

## Department of Dentistry

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### General Summary

#### 1. Clinical studies of temporomandibular disorders

We have continued studies of the evaluation of quality of life and screening questionnaires for temporomandibular disorders (TMDs) and the development of new therapies. We also examined the background of patients with TMDs.

#### 2. Basic studies of oral mucosal keratinocytes in wound healing

We examined the effects of various growth factors, including trefoil factor 3 (TFF3) and nerve growth factor, on human oral mucosal keratinocytes in vitro, focusing on cell proliferation and migration.

### Research Activities

#### *Clinical studies of TMDs*

##### 1. Sex-related differences in daily functions of patients with TMDs

We developed a questionnaire of the pain-related limitations of daily function (LDF-TMDQ) for Japanese patients with TMDs. Furthermore, we reported on the validity of the LDF-TMDQ, using results from 2 groups of subjects (from 2000 and 2004).

Objective: To examine the homogeneity of the 2 groups, and sex-related differences in the LDF-TMDQ scores in Japanese patients with TMDs under conditions of homogeneity.

Methods: A total of 1,073 outpatients were recruited, of whom 866 patients (81%), including 421 patients from 2000 (88 men and 333 women) and 445 patients from 2004 (139 men and 306 women), completed the questionnaire and were eligible for the analysis. In this study, we addressed the issues of homogeneity and sex-related differences by means of multigroup analysis and mean structure modeling (SPSS version 12, AMOS version 5).

Results: On multigroup analysis, the 2 groups showed homogeneity. On mean structure modeling, male patients showed significantly lower scores for all latent variables.

Conclusions: In female patients, limitations of daily function (executing a certain task, mouth opening, and sleeping) are more severe than in male patients.

##### 2. Comparative study of limitations of daily functions between patients with TMDs and those with other dental diseases

Purpose: To compare limitations of daily functions between patients with TMDs and patients with other dental diseases.

Methods: A questionnaire survey was administered to 1,575 patients who had consulted our hospital in the year after January 16, 2006. A total of 1,535 valid responses (TMD prevalence, 13%) were obtained. The items of the questions could be classified into 3

groups: limitations in executing a certain task (5 items), limitations of mouth opening (3 items), and limitations of sleeping (2 items).

Results: Patients with TMDs showed higher values for limitations in executing a certain task, limitations of mouth opening, and limitations of sleeping than did other patients. However, limitations of sleeping were rare in patients with TMDs and patients with other dental disorders.

Conclusion: Limitations in executing a certain task and limitations of mouth opening are important disorders of daily functions in patients with TMDs.

### 3. Validity of the grading of the severity of chronic pain in Japanese patients with TMDs

Objectives: Recently, many authors have evaluated the performance of the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD). The RDC/TMD have been translated into 18 languages and is being used by a consortium of RDC/TMD-based international researchers. We set out to validate the Grading of Severity of Chronic Pain (GSCP) in RDC/TMD for Japanese patients with TMDs.

Methods: We used the GSCP in the Japanese version of the RDC/TMD. A total of 448 of 542 patients with TMD were analyzed. The GSCP included 7 questions for 3 items: Characteristic Pain Intensity (item 1, 3 questions), and Disability score (item 2, 3 questions), and Disability days (item 3, 1 question). To assess the cross-validity of the GSCP, patients were randomly divided into 2 halves (group 1 and 2). We used 3 statistical methods to check the validation: Mokken analysis for a cross-validity, structural equation modeling for factor validity, and the Spearman correlation coefficient for criterion-based validity.

Results: Using Mokken scale analysis, item coefficient H ranged from 0.64 to 0.72 in group 1 and from 0.43 to 0.62 in group 2, and scale coefficient H was 0.70 and 0.57, respectively, in these groups. The results indicated monotone homogeneity. Furthermore, the reliability of the scales in groups 1 and 2 was 0.83 and 0.77, respectively, indicating double monotonicity. Structural equation modeling yielded a substantially excellent model fit. The GSCP showed criterion-based validity with a visual analog scale and a questionnaire to assess pain-related limitations of daily functions.

Conclusion: In this series of Japanese patients with TMDs, cross-validity, factor validity, and criterion-based validity of the GSCP were shown, and the GSCP subscales were used to compare Japanese and English-speaking patients with TMDs.

### 4. Teeth-contacting habit as a factor contributing to chronic pain in patients with TMDs

Many different factors are known to cause and perpetuate the symptoms of TMDs. However, the roles of parafunctional factors have not been clarified. We found one of these habits in the clinical setting. This parafunctional habit involves daily light touching of the upper and lower teeth when the mouth is closed. We named this habit the teeth-contacting habit (TCH).

