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Evaluation of Bone Quality by Ultrasonogaphy

– Implant surgery and imbedded jawbone marrow defects

In Ceramic Implants Vol. 5 • Issue 2/2021 „*Measuring Bone Density for Secure Implant insertion by Intraoral Ultrasound*" we discussed the objective validation of the bone quality **before implant insertion** with the question: Is the level of mineralisation in the jawbone able to ossify an implant without any issues and to keep it secure in a stable bone bed for a long time? In this following article we want to enlighten the question **after implant insertion**:

- Did we insert the implant in badly healed bone?

- Is implant failure directly associated to incomplete wound healing of the implant site?

This leads to the perspective that CaviTAU® can be used to detect focal inflammation areas around implants that cannot be identified by X-ray. For more information on this relatively unknown problem, please also refer to our own PubMed indexed publication. [Lechner J, Noumbissi S and von Baehr V. Titanium implants and silent inflammation in jawbone—a critical interplay of dissolved titanium particles and cytokines TNF-α and RANTES/CCL5 on overall health? EPMA Journal 9, 331–343 (2018). https://doi.org/10.1007/s13167-018-0138-6.] The main problem in practice related to the "X-ray imaging in implantology" is
that typical hardening artifacts occur in the CBCT/DVT, caused by ceramic implants in particular. The regions between the implants and the implant-bone interface cannot

be visually reconstructed correctly for technical reasons. [Schulze RKW, Berndt D, d'Hoedt B. On cone-beam computed tomography artifacts induced by titanium implants. Clin Oral Impl Res 2009 (Online-Vorabpublikation am 21.10. 2009.]

How to forecast the success of dental implants?

The measurement of quantitative ultrasound transmission rate (UTV) has been established as an innovative, objective, valid, and reliable method for repeated, non-invasive measurements of bone quality before dental implantations [Al-Nawas B, Klein MO, Goetz H, Vaterod J, Dushner H, Grotz, KA & Kann PH. (2008) Dental implantation: ultrasound transmission velocity to evaluate critical bone quality- an animal mode. Ultraschall in der Medizin 29: 302–307.].The intraindividual correlation of the UTV values of the maxillary and mandibular lateral regions makes the data easy to interpret. The use of a small UTV device in this study enabled the recording of intraoral UTV values in a large and heterogeneous patient population. Assessment of alveolar-ridge UTV could provide a method for identifying critical bone quality before implant insertion or to monitor bone healing (mineralisation) after augmentation procedures. [Klein M. O. et al. Ultrasound in Medicine and Biology Volume 34, Number, 2008.].The main advantages of ultrasound are that it is non-ionising, non-invasive, tolerable and available at relatively low costs. Furthermore, the examination is not a complicated process and can be easily performed by clinicians [Abendschein W, Hyatt GW. Ultrasonics and selected physical properties of bone. Clin Orthop Relat Res 1970; 69: 294 –301. /// Kann P, Schulz U, Nink M, Pfutzner A, Schrezenmeir J, Beyer J. Architecture in cortical bone and ultrasound transmission velocity.Clin Rheumatol 1993;12:364 –367.].

The new technology of trans-alveolar ultrasound (TAU) measurement by new ultrasonography device CaviTAU® can reliably identify regions of low mineralisation density in bone marrow cavities with signs of chronic ischemic inflammation.[Lechner J, Zimmermann B, Schmidt M, von Baehr V. Ultrasound Sonography to Detect Focal Osteoporotic Jawbone Marrow Defects: Clinical Comparative Study with Corresponding Hounsfield Units and RANTES/CCL5 Expression. *Clin Cosmet Investig Dent*. 2020;12:205-216. https://doi.org/10.2147/CCIDE.S247345 //// Lechner J, Zimmermann B, Schmidt M. *Focal Bone-Marrow Defects in the Jawbone Determined by Ultrasonography—Validation of New Trans-Alveolar Ultrasound Technique for Measuring Jawbone Density in 210 Participants.* Ultrasound in Medicine & Biology. Elsevier Published:August 12, 2021. https://doi.org/10.1016/j.ultrasmedbio.2021.07.012]

Connection between implant insertion and occurrence of FDOJ

There is no doubt that dental implantology has achieved a very high reliability and success rate in recent years. Despite this, there is increasing evidence that, in addition to the success criteria of the stability and length of time the implant is placed for, other medical assessment criteria should also form part of the discussion. Further questions on implant insertion emerge, such as:

- Does the jawbone around the implant heal in a manner that means no silent chronic inflammation would go undetected?
- Are good stability and loading capacity of an implant the only assessment criteria for implant success, or
- are there also chronic immunological links?

Are there areas of bone around implants with specific systemically relevant immune or cytokine patterns?

Figure 1 clearly shows the problem of X-ray imaging in implantology: 2D-OPG displays a directly attached fatty-degenerative morphology to the implant that has healed in inconspicuously.

