

An Introduction to the Use of Biomarkers and Sub-Gingival Temperature in the Assessment of Periodontists and Peri-Implantitis

Mohamad Hani Nouri Dalati^{1*} and Mazen Tamimi²

¹Consultant Orthodontist and Medical Director at Tajmeel Specialized Medical Center, Abu Dhabi, UAE

²Consultant OMFS, President of the IBOI and Member of the Scientific Advisory Board of IMC, Duisburg, Essen University, Germany

***Corresponding Author:** Mohamad Hani Nouri Dalati, Consultant Orthodontist and Medical Director at Tajmeel Specialized Medical Center, Abu Dhabi, UAE.

Received: July 01, 2020; **Published:** July 15, 2020

Abstract

The conventional methods of assessing the level of periodontal or peri-implant destruction at individual sites (such as bleeding on probing, attachment loss, inflammation signs etc.) have been heavily criticized over the years for not being accurate, quantitative, objective and not being able to predict the progress of the disease accurately. These traditional methods were mainly classified as being subjective and retrospective in nature and that was simply due to their well-known limitations.

There has been, therefore, a steady growing trend during the last two decades to develop tools to try to predict, detect, measure and monitor both the progress and the response to treatment of oral diseases such as periodontitis and peri-implantitis. These developments covered a wide spectrum of tools such as sub-gingival temperature, various Biomarkers such as pro-inflammatory and anti-inflammatory Cytokines, bone loss markers, enzymes, genetic analysis and molecular Assays.

More development and well-designed longitudinal studies are, however, still needed in order to help us in understanding the various mediators implicated on the initiation and progression of periodontitis and peri-implantitis.

Keywords: Biomarkers; Sub-Gingival Temperature; Periodontists; Peri-Implantitis

Introduction

Dental implants are often considered as the best choice to replace missing teeth in adults. Success rates used to be reported as being more than 95% [1] but in the last decade increasing evidence emerged on the presence of peri-implant inflammation as being one of the most frequent complications affecting both the surrounding soft and hard tissues around the implant which, if not treated properly, can lead to the eventual loss of the implant.

Classification

This Peri-implant inflammation could be classified to two main groups: Peri-Implant Mucositis (Prevalence 43%) and Peri-implantitis (prevalence 22%) [2-4]. Mucositis is usually a bacteria-induced, reversible inflammation in the peri-implant soft tissue that is associated with various degrees of reddening, swelling and bleeding on periodontal probing but not with bone loss [2-6]. Peri-implantitis on the other hand, is more of a progressive and irreversible inflammation of the hard and soft tissues surrounding the implant and is often accompanied with bone resorption, decreased level of osseointegration, increased pocket formation and purulence [2-6]. Bone loss should be ≥ 3 mm according to the 2017 World Workshop on the Classification of Periodontal and Peri-implant Diseases and Conditions [7].

Risk factors

In general, it was agreed that there is an increased risk of developing Peri-Implant inflammation in patients with history of severe periodontitis, poor plaque control, and no regular maintenance care after implant therapy [7].

Many factors have been reported as risk factors for the development of peri-implantitis, few examples of which are [8-13]:

- Smoking: As it will significantly increase the risk of complications especially in the presence of a positive combined IL-1 genotype polymorphism.
- Previous history of active periodontitis.
- Lack of motivation, compliance and below average status of oral hygiene (including missing checkups).
- Systemic diseases (e.g. uncontrolled diabetes mellitus, cardiovascular disease, immunosuppression).
- Iatrogenic causes (e.g. "Cementitis").
- Soft tissue defects or poor-quality hard or soft tissue at the site of the implant (e.g. severe bone loss, lack of keratinized gingiva etc).
- History of one or more failures of implants.

Studies indicated that smoking could be considered as the greatest identifiable and most often cited risk factor for peri-implant disease followed by a history of chronic periodontitis. Both factors found to be related to higher prevalence of peri-implantitis [10].

Causing factors

Periodontal diseases, in general, are of a complex and multifactorial nature but could be simplified to be the result of:

- Environmental factors,
- Host factors,
- Bacterial factors [15].

