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新潔明牙醫診所 ー李佶翰 醫師

# Salivary Biomarkers for Monitoring and Predicting the Response to Non-Surgical Periodontal Therapy

1.Department of Dentistry, National Taiwan University Hospital, Taipei, Taiwan
2.Graduate Institute of Clinical Dentistry, School of Dentistry, National Taiwan University, Taipei, Taiwan
3.Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan

## Abstract

Background: The response to non-surgical periodontal therapy varies among patients and the development of a diagnostic kit to predict the sensitivity to treatment is highly desirable. This study assessed the potential of salivary biomarkers for monitoring and predicting the sensitivity to non-surgical periodontal therapy.

Material and Methods: This study recruited 25 participants with severe chronic periodontitis (the test group) and 20 participants without periodontal destruction in any teeth (the control group) from September 2013 to June 2015. Participants in the test group received non-surgical periodontal therapy and were further divided into a low-responder (n=13) and a high-responder (n=12) subgroups based on probing depth reduction. Clinical periodontal parameters were recorded, and saliva biomarkers, including interleukin-1 beta (IL-1β), interleukin-1 receptor antagonist (IL-1ra), interleukin-6 (IL-6), interleukin-8 (IL-8), platelet-derived growth factor-BB (PDGF-BB), vascular endothelial growth factor (VEGF), matrix metalloproteinase-8 (MMP-8), matrix metalloproteinase-9 (MMP-9), C-reactive protein (CRP), and lactoferrin, were analyzed before and after non-surgical periodontal therapy.

Results: Compared with the participants in the control group, the participants in the test group had significantly greater periodontal pocket depth, clinical attachment level, and salivary IL-1 β and MMP-8 levels, before treatment, and all of these parameters were significantly reduced after non-surgical periodontal therapy. The participants in the high-responder subgroup had significantly higher levels of MMP-8 and lactoferrin than those in the low-responder subgroup before treatment. Based on the analysis from a dichotomous table, MMP-8 and lactoferrin also showed greater odds ratios with statistical significance for discriminating the high- and low-responder subgroups.

Conclusion: Salivary IL-1 β and MMP-8 might be useful for diagnosing periodontitis and monitoring the recovery of periodontitis following non-surgical periodontal therapy. MMP-8 and lactoferrin showed potential for predicting the sensitivity to non-surgical periodontal treatment.

## Materials and Methods

**Participants**

A total of 25 participants (12 males and 13 females) who met the definition of severe chronic periodontitis according to the classification defined by the American Association of Periodontology in 1999 were recruited in the test group, and additional 20 participants (10 males and 10 females) without any site exhibiting a probing pocket depth (PPD) ≥ 5 mm or clinical attachment level (CAL) ≥ 5 mm were recruited in the control group.

Other inclusion criteria:

1.25–75 years of age and systemically healthy

2.Having at least 20 teeth present

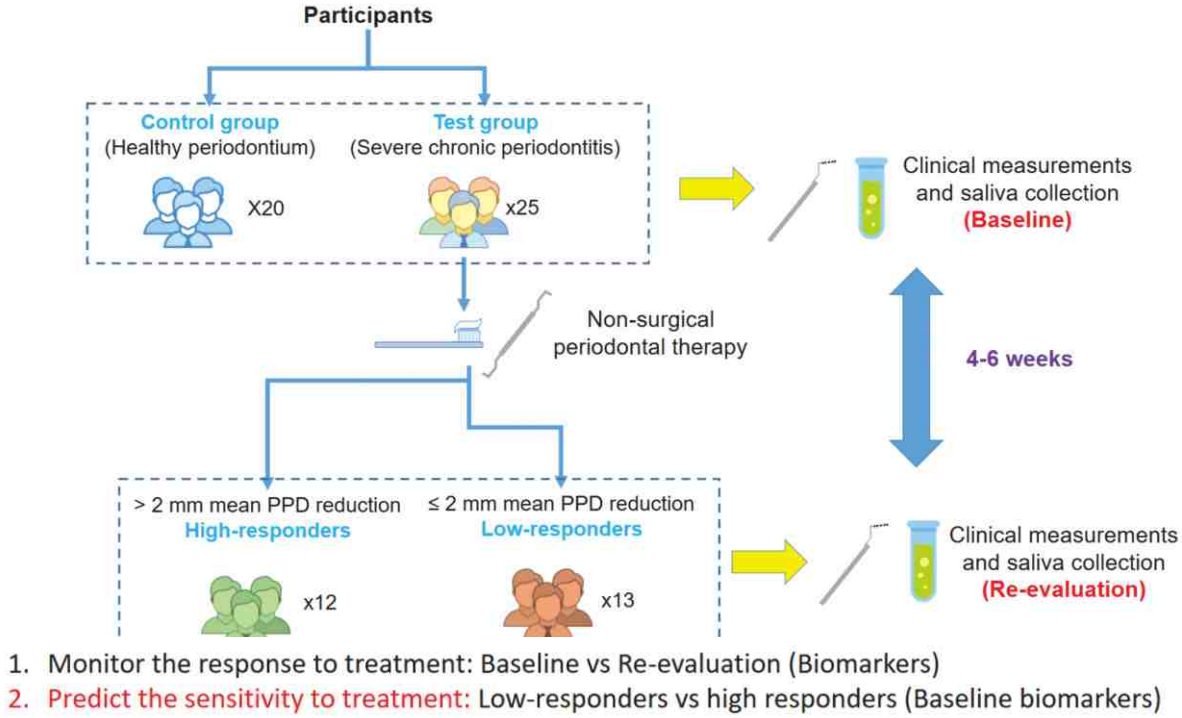
3.No orthodontic or intra-oral surgical history

