspiration or penetration could be due to the technique (VE vs. VF) utilized to assess the swallowing disorders. Although a number of methods have been used to detect the symptoms of dysphagia, it is very difficult to evaluate 'silent aspiration of saliva' with a bedside clinical assessment alone, because it has been shown that it is missed in up to 40% of the patients aspirating silently (31, 32). At present, VF and VE are regarded as the best methods to evaluate swallowing function. In particular, VF has been used as a gold standard to evaluate swallowing because it can detect aspiration. However, it may not be as accurate in identifying 'silent aspiration of saliva', as compared to VE, because the latter enables direct visualization of the aspiration of saliva (18, 33, 34). Kelly *et al.* (35) reported that penetration and aspiration are perceived more sensitively in VE images than in VF images of the same swallows. It is also well known that VE can identify the microaspiration and aspiration of secretions with a high reliability, whereas VF cannot (36, 37). Additional advantages of VE are related to its application. Inpatients may become agitated or fatigued in the radiology suite or may not respond well to the taste of barium-coated boluses, or may even reject the radiation exposure, limiting the applications of VF. Videoendoscopy allows the patient's examination to be performed regardless of his/her altered mental status or immobility (38). Finally, Wu *et al.* (39) stated that VE is conclusively a safe, more efficient and sensitive method than VF for evaluating swallowing.

Another reason for the discrepancy could be the effect of the feeding therapy provided in this study, which could have reduced the symptoms of dysphagia,

Table 2. The relationship between the clinical/VE signs and the change in body weight

	Total subjects	Gain/no change (n = 90)	Weight loss (n = 46)	P-value
Age (mean ± s.d.)	136	84·6 ± 8·0	85·7 ± 8·6	0·464†
Male/female	136	25/65	13/33	0·553††
Self-feeding (yes/no)	136	29/61	16/30	0·454††
Barthel Index (mean ± s.d.)	107*	14·9 ± 18·7	9·6 ± 17·0	0·163†
BMI < 18·5	110**	30/74 (40·5%)	13/36 (36·1%)	0·655††
Pharyngeal residue	136	61 (67·8%)	27 (58·7%)	0·294††
Laryngeal penetration	136	44 (48·9%)	18 (39·1%)	0·2797††
Aspiration of food	136			0·975††
Silent aspiration	19	13	6	
Aspiration	38	25	13	
No aspiration	79	52	27	
Aspiration of saliva	136			0·342††
Silent aspiration	7	4	3	
Aspiration	7	3	4	
No aspiration	122	83	39	

Weight loss was diagnosed as the loss of 3% or more of the body weight from the baseline measurement.
*Of the 107 patients, 72 were in the gain/no change group and 35 were in the weight loss group.
**Of the 110 patients, 74 were in the gain/no change group and 36 were in the weight loss group.
†T-test.
††Chi-square test.

Table 3. The results of the Cox proportional hazard analysis for the possible predictors of the incidence of pneumonia

Predictors	B	P-value	HR	95% CI
Age	0·011	0·860	1·011	0·900–1·135
Self-feeding	0·105	0·909	1·111	0·182–6·785
Barthel Index	−0·010	0·769	0·990	0·927–1·057
BMI < 18·5	2·064	0·070	7·874	0·844–73·440
Pharyngeal residue	−0·621	0·615	0·537	0·048–6·067
Laryngeal penetration	0·571	0·642	1·771	0·160–19·644
Aspiration of food (negative/positive/positive with SA)	−0·216	0·830	0·805	0·112–5·794
Aspiration of saliva (negative/positive/positive with SA)	1·290	0·025	3·634	1·174–11·242

HR, hazard ratio; CI, confidence interval; SA, silent aspiration.

