

# Biomarkers in Peri Mini Screw Implant Crevicular Fluid in Orthodontics - A Review

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## Abstract

Miniscrews have become an important addition to the orthodontic armamentarium since their use in enhancing anchorage. They are now the most sought after options in orthodontic anchorage for their ease in positioning at diverse areas in the oral cavity. The reported success rate of the miniscrews ranged from 71.4% to 100%. Peri-implantitis accounts for about 30% of miniscrew failures. Peri-implantitis is a progressive peri-implant bone loss in conjunction with soft tissue inflammatory lesion. Analysis of PMICF helps provide an early and non-invasive indication of infection and the prognosis of the implants. PMICF is an inflammatory exudate, with its constitution being analogous to that of the gingival crevicular fluid, it contains host-derived enzymes, their inhibitors, inflammatory mediators, host response modifiers and tissue breakdown products. Evaluation of PMICF helps in assessing host response in peri-miniscrew disease and also serve as an early manifestation of patients at the prospect for active disease. Mediators of interest in PMICF are – Cytokines -interleukins (ILs) (IL-1 $\alpha$ , IL-1 $\beta$ , IL-1RA, IL-8, IL-2, IL-6, and IL-15) , Receptor antagonist IL-1RA, TNF- $\alpha$ , Macrophage CSFs, RANK / RANKL /OPG ,chondroitin sulphate, extracellular high mobility box protein (HMGB1) for the production of interleukins-1 $\beta$ , 6, 17 and RANKL, Certain matrix metallo proteins like 1, 2, 3, 7, 8, 9, 12, 13 have been proved to be potential biomarkers for remodelling and also serve as an indicator for MSI stability. Conclusion -There is a need of the hour for future research of all the inflammatory mediators associated with inflammation and bone resorption at the biochemical level.

**Keywords:** *Miniscrews, Biomarkers, Peri Miniscrew Implant Crevicular Fluid*

## 1. INTRODUCTION

The temporary anchorage devices like miniscrew implants (Fig.1) serve of great importance in the management of malocclusions of high severity and also aid in complex tooth movements by preventing anchorage loss (Fig.2). Although an array of factors are responsible for the success and stability of miniscrew implants, the biological interface of MSI with bone and soft tissue plays an important role in the success of implants.



**Figure 1: Traditional implant and Mini implant**



**Figure 2: Mini implant placed in the oral cavity**

The inflammation associated with MSI can be assessed via biomarkers in peri-miniscrew implant crevicular fluid which is similar to the GCF in composition. Evaluation of the biomarkers present in PMICF gives an indication of inflammation associated with the implant site, osteoclast activation and differentiation, bone resorption and turnover.<sup>1</sup> The methods of collection of PMICF for assessing the biomarkers

can be through non-invasive means like paper strips, periopaper or micro capillary pipettes and the methods of analysis are enzyme-linked immunosorbent assay or immunoassays. The inflammatory markers and mediators that have been reviewed earlier in association to orthodontic tooth movement include interleukins, growth factors, proteins like tumour necrosis factor, receptor activator of nuclear factor kappa-B ligand, chondroitin sulphate and osteoprotegerin.<sup>2</sup> Studies have shown the difference in the concentrations of biomarkers can be an indication of the success of MSIs.<sup>3</sup> The markers collected from the sulcus or periodontal pocket is very valuable and little invasive diagnostic procedure. There are number of methods for collecting fluid from the sulcus described: Micro-capillary drainage, micropipette drainage, rinsing pocket or drainage with the use of methylcellulose strips (Periopaper strips – Oraflow Inc.) and then reading with Periotron (Oraflow Inc.).(Fig.3)

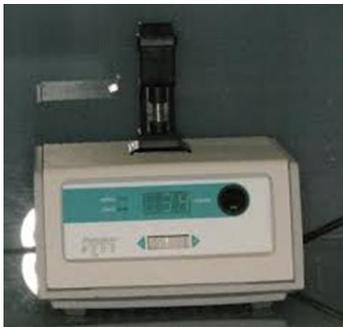


Figure 3: Periotron

## 2. BIOMARKERS IN PMICF

The composition of PMICF is similar to that of GCF. It is an inflammatory exudate surrounding the MSI crevice, comprising of inflammatory biomarkers, growth factors and other proteins. There is significant increase in the amount of PMICF and concentration of inflammatory biomarkers in case of inflammation. To analyze these mediators of inflammation, the standard methods of PMICF collection are via paper strips,

microcapillary pipettes or periopaper.