4.No smoking history

5.No long-term (> 2 weeks) use of medications known to affect periodontal or systemic conditions

6.No antibiotics, anti-inflammatory drugs, or statins taken within the past 3 months.

Based on the results of power analysis, the minimal required sample size was 12 participants per subgroup.




1. Monitor the response to treatment: Baseline vs Re-evaluation (Biomarkers)
2. Predict the sensitivity to treatment: Low-responders vs high responders (Baseline biomarkers)

**Study Design**

All participants underwent a full-mouth periodontal examination and saliva collection at baseline, and all examiners were blinded to the details of the study.

1. Clinical examination: PPD, gingival recession (REC), CAL, gingival bleeding index (GBI), and plaque score (PS) were measured at 6 surfaces of all teeth.
2. Saliva collection: Unstimulated whole saliva (2–5 mL) was collected using a sterile container, and samples were centrifuged to remove insoluble particles.

Participants in the test group received non-surgical periodontal therapy, including an initial periodontal examination, oral hygiene instruction and reinforcement, full-mouth scaling and root planing, and a follow-up re-evaluation after initial clinical examination and saliva collection, and no antibiotics were prescribed. Clinical re-evaluation and saliva collection was conducted 4 to 6 weeks after the last appointment for scaling and root planning.

Participants with a mean PPD reduction of > 2 mm after non-surgical periodontal therapy at the sites with PPD ≥ 5 mm at baseline were defined as high-responders, and the others were defined as low-responders (Hayes et al, 1992; Hung et al, 2002).

**Measurements of the Salivary Biomarkers**

1. Commercialized ELISA kits were used to determine the levels of MMP-8 , MMP-9, C-reactive protein (CRP) , and lactoferrin.
2. A multiplex immunoassay system was used to evaluate the levels of IL-1b, IL-1ra, IL-6, IL-8, TNF-a, PDGF-BB, and VEGF.

All the experiments were conducted in triplicate.