Table 4. The results of the Cox proportional hazard analysis for the possible predictors of a body weight loss of 3% or more

Predictors	B	P-value	HR	95% CI
Age	0·019	0·448	1·019	0·971–1·070
Self-feeding	0·530	0·228	1·698	0·718–4·014
Barthel Index	0·000	0·992	1·000	0·976–1·025
BMI < 18·5	0·859	0·032	2·362	1·074–5·191
Pharyngeal residue	−0·060	0·896	0·942	0·381–2·325
Laryngeal penetration	0·019	0·970	1·019	0·374–2·780
Aspiration of food (negative/positive/positive with SA)	−0·203	0·569	0·816	0·405–1·644
Aspiration of saliva (negative/positive/positive with SA)	1·186	0·000	3·275	1·828–5·866

HR, hazard ratio; CI, confidence interval; SA, silent aspiration.

pharyngeal residue, laryngeal penetration, and aspiration of food, as demonstrated by the fact that 66% of the subjects were able to increase their body weight or keep the body weight loss to within 3%. Nevertheless, a detailed analysis of the effectiveness of feeding therapy on the reduction of the symptoms of dysphagia could not be performed, because it was beyond the scope of this study.

Additionally, the differences in the target populations and their respective medical conditions could also have affected the overall incidence of pneumonia. This study gathered a heterogeneous patient population consisting of patients presenting with well-known disorders/diseases associated with the symptoms of dysphagia (e.g. stroke, Parkinson's disease, dementia) as well as other non-debilitating diseases/disorders (hypertension, fractures). On the other hand, a strong point in this study was the inclusion of a relatively high number of subjects from six nursing care facilities, which was large compared to other follow-up studies. Therefore,

the incidence of pneumonia may have been relatively lower in such a large heterogeneous study sample.

Regarding the risk factors associated with the development of pneumonia, some of them were reported to be age, primary disease, consciousness disorders, nutritional status, poor ADL, poor oral status, and swallowing dysfunction (40, 41). In the present study, among the analysed predictors, the 'aspiration of saliva' detected by VE was the only significant risk factor for pneumonia. In cases of bad oral health, saliva contains numerous bacteria. Therefore, patients with silent aspiration of saliva (without a cough reflex) are aspirating bacteria, which may be the main factor responsible for increasing the risk of pneumonia.

Additionally, even with the elaborative feeding therapy provided in this study, the control of aspiration of saliva or silent aspiration of saliva was generally difficult. In the present study, there was also a tendency for there to be a higher incidence of pneumonia in poor ADL patients. Langmore *et al.* (42) also reported that severely dependent functional status was an especially potent predictor of aspiration pneumonia. Riquelme *et al.* (40) reported that there was a significant relationship between the ADL and mortality rate. It was also observed that patients with a BMI < 18·5 had a higher tendency to develop pneumonia ($P = 0{\cdot}070$) compared with those with a poor ADL ($P = 0{\cdot}769$). It is well known that a lower nutrition condition affects the host immunological function, thus making the subjects more susceptible to pneumonia (43).

On the other hand, aspiration of saliva was also detected as a significant risk factor for body weight loss in this study. This finding could be explained by the possible presence of subclinical aspiration-related pneumonia in those subjects with a body weight loss of 3% or more.

The overall findings in this study demonstrated that it is still very difficult to prevent aspiration of saliva even if physicians provide elaborative feeding therapy and even if patients do not eat and drink anything through the mouth. Effective strategies to prevent the silent aspiration of saliva will therefore be an important target for future research.

Conclusion

The results of this study showed that, even with elaborative feeding therapy, 'aspiration of saliva' as detected by videoendoscopic examination was found to be a significant risk factor for pneumonia and a body weight loss of 3% or more in elderly patients living in nursing homes.