According to a literature search, the following biomarkers can be found in PMICF:

**Interleukins:** These belong to a group of regulatory proteins that are produced by the fibroblasts, osteoclasts, PMNLs and play an important role in bone remodelling. They consist of several markers such as IL-1B, IL-2, IL-6, IL-8 and these can be detected in the GCF and PMICF.

**Interleukin 1 $\beta$ :** A cytokine which is coded by the IL1 $\beta$  gene. It is an inflammatory response mediator of the IL-1 cytokine family. It is released in response to various stimuli like release of other cytokines, bacterial products or mechanical stimuli. It acts by promoting bone resorption and inhibiting bone formation through the RANK-RANKL pathway by stimulation of endothelial cells, osteoblasts and osteoclasts.<sup>9</sup>

A study conducted by Monga *et al.* evaluated the changes in IL-1 $\beta$  clinically and biochemically in PMICF during orthodontic tooth movement. It reviewed the analysis of IL-1 $\beta$  in PMICF obtained from around the mini screws from 11 patients. Mini screws were loaded at 21 days post placement of 200g closed coil springs of Nitinol of 9mm length for en masse retraction. PMICF was collected at the time of placement, at 3 weeks, and on loading at 0, 1, 21, 72, 120, 180 and 300 days respectively. Levels of IL-1 $\beta$  were estimated by ELISA. The study concluded that the varying levels of IL-1 $\beta$  in PMICF are indicative of the concealed inflammatory process. IL-1 $\beta$  levels in PMICF show a significant rise during mini screw insertion and on immediate loading. The gradually lowered IL-1B levels over the period after loading towards baseline is suggestive of adaptive bone response to stimulus.<sup>3</sup>

A study by Sari *et al.* measured the levels of IL-1 $\beta$  in PMICF around 20 implants and this was



compared to the levels of IL-1 $\beta$  in the gingival crevicular fluid of the treatment group. The sample was collected at 1 hour, 24 hours, 48 hours, 168 hours, 2 weeks and 3 weeks after loading. The IL-1 $\beta$  levels were significantly increased in the treatment group at 24h than those in the implant and that of the control group. There was no significant change observed between the levels of the control and implant groups at all times. Thus it can be concluded that the use of mini implants was favorable in obtaining absolute anchorage.<sup>10</sup>

### 2.1 Interleukin 2, 6 and 8

These pro-inflammatory cytokines are also indicators of inflammation of the periodontium and resorption during orthodontic tooth movement and can serve as indicators for inflammation during placement and loading of MSIs. IL-2 encourages osteoclast activity and helps in bone resorption and also in the progression of periodontal diseases. IL-6 is involved in the induction of osteoclastic bone resorption and its presence indicates inflammatory periodontal diseases. There are increased levels of IL-8 in periodontitis and studies reveal increased levels of IL-8 at the PDL in the tension sites during canine retraction which aid in bone remodelling.<sup>4</sup>

A study by Hamamci *et al.* assessed levels of IL-2, IL-6 and IL-8 in gingival crevicular fluid and PMICF of 16 patients who were undergoing enmasse retraction using mini screw implants for anchorage purposes. The PMICF samples were obtained from GCF of the treatment teeth, the control teeth, and from around the MSI's in implant group. The sample collection was started 2 weeks post MSI insertion followed by 6 observation time points. Results showed higher levels of IL-2 and IL-8 in the implant group when compared to that of the control group at 24hour after loading. The levels of IL-6 remained the same. This helps conclude that the force applied

during orthodontic loading on the MSIs leads to secretion of cytokines which causes screw loosening.<sup>5</sup>