# Results

**Table 1. Baseline Information and Clinical Treatment Outcome.**

| Clinical parameters | Control (N=20) | Test | | | | | |
|---|---|---|---|---|---|---|---|
| | | All (N=25) | | Low-Responder (N=13) | | High-Responder (N=12) | |
| | | Baseline | Re-evaluation | Baseline | Re-evaluation | Baseline | Re-evaluation |
| Participants (n) | 20 | 25 | | 13 | | 12 | |
| Male (%) | 50 | 48 | | 46.2 | | 50.0 | |
| Female (%) | 50 | 52 | | 53.8 | | 50.0 | |
| Age (years) | 44.5± 16.9 | 46.5± 13.9 | | 46.1± 14.8 | | 47.2± 13.1 | |
| Number of teeth | 27.9± 0.9 | 26.5± 3.0 | 26.0± 2.7 | 26.6± 2.2 | 26.4± 2.2 | 26.4± 3.9 | 25.6± 3.2 |
| Mean PPD (mm) | 2.02± 0.29 | 3.39± 0.59 | 2.66± 0.35 | 3.31± 0.44 | 2.82± 0.25 | 3.47± 0.73 | 2.48± 0.35 |
| Mean PPD = 5 mm (mm) | N/A | 5.73± 0.53 | 3.8± 0.5† | 5.56± 0.42 | 4.02± 0.46† | 5.95± 0.61 | 3.45± 0.46†‡ |
| Site with PPD = 5 mm (%) | N/A | 24.3± 14.2 | 7.7± 5.6† | 22.0± 11.8 | 8.5± 5.4† | 27.2± 16.9 | 6.7± 5.9† |
| Tooth with PPD=5 mm (%) | N/A | 58.6± 22.1 | 25.4± 15.8† | 55.5± 19.7 | 27.4± 15.6† | 62.6± 25.1 | 22.8± 16.3† |
| Mean REC (mm) | 0.08± 0.24 | 0.49± 0.62 | 0.85± 0.62† | 0.48± 0.57 | 0.76± 0.76† | 0.50± 0.70 | 0.94± 0.42† |
| Site with REC = 2 mm (%) | N/A | 14.4± 14.8 | 24.3± 16.8† | 22.1± 25.1 | 35.4± 31.9† | 15.2± 14.7 | 27.1± 13.0† |
| Tooth with REC = 2 mm (%) | N/A | 34.1± 25.8 | 49.1± 25.4† | 31.7± 28.1 | 43.4± 29.0† | 37.2± 23.5 | 56.3± 18.7† |
| Mean CAL (mm) | 2.10± 0.22 | 3.87± 0.76 | 3.51± 0.74 | 3.78± 0.73 | 3.59± 0.87 | 3.97± 0.82 | 3.42± 0.59 |
| Mean CAL = 5 mm (mm) | N/A | 6.10± 1.10 | 4.81± 1.10† | 5.91± 0.98 | 4.87± 1.17† | 6.35± 1.24 | 4.73± 1.06† |
| Site with CAL = 5 mm (%) | N/A | 29.8± 16.3 | 21.2± 15.3† | 27.0± 15.2 | 21.9± 17.1† | 33.3± 17.8 | 20.3± 13.3† |
| Tooth with CAL = 5 mm (%) | N/A | 65.9± 22.3 | 47.5± 25.7† | 62.7± 22.5 | 46.8± 28.0 | 70.0± 22.4 | 62.7± 22.5 |
| Gingival bleeding index(%) | 22.80± 9.25 | 56.73± 10.49 | 20.58± 5.87† | 55.86± 12.25 | 21.12± 6.61† | 57.60± 9.78 | 20.04± 5.75† |
| Plaque score(%) | 47.24± 15.61 | 49.53± 18.43 | 17.84± 7.93† | 47.33± 19.11 | 15.89± 7.53† | 51.73± 18.37 | 19.61± 8.22† |

*Significant differences between the baseline and the re-evaluation in the same treatment response group: p<0.05
†Significant differences between the baseline and the re-evaluation in the same treatment response group: p<0.01
‡Significant differences between high-responder and low-responder subgroups at the baseline: p<0.01

1. The mean PPD, REC, and CAL were significantly higher in the test group relative to the control group, and none of the participants in the control group exhibited PPD ≥ 5 mm, REC ≥ 2 mm, or CAL ≥ 5 mm.
2. The sites and number of teeth with PPD ≥ 5 mm or CAL ≥ 5mm decreased significantly after treatment in both the low- and high-responder subgroups. High-responders showed a greater reduction in the mean PPD ≥ 5 mm relative to low-responders.
3. In the test group, the baseline GBI was significantly higher, and the PS was statistically similar relative to the control group, but both parameters decreased statistically after non-surgical periodontal therapy. The baseline level and longitudinal change of GBI and PS were similar between the low- and high-responder subgroups.

