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Peri-implantitis
Treatment and effects of enamel matrix derivative

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Akademisk avhandling

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Abstract
Biological complications affecting osseointegrated dental implants are a growing treatment problem in clinical practice. Peri-implantitis, inflammatory degradation of the implant-supporting jawbone, affects approximately 20% of all implant carriers and approximately 10% of all implants. Implant surfaces are colonised by microbes that may cause an inflammatory process in the soft tissue around the implant. In some sensitive individuals, the inflammatory response leads to disturbed jawbone remodelling, with increased recruitment and activity of bone-resorbing osteoclasts, which could ultimately lead to implant loss. The current view is that pro-inflammatory cytokines and prostaglandins, produced by infiltrating leukocytes and cells of mesenchymal origin in the inflamed connective tissue, are responsible for local osteoclast recruitment and activation. Pro-inflammatory factors and tissue degradation products will leak into the exudate in the peri-implant sulci. Analysis of the exudate could be of use for predicting and monitoring peri-implantitis, as well as identifying new targets for treatment. The standard treatment for peri-implantitis is surgery in combination with mechanical cleaning of the implant surface and optimisation of oral hygiene, which has a moderate effect on healing of the peri-implantitis lesion. The use of adjunctive bone grafts, membranes and antimicrobials has thus far not been shown to achieve a more successful outcome. Adjunctive treatment with enamel matrix derivative (EMD) during regenerative periodontal surgery contributes to wound healing and increased tissue support, but the adjunctive effect of EMD during surgical treatment of peri-implantitis remains unknown.

The overall aim of this thesis was to investigate the outcome of a regenerative surgical treatment with and without adjunctive EMD treatment from the short- and long-term perspectives and to increase our knowledge of microbial flora and biomarkers in the peri-implant. Furthermore, an additional aim was also to investigate whether EMD could directly affect osteoclast formation and activity.

We performed a randomised controlled clinical trial of a surgical intervention for peri-implantitis with and without EMD. In multivariate modelling, an increased marginal bone level at the implant site 12 months after surgery was significantly associated with EMD, the number of osseous walls in the peri-implant bone defect and a gram-positive/aerobic microbial flora, whereas a reduced bone level was associated with a gram-negative/anaerobic microbial flora and the presence of bleeding and pus. Five years after treatment, no significant differences in bone level changes were observed between groups, but fewer implants were lost to follow-up due to reinfections in the EMD-treated group.

We used mass spectrometry to analyse the protein content in peri-implant crevicular fluid (PICF) before and up to 12 months after treatment. The total protein amount and diversity displayed decreasing trends 3, 6 and 12 months after treatment. Multivariate analysis of the PICF protein content revealed two major groups, cluster 2 was associated with an increased risk of implant loss and cluster 3 was associated with EMD treatment and increased implant survival.

To test whether EMD affects osteoclast formation or bone resorption, we added purified EMD to RANKL-stimulated mouse bone marrow macrophage cultures in plastic dishes and counted the number of osteoclasts. We also cultured the cells on bone slices and measured the secretion of TRAP5b and the release of CTX-1 into the culture medium as biomarkers of osteoclast numbers and bone resorption, respectively, but no effect of EMD was observed.

In conclusion, adjunctive EMD during surgical treatment of peri-implantitis changed the microbial flora to a less pathogenic microbiota, and similar changes in the inflammatory protein profile of PICF were observed; these effects were associated with implant survival. However, the trend toward a positive healing response after EMD treatment was not associated with a significant radiographic bone gain in this study and needs to be further explored. In addition, our finding that EMD did not affect osteoclast formation or bone resorption *in vitro* indicates that the effect of EMD on bone regeneration, as seen in periodontitis treatment, does not seem to depend on a direct inhibitory effect on osteoclast formation or bone resorption.

Keywords
Peri-implantitis, enamel matrix derivative, regenerative treatment, peri-implant crevicular fluid, bone resorption

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