### 2.2 Tumour Necrosis Factor (TNF-a)

TNF-a plays a major role in regulating an assessment of periodontal inflammation and peri implantitis. Lowney *et al.* found an increase in TNF-a in GCF during orthodontic force application.<sup>7</sup> Kaya *et al.* reported that the difference in the levels of TNF-a were not significant in the implant and the control group 24 hours after loading but higher in treatment group.<sup>6</sup> Thus favoring MSI's for absolute anchorage.

This review was attempted to shed light on biomarkers in PMICF in orthodontic patients with MSI's used for anchorage. 4 studies were found on the biomarkers present in PMICF which included 1 on IL-2, IL-6 and IL-8, 2 on IL-1 $\beta$  and 1 on TNF-a. The PMICF sample collection method was paper strips for all the studies on IL-2, IL-6 and IL-8 and TNF-a but IL-1 $\beta$  was collected with the use of micro capillary pipettes.<sup>15</sup>

### 2.3 Prostaglandins

Prostaglandins especially PGE2, are potent local regulators of bone metabolism. PGE2 has been found in inflamed periodontal tissue and in GCF, and at higher levels in active disease sites. IL-1 $\beta$  has been shown to induce the production of prostaglandins by macrophages and fibroblasts in periodontal tissues.<sup>20</sup> IL-1 $\beta$  can stimulate "macrophage colony stimulating activity" and PGE2 production. It also has the capacity to dampen or suppress the production of IL-1 $\beta$  and TNF-, thereby regulating the character of the inflammatory response by a feedback loop.<sup>8</sup>

### 2.4 Matrix Metalloproteinases

Meikle *et al.* have proposed that a major cause of tissue destruction in periodontal disease is the



interaction between bacterial antigens and the inflammatory cells. This leads to the production of IL-1 $\beta$  and TNF-, which in turn stimulates MMP production and thus degradation of the periodontium. Birkedal-Hansen *et al.* found that periodontal microbial pathogens on cultured epithelial cells can directly produce factors that stimulate degradation of collagen fibrils. Active and latent MMPs (also known as pro-MMPs) have been detected in chronically inflamed gingival tissue and in GCF samples.<sup>13</sup>

### 2.5 RANK/ RANKL/ OPG

In a study done by Mia Rakic *et al.* it was found that, in peri-implantitis patients the RANK concentrations were significantly higher, whereas in periodontitis, the RANKL concentrations and the RANKL/OPG ratios were the ones significantly higher which were collected from the patients. In higher concentrations of pro-inflammatory cytokines may up-regulate RANK and RANK activity and hence, increase the osteoclastogenesis in peri-implantitis.<sup>11</sup>

### 2.6 Chondroitin Sulphate

CS (WF6 epitope) levels in PMICF can be detected and may be used as biomarkers for assessing alveolar bone remodelling around miniscrew implants during orthodontic loading. Increased levels of glycosaminoglycans, particularly CS, in peri-implant crevicular fluid can be a marker for adverse tissue responses, particularly for bone resorption.<sup>16</sup>

### 3. CONCLUSION

Alterations in the levels of IL-1 $\beta$ , IL-2, IL-6, IL-8 and TNF- $\alpha$  observed in PMICF on placement and loading of mini screw implants. IL-1 $\beta$  increased in PMICF upon loading the mini screw implant, peaking in 24 hours, then significantly decreased in 21 days. PMICF showed a decrease of 6.87% in IL-2 levels prior to loading and an increase of 5.97% post-loading. IL-8 showed an

increase of 6.31% after loading. Levels of IL-6 increased by 3.08% prior to loading the MSI and 15.06% post loading TNF- $\alpha$  levels did not exhibit any significant difference during the insertion or the loading of mini screw implants.

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