**Table 2. Levels of Salivary Biomarkers in Response to the Non-surgical periodontal therapy.**

| Bio-markers | Control (N=20) | Test | | | | | |
|---|---|---|---|---|---|---|---|
| | | All (N=25) | | Low-Responder (N=13) | | High-Responder (N=12) | |
| | | Baseline | Re-evaluation | Baseline | Re-evaluation | Baseline | Re-evaluation |
| IL-1b(pg/ml) | 112.1 (26.0-229.4) | **304.9 (124.2-692.2)** | 65.5 (17.6-192.9)* | 203.6 (117.3-645.8) | 65.5 (14.1-204.6)† | 494.5 (128.6-913.5) | 63.2 (21.1-178.7)† |
| IL-1ra(pg/ml) | 8909 (4302-13285) | 4364 (3687-9359) | 5862 (3523-9980) | 6673 (3337-14338) | 6449 (2120-10498) | 4017 (3677-8435) | 5696 (4994-9377) |
| IL-6 (pg/ml) | 3.4 (2.2-5.7) | 4.1 (1.9-13.8) | 8.6 (4.5-34.4) | 8.9 (4.5-55.0) | 7.5 (4.5-31.9) | 3.1 (1.8-7.1) | 20.8 (4.7-35.5)† |
| IL-8 (pg/ml) | 595.0 (235.7-1049.0) | 1020.0 (338.0-2243.0) | 896.3 (407.8-1453.0) | 1578.0 (410.5-2780.0) | 952.2 (347.2-1546.0) | 693.7 (177.8-1162.0) | 765.9 (391.5-1202.0) |
| PDGF-BB (pg/ml) | 2.8 (0.0-7.2) | 3.6 (0.0-7.9) | 4.2 (0.0-8.8) | 2.85 (0.0-7.7) | 4.8 (0.0-18.1) | 3.8 (1.0-8.8) | 4.0 (1.2-6.6) |
| VEGF(pg/ml) | 656.5 (375.9-1417.0) | 825.2 (498.6-1506.0) | 645.9 (294.7-1366.0) | 825.2 (627.7-1410.0) | 645.9 (250.7-1223.0)† | 841.8 (404.7-1692.0) | 720.7 (353.5-1627.0) |
| MMP-8 (ng/ml) | 36.8 (16.9-295.5) | **182.6 (84.4-579,8)** | 47.9 (21.9-166.8) | 87.8 (74.0-231.0) | 26.8 (16.6-76.6)† | 491.3 (161.5-1549.0)‡ | 76.1 (24.3-320.7) |
| MMP-9 (ng/ml) | 93.8 (14.8-508.5) | 192.0 (113.8-542.3) | 103,3 (31.3-314.5) | 186.7 (68.3-544.7) | 91.8 (26.8-274.7) | 194.8 (125.0-544.6) | 135.7 (40.0-354.6) |
| CRP(pg/ml) | 1219 (911-3688) | 1808 (933-3133) | 1243 (926-1895) | 1458 (895-4008) | 1243 (926-2970) | 1858 (901-2664) | 1220 (849-1540)† |
| Lactoferrin (ng/ml) | 10877 (5808-20937) | 15801 (12707-18687) | 11861 (4844-17144) | 14467 (4540-17793) | 10475 (3628-19597) | 18083 (15692-18739) ‡ | 12034 (6030-14733)† |

*Significant differences between the baseline and the re-evaluation in the same treatment response group: p<0.01
†Significant differences between the baseline and the re-evaluation in the same treatment response group: p<0.05
‡Significant differences between high-responder and low-responder subgroups at the baseline: p<0.05

1.IL-1b and MMP-8 decreased significantly after treatment in both high- and low-responder subgroups, suggesting that these 2 biomarkers respond favorably to non-surgical periodontal therapy.

2.MMP-8 and lactoferrin exhibited significantly higher levels in the high-responder subgroup relative to the low-responder subgroup suggesting that they may be candidate biomarkers to predict the sensitivity to treatment.

**Table 3. Levels of Salivary Biomarkers in Response to the Non-surgical periodontal therapy.**

| | Threshold | Above threshold | Treatment Response | | Sensitivity | Specificity | OR | 95% CI | p value |
|---|---|---|---|---|---|---|---|---|---|
| | | | Low | High | | | | | |
| IL-1b (pg/ml) | 304.9 | - | 8 | 4 | 0.67 | 0.62 | 3.20 | 0.62-16.49 | 0.165 |
| | | + | 5 | 8 | | | | | |
| IL-1ra (pg/ml) | 4364.4 | - | 5 | 7 | 0.42 | 0.38 | 0.45 | 0.09-2.22 | 0.324 |
| | | + | 8 | 5 | | | | | |
| IL-6 (pg/ml) | 4.1 | - | 4 | 8 | 0.31 | 0.33 | 0.22 | 0.04-1.19 | 0.080 |
| | | + | 9 | 4 | | | | | |
| IL-8 (pg/ml) | 1020.3 | - | 5 | 7 | 0.42 | 0.38 | 0.45 | 0.09-2.22 | 0.324 |
| | | + | 8 | 5 | | | | | |
| PDGF-BB (pg/ml) | 3.6 | - | 7 | 5 | 0.58 | 0.54 | 1.63 | 0.33-7.95 | 0.544 |
| | | + | 6 | 7 | | | | | |
| VEGF (pg/ml) | 825.2 | - | 6 | 6 | 0.50 | 0.46 | 0.86 | 0.18-4.13 | 0.848 |
| | | + | 7 | 6 | | | | | |
| MMP-8 (ng/ml) | 182.6 | - | 9 | 3 | 0.75 | 0.69 | 6.75 | 1.16-39.20 | 0.003 |
| | | + | 4 | 9 | | | | | |
| MMP-9 (ng/ml) | 192.0 | - | 7 | 5 | 0.58 | 0.54 | 1.63 | 0.33-7.95 | 0.544 |
| | | + | 6 | 7 | | | | | |
| CRP (pg/ml) | 1807.5 | - | 7 | 5 | 0.58 | 0.54 | 1.63 | 0.33-7.95 | 0.544 |
| | | + | 6 | 7 | | | | | |
| Lactoferrin (ng/ml) | 15801.3 | - | 9 | 3 | 0.75 | 0.69 | 6.75 | 1.16-39.20 | 0.003* |

*Significant differences between high-responder and low-responder subgroups at the baseline: p<0.01

MMP-8 and lactoferrin showed greater potential in predicting the sensitivity to treatment.