Similarly, Peri-implantitis exhibits a chronic inflammatory response to the bacterial biofilm on the implant surface [16]. In contrast to periodontitis, peri-implantitis lesions harbor bacteria that are not part of the typical periodontopathic microbiota. In particular, *Staphylococcus aureus* appears to play a predominant role for the development of a peri-implantitis. This bacterium shows a high affinity to titanium and has according to the results of Salvi, *et al.* a high positive (80%) and negative (90%) predictive value [17]. High counts of 19 bacterial species, including *Porphyromonas gingivalis* and *Tannerella forsythia* were found to be associated with Peri-implantitis among others [4]. Some individuals, however, are believed to be more susceptible to peri-implantitis than others due to differences in the host response and to the potential influence of various gene polymorphisms in the pathogenesis of peri-implantitis.

Peri-Implant mucositis usually precedes peri-implantitis but in some cases the progression often appears to be faster than periodontitis around natural teeth hence the peri-implant mucositis stage in such cases could hardly be defined [4]. Peri-implant mucositis is primarily caused by a disruption of the host-microbe homeostasis at the implant-mucosa interface and is a reversible condition [3]. There is general agreement on that, in most cases, surgical approach achieves better results than other conservative approaches but there is no consensus on which surgical intervention is most reliable in controlling peri-implantitis [18].

Limitations of the traditional diagnostic methods

The traditional diagnostic methods such as clinical examination, periodontal probing and radiographs are still not fully trustworthy, hence, the accurate diagnosis of peri-implant inflammation remains very challenging. Current diagnostic methods are retrospective and can only grade the pre-existing inflammation and show the pre-existing damage but cannot predict if this implant will have an inflammation in the near future more than the other implants in the mouth or even determine the true current disease activity or to accurately predict its progression and response to treatment.

The difficulties in determining the accuracy of the traditional diagnostic process could be summarized in simple facts such as that clinical scenarios may vary between peri- implant mucositis and peri-implantitis cases and between different stages of the disease progression. Standardizing the radiographs in order to allow true and accurate comparison to the reference radiographs taken at the time the implant was placed in function is very difficult sometimes especially if implants were placed at another center. Furthermore, there is no practical model to predict the progression of Peri-Implantitis [19]. The absence of a periodontal ligament around implants in addition to the different prosthetic designs may play a role in making the assessment of pocket probing depth measurements difficult to be performed or interpreted. Additionally, due to the lack of the various periodontal ligaments, the implant mucosal seal may have less resistance to probing force compared to natural teeth. This may lead to mechanically induced bleeding due to a simple trauma when probing around healthy implants and can be considered as an additional imitation to the traditional diagnostic methods.

Sub-gingival temperature measurements

Increased local temperature is usually correlated to active inflammatory process and therefore, many studies attempted finding relationship between the differences in the sub-gingival and sub-lingual temperatures and between the stable and active periodontal diseases.

Dr. Dalati and colleagues in 1999 used the Periotemp™ System (Figure 1-4) and demonstrated that mean sub-gingival temperature in healthy sites was, on average, 2°C lower than the sublingual temperature. When studying the correlation between the changes in the sub-gingival and sub-lingual temperature and the inflammatory cytokines in the gingival crevicular fluid of adult patients with periodontal disease; they found a strong correlation between Interleukin -1β levels and the sub-gingival temperatures in healthy and diseased (stable) sites [20]. In 2000, they further investigated the cytokine IL-1β and its receptor antagonist IL-1ra in gingival crevicular fluid (GCF), in a larger group of patients with adult periodontitis. They have used the Periopapers strips to collect the GCF samples and then used the Periotron 6000™, A Quantikine™ Human IL-1β Immunoassay Kit to perform the ELISA procedure on all samples collected. Their results suggested a strong relationship between the severity of adult periodontitis and the increasing GCF levels of IL-1β and decreasing levels of IL-1ra which is an antagonist to the IL-1β [21]. This has proved quantitatively the inverse relationship between IL-1β and IL-ra levels in the GCF and proved that biomarkers could be used to accurately determine and measure the periodontal disease status with or without sub-gingival temperature measurements.