Objectives: To investigate the following hypotheses: 1) TCH is associated with perpetuation of chronic pain in patients with TMDs; and 2) TCH is associated with other behavioral factors.

Methods: A total of 229 outpatients with TMDs and chronic pain were analyzed with

multivariate logistic regression models.

Results: The TCH was present in 52.4% of patients. Patients with TCH and pain lasting for more than 4 months were less likely to show a decrease in pain at the first visit (odds ratio [OR] = 1.944,  $p=0.043$ ). Other factors associated with TCH were unilateral chewing (OR = 2.802) and involvement in a precision job (OR = 2.195).

Conclusion: The TCH can prolong TMD pain and is associated with other behavioral factors.

#### 5. Selection of question items for screening of patients with TMDs

No questionnaire has been available for epidemiologic studies estimating the cross-validation of question items for screening for TMDs.

Purposes: To estimate selection methods for screening for TMDs disorders.

Methods: We created 5 physical estimation items, 4 psychological estimations (5-point numeric rating scale), and 11 exclusion items (binary scale) of TMDs. We analyzed 222 patients (TMD prevalence rate: 10.2%) who visited either of 4 dental treatment facilities. We used factor analysis, receiver operating characteristic (ROC) curves, and a non-parametric item scalability test (Mokken analysis) for item selection.

Results: Four psychological items and 5 physical items (5-point numeric rating scale) were selected from 20 items predetermined with factor analysis as the first and second factors, respectively. With Mokken analysis, 4 physical items were selected (Scale H = 0.53, Rho = 0.79), and their ROC curve value was 0.908. Three psychological items were selected with Mokken analysis (Scale H = 0.72, Rho = 0.86), and their ROC curve value was 0.595.

Conclusions: These results show that factor analysis, Mokken analysis, and ROC curves are useful for selecting screening items for TMDs.

#### *Basic study of oral mucosal keratinocyte in wound healing*

##### 1. Salivary TFF3 enhances migration of normal oral keratinocytes

Purpose: TFF3 is a small peptide (7 kDa) secreted by the submandibular gland and is 1 of 3 members of the trefoil factor family. Studies of the gastrointestinal tract have shown that members of this family play important roles in maintaining and protecting mucosal surfaces. TFF3 promotes restitution, i.e., the rapid movement of neighboring epithelial cells into a wound area. We investigated the potential positive role of TFF3 in oral wound healing.

Methods: We performed a wound-healing assay of keratinocytes isolated from oral mucosa ( $n=3$ ). Cells in serum-free medium at passages 2 to 4 were grown to confluence. The monolayer was wounded with the tip of a 200- $\mu$ l pipette and allowed to migrate for 12 hours after stimulation with 0.25 or 0.5  $\mu$ M of TFF3. The wounded areas were photographed before and after migration, and the area recovered by migrating cells was measured. To demonstrate that the observed cell movement was not related to an increased number of cells, we added mitomycin C (an inhibitor of mitosis) to the cultures before wounding and stimulation. Conversely, to demonstrate that the cells had actively migrated, we added cytochalasin B (an inhibitor of migration) to the cultures before wounding and stimulation.

Results: Cells stimulated with TFF3 showed a higher migration index than did un-

stimulated controls ( $P=0.005$ , paired t-test). Treatment with mitomycin C did not impair the observed cell migration and indicates that the movement is independent of mitosis. Treatment with cytochalasin B completely inhibited cell movement.

Conclusion: Our results show that stimulation of normal keratinocytes with TFF3 promotes migration. On the basis of these findings, we hypothesize that TFF3 is one of many factors involved in the rapid wound healing of the oral mucosa.

#### Publications

**Sugisaki M, Kino K<sup>1</sup>, Kuruma E, Yoshida N, Tamai K, Haketa T<sup>1</sup>, Shibuya T<sup>1</sup>, Ishikawa T<sup>1</sup>, Takaoka M<sup>1</sup>, Ohta T<sup>1</sup>, Sato F<sup>1</sup> (<sup>1</sup>Tokyo Med Dent Univ), Narita N<sup>2</sup> (<sup>2</sup>Nihon Univ Sch Dent Matsudo).**

Validity of the grading of severity of chronic pain in Japanese patients with temporomandibular disorders (in Japanese). *Nihon Gakukansetsu Gakkai Zasshi* 2006; **18**: 187-93.

**Sato F<sup>1</sup>, Kino K<sup>1</sup>, Sugisaki M, Haketa T<sup>1</sup>,**

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