## Conclusion

**IL-1b and MMP-8** in saliva might be used to diagnose and monitor periodontitis, and **MMP-8 and lactoferrin** show potential for predicting the sensitivity to non-surgical periodontal therapy. Additional large-scale studies with long-term follow-up to confirm the clinical feasibility of these biomarkers are still necessary.

# Salivary Biomarkers for Monitoring and Predicting the Response to Non-Surgical Periodontal Therapy

新潔明牙醫診所 李佶翰醫師

1.Department of Dentistry, National Taiwan University Hospital, Taipei, Taiwan
2.Graduate Institute of Clinical Dentistry, School of Dentistry, National Taiwan University, Taipei, Taiwan
3.Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan

## Abstract

Background: The response to non-surgical periodontal therapy varies among patients and the development of a diagnostic kit to predict the sensitivity to treatment is highly desirable. This study assessed the potential of salivary biomarkers for monitoring and predicting the sensitivity to non-surgical periodontal therapy.

Material and Methods: This study recruited 25 participants with severe chronic periodontitis (the test group) and 20 participants without periodontal destruction in any teeth (the control group) from September 2013 to June 2015. Participants in the test group received non-surgical periodontal therapy and were further divided into a low-responder (n=13) and a high-responder (n=12) subgroups based on probing depth reduction. Clinical periodontal parameters were recorded, and saliva biomarkers, including interleukin-1 beta (IL-1β), interleukin-1 receptor antagonist (IL-1ra), interleukin-6 (IL-6), interleukin-8 (IL-8), platelet-derived growth factor-BB (PDGF-BB), vascular endothelial growth factor (VEGF), matrix metalloproteinase-8 (MMP-8), matrix metalloproteinase-9 (MMP-9), C-reactive protein (CRP), and lactoferrin, were analyzed before and after non-surgical periodontal therapy.

Results: Compared with the participants in the control group, the participants in the test group had significantly greater periodontal pocket depth, clinical attachment level, and salivary IL-1 β and MMP-8 levels, before treatment, and all of these parameters were significantly reduced after non-surgical periodontal therapy. The participants in the high-responder subgroup had significantly higher levels of MMP-8 and lactoferrin than those in the low-responder subgroup before treatment. Based on the analysis from a dichotomous table, MMP-8 and lactoferrin also showed greater odds ratios with statistical significance for discriminating the high- and low-responder subgroups.

Conclusion: Salivary IL-1 β and MMP-8 might be useful for diagnosing periodontitis and monitoring the recovery of periodontitis following non-surgical periodontal therapy. MMP-8 and lactoferrin showed potential for predicting the sensitivity to non-surgical periodontal treatment.

## Materials and Methods

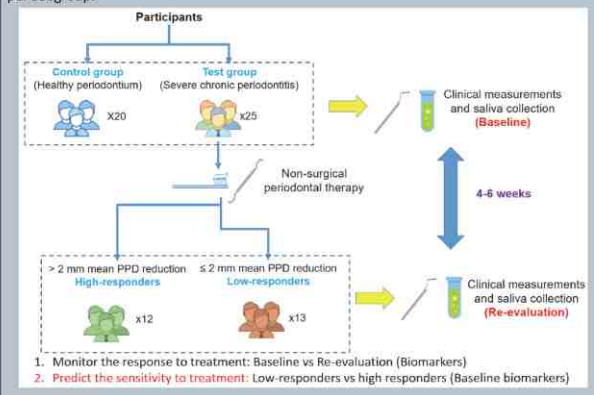
### Participants

A total of 25 participants (12 males and 13 females) who met the definition of severe chronic periodontitis according to the classification defined by the American Association of Periodontology in 1999 were recruited in the test group, and additional 20 participants (10 males and 10 females) without any site exhibiting a probing pocket depth (PPD) ≥ 5 mm or clinical attachment level (CAL) ≥ 5 mm were recruited in the control group.

Other inclusion criteria:

1. 25–75 years of age and systemically healthy
2. Having at least 20 teeth present
3. No orthodontic or intra-oral surgical history
4. No smoking history
5. No long-term (> 2 weeks) use of medications known to affect periodontal or systemic conditions
6. No antibiotics, anti-inflammatory drugs, or statins taken within the past 3 months.

Based on the results of power analysis, the minimal required sample size was 12 participants per subgroup.