Figure 1: The Periotemp™ device.

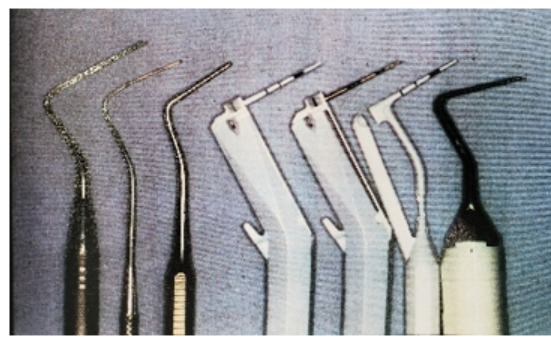


Figure 2: The Periotemp special probe has a similar shape and size and marking to the other commercially available periodontal probes.



Figure 3: The temperature probe in use.

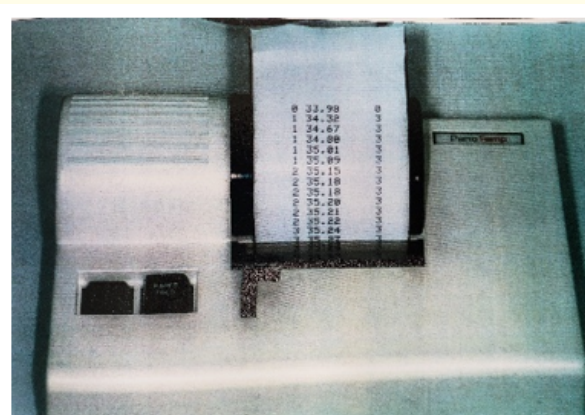


Figure 4: The Periotemp™ electronic printer.

Biomarkers in dentistry

Biomarkers are often used in the medical and dental fields in order to try objectively to predict diseases, determine disease status, or even responses to therapeutic interventions. Periodontal Biomarkers studies on the gingival crevicular fluid components proved to have some promising diagnostic validity in terms of staging and grading of the disease. This could include but not limited to:

- Disease mediators such as pro-inflammatory Cytokines (such as: IL-1 β , TNF Alfa, IL-6, IL-17 and TGF-Beta 2) and anti-inflammatory Cytokines (such as: IL-10, IL- 4, IL-8 and IL -1) and antagonists.
- Different bone loss markers (such as: Soluble RANKL, OPG, C-telopeptide pyridinoline cross linkage of type I collagen - ICTP).
- Different enzymes (such as: Cathepsin K, TIMP-1, TIMP-2, VEGF, MMPs groups - mainly MMP-1, 8, 9, 13).

This has encouraged their use in the periodontal and the peri-implantitis studies using some commercially available chair-side test kits for pro-inflammatory markers and cytokines in the peri-implant sulcular fluid such as Interleukins (IL-1 β , IL-6, IL-12, TNF Alfa and MMP-8), proteomic, metabolomics and enzymes.

The leading manufacturers aimed at developing a quick, inexpensive, easy-to-use, chair-side diagnostic kit that will be of high validity, high accuracy, of high specificity/sensitivity and can help in predicting the risk of disease progression at any implant site at any given time.

Recent studies showed that in periodontal and peri-implantitis tissues, cytokines, tumor necrosis factors and transforming growth factors have important roles in regulating and amplifying inflammatory response [22-24]. Interleukin (IL)-1 β is one of the most potent cytokines in the inflammatory process in the oral cavity triggered by various stimuli including neurotransmitters, bacterial products, and by other cytokines and mechanical forces. The action of IL-1 β includes, but not limited to, attracting leucocytes and stimulating fibroblasts, endothelial cells, osteoclasts and osteoblasts to promote bone resorption and to inhibit bone formation [25].

Renvert., *et al.* studies on Cytokine and microbial profiles in relation to the clinical outcome following treatment of peri-implantitis showed that clinically stable treatment outcomes of peri-implantitis are associated with lower levels of putative pathogens total bacterial load and with reduction of IL-1 β , IL-6, and VEGF levels in PICF [26].