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Correspondence: Takeshi Kikutani, Division of Oral Rehabilitation, The Nippon Dental University Graduate School of Life Dentistry, 9-20 Fujimi1-chome, Chiyoda-ku, Tokyo 102-8159, Japan.
E-mail: kikutani@tky.ndu.ac.jp

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Pannexin 3 functions as an ER Ca^{2+} channel, hemichannel, and gap junction to promote osteoblast differentiation

Masaki Ishikawa,[1] Tsutomu Iwamoto,[1,2] Takashi Nakamura,[1,2] Andrew Doyle,[1] Satoshi Fukumoto,[2] and Yoshihiko Yamada[1]

[1]Laboratory of Cell and Developmental Biology, National Institute of Dental and Craniofacial Research, National Institutes of Health, Bethesda, MD 20892
[2]Department of Pediatric Dentistry, Tohoku University Graduate School of Dentistry, Sendai 980-8576, Japan

The pannexin proteins represent a new gap junction family. However, the cellular functions of pannexins remain largely unknown. Here, we demonstrate that pannexin 3 (Panx3) promotes differentiation of osteoblasts and ex vivo growth of metatarsals. Panx3 expression was induced during osteogenic differentiation of C2C12 cells and primary calvarial cells, and suppression of this endogenous expression inhibited differentiation. Panx3 functioned as a unique Ca^{2+} channel in the endoplasmic reticulum (ER), which was activated by purinergic receptor/phosphoinositide 3-kinase (PI3K)/Akt signaling, followed by activation of calmodulin signaling for differentiation. Panx3 also formed hemichannels that allowed release of ATP into the extracellular space and activation of purinergic receptors with the subsequent activation of PI3K–Akt signaling. Panx3 also formed gap junctions and propagated Ca^{2+} waves between cells. Blocking the Panx3 Ca^{2+} channel and gap junction activities inhibited osteoblast differentiation. Thus, Panx3 appears to be a new regulator that promotes osteoblast differentiation by functioning as an ER Ca^{2+} channel and a hemichannel, and by forming gap junctions.

Introduction

Gap junctions mediate intracellular signaling events, which in turn regulate various downstream cellular and physiological functions (Bennett and Verselis, 1992; Scemes et al., 2007). Gap junction proteins allow ions and small molecules to pass between adjacent cells via gap junctions, and between cells and the extracellular space via hemichannels (Unger et al., 1999; Bruzzone et al., 2001). In vertebrates, gap junction proteins are categorized into two families, connexins (Cxs) and pannexins (Panxs; Vinken et al., 2006). The connexin family has >20 members and has been relatively well characterized. Dysregulation and mutations of connexins cause several human diseases, including cancer, hypertension, atherosclerosis, and developmental abnormalities (Laird, 2006). The pannexin family is less well known and consists of only three members: Panx1, -2, and -3 (Panchin et al., 2000; Baranova et al., 2004; D'hondt et al., 2009).

Correspondence to Yoshihiko Yamada: yoshi.yamada@nih.gov

Abbreviations used in this paper: ALP, alkaline phosphatase; CA, constitutively active; CaM, calmodulin; CaMKII, CaM kinase II; CBX, carbenoxolone; CN, calcineurin; DN, dominant negative; IP3R, inositol trisphosphate 3 receptor; Ocn, osteocalcin; PI3K, phosphoinositide 3-kinase; PLC, phospholipase C; PPADS, pyridoxal-phosphate-6-azophenyl-2′,4′-disulfonate; RyR, ryanodine receptor; SERCA, sarco/endoplasmic reticulum Ca^{2+}-ATPase.

Panx1 is ubiquitously expressed, especially in the central nervous system. Panx2 is also expressed in the central nervous system (Bruzzone et al., 2003). Panx3 is expressed in skin, cochlea, and in developing hard tissues including cartilage and bone (Penuela et al., 2007; Penuela et al., 2008; Wang et al., 2009; Iwamoto et al., 2010). Panx3 is induced in the prehypertrophic zone in developing growth plates, and it inhibits parathyroid hormone–mediated chondrocyte proliferation through its hemichannel activity and promotes differentiation in culture (Iwamoto et al., 2010). Panx3 expression is also known to inhibit proliferation of keratinocytes (Celetti et al., 2010), although the underlying mechanism has not yet been established.

Ca^{2+} is a universal intracellular signaling molecule that regulates cell proliferation, differentiation, morphology, and function (Berridge et al., 2000b). Intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) can rise more than fivefold via Ca^{2+} influx from the extracellular space and/or release from the ER, an intracellular Ca^{2+} storage

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