1. Monitor the response to treatment: Baseline vs Re-evaluation (Biomarkers)
2. Predict the sensitivity to treatment: Low-responders vs high responders (Baseline biomarkers)

### Study Design

All participants underwent a full-mouth periodontal examination and saliva collection at baseline, and all examiners were blinded to the details of the study.

1. Clinical examination: PPD, gingival recession (REC), CAL, gingival bleeding index (GBI), and plaque score (PS) were measured at 6 surfaces of all teeth.
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Participants with a mean PPD reduction of > 2 mm after non-surgical periodontal therapy at the sites with PPD ≥ 5 mm at baseline were defined as high-responders, and the others were defined as low-responders (Hayes et al, 1992; Hung et al, 2002).

### Measurements of the Salivary Biomarkers

1. Commercialized ELISA kits were used to determine the levels of MMP-8 , MMP-9, C-reactive protein (CRP) , and lactoferrin.
2. A multiplex immunoassay system was used to evaluate the levels of IL-1β, IL-1ra, IL-6, IL-8, TNF-α, PDGF-BB, and VEGF.

All the experiments were conducted in triplicate.

## Results

**Table 1. Baseline Information and Clinical Treatment Outcome.**

| Clinical parameters | Control (N=20) | Test | | | | | |
|---|---|---|---|---|---|---|---|
| | | All (N=25) | | Low-Responder (N=13) | | High-Responder (N=12) | |
| | | Baseline | Re-evaluation | Baseline | Re-evaluation | Baseline | Re-evaluation |
| Participants (n) | 20 | 25 | | 13 | | 12 | |
| Male (%) | 50 | 48 | | 46.2 | | 50.0 | |
| Female (%) | 50 | 52 | | 53.8 | | 50.0 | |
| Age (years) | 44.5 ± 16.9 | 46.5 ± 13.9 | | 46.1 ± 14.8 | | 47.2 ± 13.1 | |
| Number of teeth | 27.9 ± 0.9 | 26.5 ± 3.0 | 26.0 ± 2.7 | 26.6 ± 2.2 | 26.4 ± 2.2 | 26.4 ± 3.9 | 25.6 ± 3.2 |
| Mean PPD (mm) | 2.02 ± 0.29 | 3.39 ± 0.59 | 2.66 ± 0.35 | 3.31 ± 0.44 | 2.82 ± 0.25 | 3.47 ± 0.73 | 2.48 ± 0.35 |
| Mean PPD ≥ 5 mm (mm) | N/A | 5.73 ± 0.53 | 3.8 ± 0.5† | 5.56 ± 0.42 | 4.02 ± 0.46† | 5.95 ± 0.61 | 3.45 ± 0.46†‡ |
| Site with PPD ≥ 5 mm (%) | N/A | 24.3 ± 14.2 | 7.7 ± 5.6† | 22.0 ± 11.8 | 8.5 ± 5.4† | 27.2 ± 16.9 | 6.7 ± 5.9† |
| Tooth with PPD ≥ 5 mm (%) | N/A | 58.6 ± 22.1 | 25.4 ± 15.8† | 55.5 ± 19.7 | 27.4 ± 15.6† | 62.6 ± 25.1 | 22.8 ± 16.3† |
| Mean REC (mm) | 0.08 ± 0.24 | 0.49 ± 0.62 | 0.85 ± 0.62† | 0.48 ± 0.57 | 0.76 ± 0.76† | 0.50 ± 0.70 | 0.94 ± 0.42† |
| Site with REC ≥ 2 mm (%) | N/A | 14.4 ± 14.8 | 24.3 ± 16.8† | 22.1 ± 25.1 | 35.4 ± 31.9† | 15.2 ± 14.7 | 27.1 ± 13.0† |
| Tooth with REC ≥ 2 mm (%) | N/A | 34.1 ± 29.8 | 49.1 ± 25.4† | 31.7 ± 28.1 | 43.4 ± 29.0† | 37.2 ± 23.5 | 56.3 ± 18.7† |
| Mean CAL (mm) | 2.10 ± 0.22 | 3.87 ± 0.76 | 3.51 ± 0.74 | 3.78 ± 0.73 | 3.59 ± 0.87 | 3.97 ± 0.82 | 3.42 ± 0.59 |
| Mean CAL ≥ 5 mm (mm) | N/A | 6.10 ± 1.10 | 4.81 ± 1.10† | 5.91 ± 0.98 | 4.87 ± 1.17† | 6.35 ± 1.24 | 4.73 ± 1.06† |
| Site with CAL ≥ 5 mm (%) | N/A | 29.8 ± 16.3 | 21.2 ± 15.3† | 27.0 ± 15.2 | 21.9 ± 17.1† | 33.3 ± 17.8 | 20.3 ± 13.3† |
| Tooth with CAL ≥ 5 mm (%) | N/A | 65.9 ± 22.3 | 47.5 ± 25.7† | 62.7 ± 22.5 | 46.8 ± 28.0 | 70.0 ± 22.4 | 62.7 ± 22.5 |
| Gingival bleeding index (%) | 22.80 ± 9.25 | 56.73 ± 10.49 | 20.58 ± 5.87† | 55.86 ± 12.25 | 21.12 ± 6.61† | 57.60 ± 9.78 | 20.04 ± 5.75† |
| Plaque score (%) | 47.24 ± 15.61 | 49.53 ± 18.43 | 17.84 ± 7.93† | 47.33 ± 19.11 | 15.89 ± 7.53† | 51.73 ± 18.37 | 19.61 ± 8.22† |

