

# Platelet-rich fibrin interactions in oral implantology

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## Appendix I      Impact Statement

With our population getting older and older, loss of teeth will be a growing problem. An incidental circumstance is a simultaneous loss of bone. One of the challenges of artificial teeth implantation is to develop methods to stop this loss of bone and to stimulate bone regeneration, to allow stable implants. The experiments described in this thesis are the first steps to understand the process of bone regeneration with the help of blood clots and to start to develop uniform guidelines for treatment.

Loss of soft- and hard tissue is a major problem in oral implant therapies. Although autologous bone and soft tissue grafts still are “gold” standards<sup>1,2</sup> in oral implant surgery, there is growing interest in alternatives to these invasive surgical procedures. The need of a second surgical site in soft- and hard tissue augmentation procedures with autologous materials and the limited amount of harvestable material, has significant disadvantages.<sup>3</sup> Platelet-rich fibrin can contribute to less pain after surgery, less swelling i.e., a less traumatic and faster treatment process<sup>4</sup>. Application of platelet-rich fibrin clots in combination with bone substitutes in oral implantology is a potential alternative treatment. Platelet-rich fibrin, prepared from autologous patient blood, is a platelet concentrate which could have significant potential if used with a proper standardized protocol. There are currently several treatment protocols in the implantology market with untenable promises creating confusion by a continuous adaptation of protocols, which may influence clinical outcomes. There is a need for standardized procedures, in order to be able to establish a solid scientific base obtaining optimal clinical outcomes. Therefore, we used in the present research standardized protocols to study the effects of platelet-rich fibrin in oral implantology.

### Key contributions of this thesis

In 2015 we introduced the application of platelet-rich fibrin in our clinic and since then we use it on a daily basis. Using platelet-rich fibrin in our clinic for different indications, revealed the potential in clinical outcome of this autologous platelet product. These findings were the basis to the underlying research project.

First, we started to develop an optimal protocol for the use of platelet-rich fibrin in challenging cases by testing different centrifugal protocols *in vitro*<sup>5</sup>. During our research we used the same standardized platelet-rich fibrin generation protocol.

We aimed to show the importance of the use of platelet-rich fibrin in combination with DBBM (demineralized bovine bone matrix) in esthetically demanding oral implant cases, which we demonstrated in the case report study<sup>6</sup>.

Oral implant stability is a promisable tool to measure the clinical outcome of platelet-rich fibrin treatment in patients. We validated two different RFA (Resonance Frequency

Analysis) measurement devices<sup>7</sup>. Our study adds insights in current measurement methods, comprising the comparison of the accuracy of measurement between the two currently available devices for implant stability measurement. The ISQ (Implant Stability Quotient) value is an important parameter for success of oral implant therapy<sup>8,9</sup>. We tested both devices after conventional implant placement of self-tapping dental implants in post-extraction sites with ridge preservation. The ridge preservation was conducted following a standardized platelet-rich fibrin preparation protocol in combination with DBBM. Our findings support the application of both measurement devices as reliable and useful tools to determine implant stability.

There is a variability in clinical outcomes (e.g., bone formation, gingiva generation, implant stability) in patients treated with platelet-rich fibrin. Not only through different centrifugal protocols, also due to the use of different materials used to collect patients' blood. One of the major variables may be the composition of the patients own whole blood<sup>10,11</sup>. Therefore we studied the association between dental implant stability and peripheral blood cell composition and levels of coagulation factors in patients treated with alveolar ridge preservation with platelet-rich fibrin and bovine bone substitute<sup>12</sup>. We found that erythrocyte count was inversely associated with platelet-rich fibrin membrane length, but not with implant stability. Conversely, platelet count did not correlate with membrane size, but inversely correlated with implant stability at 7 and 17 weeks. In addition, we found that implant stability was directly correlated with levels FXIII, active von Willebrand Factor and total von Willebrand. In conclusion, alveolar ridge preservation with platelet-rich fibrin and demineralized bovine bone matrix is associated with circulating blood cells and coagulation factors. In particular, fibrin structure, von Willebrand Factor and Factor XIII may be important modulators of implant stability.

Another variable parameter which may influence the oral implantology treatment with platelet-rich fibrin may be the contribution of saliva. Since it has been shown that saliva contains tissue-factor (TF) and thereby may influence hemostasis and wound healing. Since there is a high variability in post-extraction/ post-surgical bleeding in patients, therefore we hypothesized this may be caused by a variation in saliva-derived TF-induced clotting activity. In the present thesis we describe our findings that saliva induces thrombin generation in plasma and showed to be tissue-factor dependent. Interesting were our findings on the inter-individual variability in saliva induced thrombin generation<sup>13</sup>. Interestingly, within subjects, saliva-induced thrombin generation was significantly increased in the morning compared to the afternoon. These findings could help clinicians in the decision making of the timepoint of treatment, for instance patients on oral anticoagulant therapy which cannot be stopped temporarily. Further research should reveal if treatment in the morning, higher TF level in saliva, leads to less bleeding after surgery. A possible cause for increased TF activity in the morning is the oral microbiome. Oral streptococci were previously demonstrated to induce

(endothelial) tissue factor activity<sup>14</sup>. In this context it could be interesting to access a possible relation between salivary TF concentration and bacterial status in the oral cavity.

## Conclusion and prospects

Guidelines have to be developed in how to correctly prepare autologous blood concentrates for specific indications. Also, we have to improve the quality of the starting material, i.e., the composition of the whole blood, quality of the collecting tubes, centrifuges, etc. Upon screening the composition of the patient's whole blood before treatment, we may develop a personalized protocol for specific patients in the future generation tailor-made precision medicine. Future research should have their focus on these possibilities. International research collaboration in the field of oral implantology is essential to develop predictable protocols for platelet-rich fibrin in different indications.

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