Analysis of the GCF or the peri-implant curricular fluid (Figure 5-7) offers a non-invasive means of studying host response in periodontal and peri-implantitis disease and may provide an early indication of patients at risk for active disease. Interleukins, in general, and mainly the IL-1 β levels could easily be estimated by an enzyme-linked immunosorbent assay (ELISA).



Figure 5: Periopaper strips in use for the collection of the GCF samples.

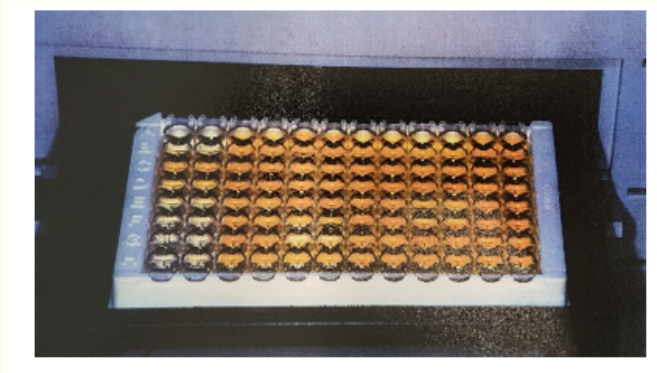


Figure 6: The microtiter plate showing color change (from blue to yellow) when stop-solution is added.



Figure 7: The Periotron 6000™ in use.

Each sample could be collected by a 1 to 5- μ l calibrated volumetric micro-capillary pipette placed carefully and in isolation at the GCF or the peri-implant crevice. Strict protocols could sometimes be applied for perfect results in accordance to the internationally accepted method described by Griffiths [27]. This method could be used for other interleukins as well and was claimed to be able to indicate active sites and help estimating risks of further diseases progression in relation to their elevated concentrations as well as giving some indication on the level of response to the treatment provided.

Biomarkers’ chair-side kits

Different chair-side kits were recently made available for the studies on various mediators and enzymes. Dr. Dalati and colleagues, in 1999, used the Quantikine™ Human IL-1 β Immunoassay Kit to perform the ELISA procedure to successfully quantify periodontal disease progression based on analysis of GCF samples from healthy and diseased subjects [20,21]. They were able to detect IL-1 β and IL-1ra in

very low levels in the collected GCF samples. Other example on this could be the commercially available ImplantSafe® quantitative device that is able to detect even minimally raised levels of MMP-8 in the oral fluids and quantify them with high sensitivity and specificity records (sensitivity of 90% and a specificity of 70% - 85%) [28-30].

In order to reduce costs and increase acceptability, some manufactures went the extra mile and made available a special diagnostic chewing-gum test which was claimed to detect elevated levels of the MMP-8. That elevation was claimed to be associated with increased bitterness taste in the mouth which indicates higher level of peri-implant inflammation, while low MMP-8 levels (lower than 20 ng/ ml) were associated with healthy peri-implant tissues and normal taste [28-30]. To our knowledge, there is still no reports on long-term randomized clinical trials to support this invention and test its accuracy.

A large number of such chair-side kits are available in the market nowadays. Some of them have more validity studies to support their use than others but in general, practitioners should insure the use of the ones that are well backed-up by valid scientific and longitudinal research, and not only on the widely available cross-sectional studies, in order to minimize false readings and any possible negative impact on their proposed treatment plans.

It should be noted that such inflammatory cytokines or other Biomarkers are not necessarily present in a representative quantity at any single unit of time of the GCF or the peri-implant crevicular fluid collection due to several systemic and local factors.

This could be simply due to the cyclic progression of the periodontal and the peri-implant diseases. The immune-inflammatory event biomarkers responsible for tissue breakdown, therefore, may not always be active in cross-sectional studies with a single moment of fluid collection [31].

A recent study by Alassy, *et al.* [32] reviewed the available evidence to support the use of such chair-side kits and they have reported that the current validity of predicting peri-implant disease is still in its infancy and that:

- Studies on bone markers are often inconclusive despite bone loss being one of the main features of peri-implantitis.
- Most reported studies were interventional trials, sampling the diseased implants before and after therapy.
- There are very few longitudinal studies sampled implants over time.
- Longitudinal studies may confirm the concentrations of biomarkers at specific sites and would theoretically show the shifts of such concentrations in diseased implants over time.
- These longitudinal investigations may aid in presenting biomarkers that predict the shift from health to disease or predicting the deterioration of a diseased implant.