*Significant differences between the baseline and the re-evaluation in the same treatment response group: p<0.05
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1. The mean PPD, REC, and CAL were significantly higher in the test group relative to the control group, and none of the participants in the control group exhibited PPD ≥ 5 mm, REC ≥ 2 mm, or CAL ≥ 5 mm.
2. The sites and number of teeth with PPD ≥ 5 mm or CAL ≥ 5mm decreased significantly after treatment in both the low- and high-responder subgroups. High-responders showed a greater reduction in the mean PPD ≥ 5 mm relative to low-responders.
3. In the test group, the baseline GBI was significantly higher, and the PS was statistically similar relative to the control group, but both parameters decreased statistically after non-surgical periodontal therapy. The baseline level and longitudinal change of GBI and PS were similar between the low- and high-responder subgroups.

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| IL-6 (pg/ml) | 3.4 (2.2-5.7) | 4.1 (1.9-13.8) | 8.6 (4.5-34.4) | 8.9 (4.5-55.0) | 7.5 (4.5-31.9) | 3.1 (1.8-7.1) | 20.8 (4.7-35.5)*† |
| IL-8 (pg/ml) | 595.0 (235.7-1049.0) | 1020.0 (338.0-2243.0) | 896.3 (407.8-1453.0) | 1578.0 (410.5-2780.0) | 952.2 (347.2-1546.0) | 693.7 (177.8-1162.0) | 765.9 (391.5-1202.0) |
| PDGF-BB (pg/ml) | 2.8 (0.0-7.2) | 3.6 (0.0-7.9) | 4.2 (0.0-8.8) | 2.85 (0.0-7.7) | 4.8 (0.0-18.1) | 3.8 (1.0-8.8) | 4.0 (1.2-6.6) |
| VEGF (pg/ml) | 656.5 (375.9-1417.0) | 825.2 (498.6-1506.0) | 645.9 (294.7-1366.0) | 825.2 (627.7-1410.0) | 645.9 (250.7-1223.0)† | 841.8 (404.7-1692.0) | 720.7 (353.5-1627.0) |
| MMP-8 (pg/ml) | 36.8 (16.9-295.5) | **182.6 (84.4-579.8)** | 47.9 (21.9-166.8) | 87.8 (74.0-231.0) | 26.8 (16.6-76.6)† | 491.3 (181.5-1548.0)*† | 76.1 (24.3-320.7) |
| MMP-9 (pg/ml) | 93.8 (14.8-508.5) | 192.0 (113.8-542.3) | 103.3 (31.3-314.5) | 186.7 (68.3-544.7) | 91.8 (26.8-274.7) | 194.8 (125.0-544.6) | 135.7 (40.0-354.6) |
| CRP (pg/ml) | 1219 (911-3688) | 1808 (933-3133) | 1243 (926-1895) | 1458 (895-4008) | 1243 (926-2970) | 1858 (901-2664) | 1220 (849-1540)† |
| Lactoferrin (pg/ml) | 10877 (5808-20937) | 15801 (12707-18687) | 11861 (4844-17144) | 14467 (4540-17793) | 10475 (3628-19597) | 18083 (15692-18739)* | 12034 (6030-14733)† |

*Significant differences between the baseline and the re-evaluation in the same treatment response group: p<0.01
† Significant differences between the baseline and the re-evaluation in the same treatment response group: p<0.05
‡ Significant differences between high-responder and low-responder subgroups at the baseline: p<0.05

1. IL-1β and MMP-8 decreased significantly after treatment in both high- and low-responder subgroups, suggesting that these 2 biomarkers respond favorably to non-surgical periodontal therapy.
2. MMP-8 and lactoferrin exhibited significantly higher levels in the high-responder subgroup relative to the low-responder subgroup suggesting that they may be candidate biomarkers to predict the sensitivity to treatment.

**Table 3. Levels of Salivary Biomarkers in Response to the Non-surgical periodontal therapy.**

| | Threshold | Above threshold | Treatment Response: Low | Treatment Response: High | Sensitivity | Specificity | OR | 95% CI | p value |
|---|---|---|---|---|---|---|---|---|---|
| IL-1b (pg/ml) | 304.9 | - | 8 | 4 | 0.67 | 0.62 | 3.20 | 0.62-16.49 | 0.165 |
| | | + | 5 | 8 | | | | | |
| IL-1ra (pg/ml) | 4364.4 | - | 5 | 7 | 0.42 | 0.38 | 0.45 | 0.09-2.22 | 0.324 |
| | | + | 8 | 5 | | | | | |
| IL-6 (pg/ml) | 4.1 | - | 4 | 8 | 0.31 | 0.33 | 0.22 | 0.04-1.19 | 0.080 |
| | | + | 9 | 4 | | | | | |
| IL-8 (pg/ml) | 1020.3 | - | 5 | 7 | 0.42 | 0.38 | 0.45 | 0.09-2.22 | 0.324 |
| | | + | 8 | 5 | | | | | |
| PDGF-BB (pg/ml) | 3.6 | - | 7 | 5 | 0.58 | 0.54 | 1.63 | 0.33-7.95 | 0.544 |
| | | + | 6 | 7 | | | | | |
| VEGF (pg/ml) | 825.2 | - | 6 | 6 | 0.50 | 0.46 | 0.86 | 0.18-4.13 | 0.848 |
| | | + | 7 | 6 | | | | | |
| MMP-8 (ng/ml) | 182.6 | - | 9 | 3 | 0.75 | 0.69 | 6.75 | 1.16-39.20 | 0.003 |
| | | + | 4 | 9 | | | | | |
| MMP-9 (ng/ml) | 192.0 | - | 7 | 5 | 0.58 | 0.54 | 1.63 | 0.33-7.95 | 0.544 |
| | | + | 6 | 7 | | | | | |
| CRP (pg/ml) | 1807.5 | - | 7 | 5 | 0.58 | 0.54 | 1.63 | 0.33-7.95 | 0.544 |
| | | + | 6 | 7 | | | | | |
| Lactoferrin (pg/ml) | 15801.3 | - | 9 | 3 | 0.75 | 0.69 | 6.75 | 1.16-39.20 | 0.003‡ |
| | | + | | | | | | | |

‡Significant differences between high-responder and low-responder subgroups at the baseline: p<0.01

MMP-8 and lactoferrin showed greater potential in predicting the sensitivity to treatment.

## Conclusion

**IL-1β and MMP-8** in saliva might be used to diagnose and monitor periodontitis, and **MMP-8 and lactoferrin** show potential for predicting the sensitivity to non-surgical periodontal therapy. Additional large-scale studies with long-term follow-up to confirm the clinical feasibility of these biomarkers are still necessary.

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# *Rehabilitation of occlusion by forced eruption and protraction of mesially impacted third molars*

Hsin-Chih Lai, Ya-Ying Teng
Department of Craniofacial Orthodontics
Chang Gung Memorial Hospital, Linkou, Taiwan

## Abstract

Third molars present the highest rate of impaction in the oral cavity. Whether or not to proceed with the extraction of impacted third molars should be decided based on a cost/benefit evaluation. Though third molars are not directly involved in orthodontic treatment, it is possible to use third molars which are normally shaped to replace a missing tooth and reconstruct occlusion in some situations. This case report details the occlusal rehabilitation via forced eruption of impacted third molars and the uprighting of mesially tilted molars.

A 23-year-old female patient presented with a chief complaint of several serious caries and protruding lips. Clinical examination and panoramic film displayed proclined upper incisors, a large overjet, a deep overbite, crowding in both dentitions, and many residual roots which included the upper right first and second molars, as well as the upper and lower left first molars. All third molars were impacted except the upper left. The cephalometric film showed a skeletal Class II jaw relation with retrognathic mandible and a high mandibular plane angle.

Extraction of four bicuspids was usually the first choice in patients with crowding and protrusion. However, instead of extraction of four premolars, an asymmetric extraction strategy in consideration of her several unrestorable teeth was provided. Forced eruption and protraction of the impacted upper right and lower left third molars into occlusion and the uprighting of tilted left upper and lower second molars was accomplished with the aid of miniscrews. After a three-year treatment, the patient had a balanced profile without exaggerated mandibular posture. Correcting deep bite by intrusive arch and solid occlusion was also achieved. Though pulling impacted molars into occlusion was time-consuming, we provided healthier teeth and preserved more natural teeth in this case.