Conclusion

As there is an increase in the prevalence of Periodontal and peri-implant diseases, there is a great need to develop some new ways to predict, detect, measure, and monitor the severity of the disease. There is a need as well, to develop ways to increase the diagnostic and the predictive accuracy of the currently available methods that study biomarkers and sub-gingival temperature in subjects with periodontal or peri-implant diseases. This will simply have a significant impact on predicting, and hopefully, preventing the disease at start and on treating it successfully if it was already established. This will definitely improve our current oral and dental care and may allow us to determine which patients, which tooth or which dental implant may be at risk of disease progression compared to others.

Sub-gingival temperature and biomarkers' measurement technologies are developing fast and they may offer in the near future some promising possibilities in detecting Periodontal and peri-implant diseases, monitoring their progress and their response to treatment. Although more research is needed, these technologies seem to be unable currently to predict peri-implantitis or peri-implant mucositis and that is maybe due to the limited available evidence of well-designed, well-controlled, longitudinal clinical trials in this field.

A good number of sub-gingival temperature measuring devices and chair-side diagnostic tests for different Biomarkers are commercially available nowadays. They could be used to detect Periodontal and peri-implant diseases with various degrees of success. Further investigations, however, are still needed in order to create some sort of fast, accurate and smart test kits for multi-biomarker measurements, bone loss markers, enzymes, un-targeted metabolomics and more sophisticated genetic susceptibility analysis and molecular assays for the detection of biomarkers on the different stages of the disease. There is still a need to discover new biomarkers, new diagnostic technologies such as nucleic acid and protein microarrays and microfluidics, and a need to develop new therapeutic approaches and enhance the use of host modulation. This will help in advancing our current risk assessment protocols and may help in developing advanced comprehensive screening systems of biomarkers.

More interventional and well-designed longitudinal trials aiming at identifying some specific and possibly unique set of biomarkers in the GCF and in the peri-implant crevicular fluids are still needed in order to help us in understanding further the mediators implicated on the initiation and the progression of periodontitis and peri-implantitis.

Bibliography

1. Lindh T, *et al.* "A meta-analysis of implants in partial edentulism". *Clinical Oral Implants Research* 9 (1998): 80-90.
2. Elani HW, *et al.* "Trends in Dental Implant Use in the U.S., 1999-2016, and Projections to 2026". *Journal of Dental Research* 97 (2018): 1424-1430.
3. Heitz-Mayfield LJA and Salvi GE. "Peri-implant mucositis". *Journal of Periodontology* 89 (2018): S257-S266.
4. Schwarz F, *et al.* "Peri-implantitis". *Journal of Periodontology* 89 (2018): S267-S290.
5. Derks J and Tomasi C. "Peri-implant health and disease. A systematic review of current epidemiology". *Journal of Clinical Periodontology* 42.16 (2015): S158-S171.
6. Araujo MG and Lindhe J. "Peri-implant health". *Journal of Periodontology* 9.1 (2018): S249-S256.
7. Berglundh T, *et al.* "Peri-implant diseases and conditions: Consensus report of workgroup 4 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions". *Journal of Periodontology* 89.1 (2018): S313-S318.
8. Schwarz F, *et al.* "Aktuelle Aspekte zur Therapie periimplantärer Entzündungen". *Quintessenz* 59 (2008): 00.
9. Periimplantäre Entzündungen.
10. Mombelli A, *et al.* "The epidemiology of peri-implantitis". *Clinical Oral Implants Research* 23.6 (2012): 67-76.
11. Charyeva O, *et al.* "Long-term dental implant success and survival-a clinical study after an observation period up to 6 years". *Swedish Dental Journal* 36 (2012): 1-6.
12. Heitz-Mayfield LJA. "Peri-implant diseases: diagnosis and risk indicators". *Journal of Clinical Periodontology* 35 (2008): 292-304.
13. Ferreira SD, *et al.* "Prevalence and risk variables for peri-implant disease in Brazilian subjects". *Journal of Clinical Periodontology* 33 (2006): 929-935.
14. Heitz-Mayfield LJ and Lang NP. "Comparative biology of chronic and aggressive periodontitis vs. peri-implantitis". *Periodontology* 2000 53 (2010): 167-181.
15. Wolff L, *et al.* "Bacteria as Risk Markers for Periodontitis". *Journal of Periodontology* 65.5 (1994): 498-510.
16. Rocuzzo M, *et al.* "Clinical outcomes of peri-implantitis treatment and supportive care: A systematic review". *Clinical Oral Implants Research* 29.16 (2018): 331-350.

17. Salvi GE., et al. "One-year bacterial colonization patterns of Staphylococcus aureus and other bacteria at implants and adjacent teeth". *Clinical Oral Implants Research* 19 (2008): 242-248.
18. Englezos E., et al. "Resective Treatment of Peri-implantitis: Clinical and Radiographic Outcomes After 2 Years". *International Journal of Periodontics and Restorative Dentistry* 38 (2018): 729-735.
19. Renvert S., et al. "Peri-implant health, peri-implant mucositis, and peri-implantitis: Case definitions and diagnostic considerations". *Journal of Periodontology* 89 (2018): S304-S312.
20. MHN Dalati., et al. "Cytokines and Sub-Gingival Temperature". *Journal of Dental Research* 78.5 (1999): 1066-1066.
21. Rawlinson A., et al. "Gingival Crevicular Fluid Levels of Interleukin-1 and IL-1 Receptor Antagonist in Adult Periodontitis". *Journal of Clinical Periodontology* 27.10 (2000): 738-743.
22. Javed F., et al. "Proinflammatory cytokines in the crevicular fluid of patients with peri-implantitis". *Cytokine* 15 (2011): 8-12.
23. Graves DT and Cochran D. "The contribution of interleukin-1 and tumor necrosis factor to periodontal tissue destruction". *Journal of Periodontology* 15.3 (2003): 391-401.
24. Sari E and Uçar C. "Interleukin 1beta levels around microscrew implants during orthodontic tooth movement". *The Angle Orthodontist* 15 (2007): 1073-1078.
25. Moxham BJ and Berkovitz BKB. "In: The Periodontal Ligament in Health and Disease. 2. Berkovitz BKB, Moxham BJ, Newman HN, editor. Mosby-Wolfe, London. The effects of external forces on the periodontal ligament (1995): 215-241.
26. Renvert S., et al. "Cytokine and microbial profiles in relation to the clinical outcome following treatment of peri-implantitis". *Clinical Oral Implants Research* 28 (2017): 1127-1132.
27. Griffiths GS. "Formation, collection and significance of gingival crevice fluid". *Periodontology 2000* 15 (2003): 32-42.
28. Alassiri S., et al. "The Ability of Quantitative, Specific, and Sensitive Point-of-Care/Chair-Side Oral Fluid Immunotests for aMMP-8 to Detect Periodontal and Peri-Implant Diseases". *Journal of Disease Markers* (2018): 1306396.
29. Al-Majid A., et al. "Matrix Metalloproteinase-8 as an Inflammatory and Prevention Biomarker in Periodontal and Peri-Implant Diseases". *International Journal of Dentistry* (2018): 7891323.
30. Kinney JS., et al. "Crevicular fluid biomarkers and periodontal disease progression". *Journal of Clinical Periodontology* 41 (2014): 113-120.
31. Dursun E and Tozum TF. "Peri-Implant Crevicular Fluid Analysis, Enzymes and Biomarkers: A Systemetic Review". *Journal of Oral and Maxillofacial Research: JOMR* 7 (2016): e9.
32. Hatem Alassy., et al. "Peri-Implantitis Diagnosis and Prognosis Using Biomarkers in Peri-Implant Crevicular Fluid: A Narrative Review". *Diagnostics (Basel)* 9.4 (2019): 214.

Volume 19 Issue 8 August 2020

©All rights reserved by Mohamad Hani Nouri Dalati and Mazen Tamimi.