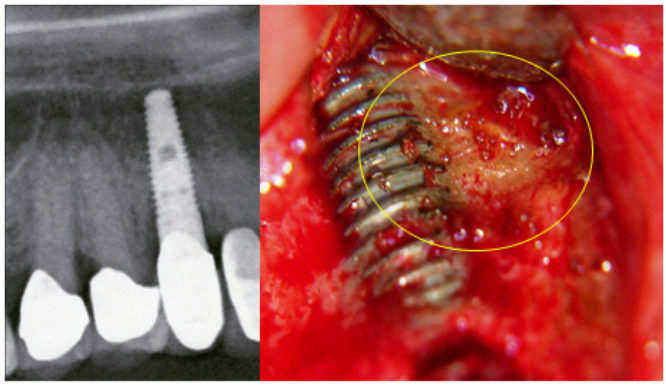

Figure 1: Left window: 2D-OPG implant, no sign of inflammation in jawbone. Right window: Fatty-degenerative osteolysis directly attached to the implant: not detectable by X-ray.

The overexpression of R/C in the alveolar and subapical regions of implants with reduced bone density in the surrounding areas, as presented in the following case reports, has been described in detail. These FDOJ areas persist in silent or subclinical inflammation without the typical signs of acute inflammation.
In bone resorption in periodontitis and periimplantitis, the acute cytokines TNF-a and IL-6 are central to the inflammatory-destructive process. A possible titanium intolerance provokes further expression of TNF-a and also of IL-1b via released titanium particles with increased bone resorption [Lechner J, Noumbissi S and von

Baehr V. Titanium implants and silent inflammation in jawbone—a critical interplay of dissolved titanium particles and cytokines TNF-α and RANTES/CCL5 on overall health? EPMA Journal 9, 331–343 (2018). https://doi.org/10.1007/s13167-018-0138-6.]. However, beyond this easily accessible therapeutic level, there are other bone resorption processes in the deeper layers of the bone marrow referred to as “bone marrow defects” or “marrow edema”. These fatty degenerative osteolyses in the jawbone (FDOJ) morphologically show bone softening and TNF-a and IL-6 are far below the levels found in the healthy medullary cavity. In contrast, there is up to a 35-fold overexpression of the chemokine RANTES/CCL5 (R/C) [Lechner J, von Baehr V. Hyperactivated Signaling Pathways of Chemokine RANTES/CCL5 in Osteopathies of Jawbone in Breast Cancer Patients—Case Report and Research. Breast Cancer: Basic and Clinical Research 2014:8 89–96.]. With this chronic R/C signal transduction, FDOJ appears to represent a unique pattern of inflammation with osteolysis in the body.

The local periodontal production of inflammatory cytokines such as TNF-a and IL-1b/IL-6 dysregulates regulatory and compensatory mechanisms that contribute to the formation of these implant-related FDOJ in the bone marrow. Arising from an intramedullary overexpression of R/C, this phenomenon seems to be more widespread than originally thought. However, surgical removal of FDOJ areas can stop the induction of R/C signalling pathways and thus inhibit the progression of associated symptoms [Lechner J, von Baehr V. Hyperactivated Signaling Pathways of Chemokine RANTES/CCL5 in Osteopathies of Jawbone in Breast Cancer Patients—Case Report and Research. Breast Cancer: Basic and Clinical Research 2014:8 89–96.].

The implant is placed in an ischemic area of the subclinical FDOJ due to the radiographically unremarkable FDOJ morphology and the lack of alternative methods

for measuring bone density. Perala demonstrated the induction of TNF-a in vitro after co-incubation of native implant material, which ensures that immunogenic particles are released from the materials [Perala et al. Relative production of IL-1b and TNF-a by mononuclear cells after exposure to dental implants. J Periodontol 63(5): 426–430, 1992.]. With regard to cytokine expression in the context of an implant and the associated phases of healing, analysis during different stages of implantation reveals several new phases of cytokine-triggered signalling pathways. Acute wounding initiated by implant placement, which induces the release of acute cytokines through surgical trauma, provokes inflammatory cascades of TNF-a, IL-6 and IL-1b expression. TNF-a expression provokes increased secretion of RANTES/CCL5 in the bone imbedding the implant medium to long term (Figure 2). [Nakashima Y, Sun DH, Trindade MC, Maloney WJ, Goodman SB, Schurman DJ, Smith RL: Orthopaedic Research Laboratory, Stanford University Medical Center, California 94305-5341, USA: Signaling pathways for tumor necrosis factor-alpha and interleukin-6 expression in human macrophages exposed to Titanium-alloy particulate debris in vitro. J Bone Joint Surg Am 1999 May;81(5):603-15. /// Sterner T. Schütze N, Saxler G et al. Effects of clinically relevant alumina ceramic, zirconia ceramic and Titanium particles of different sizes and concentrations on TNF-alpha release in a human macrophage cell line. Biomed Tech (Berl) 2004; 49: 340-344. //// Skurk T,Mack I,Kempf K,Kolb H,Hauner H,Herder C.Expression and secretion of R/C(CCL5) in human adipocytes in response to immunological stimuli and hypoxia. Horm Metab Res.2009 Mar;41(3):183-9. //// Hensley K, et al..Message and protein-level elevation of tumor necrosis factor α (TNFα) and TNFα-modulating cytokines in spinal cords of the G93A-SOD1 mouse model for amyotrophic lateral sclerosis. Neurobiology of Disease. Volume 14, Issue 1, October 2003, Pages 74–80).]

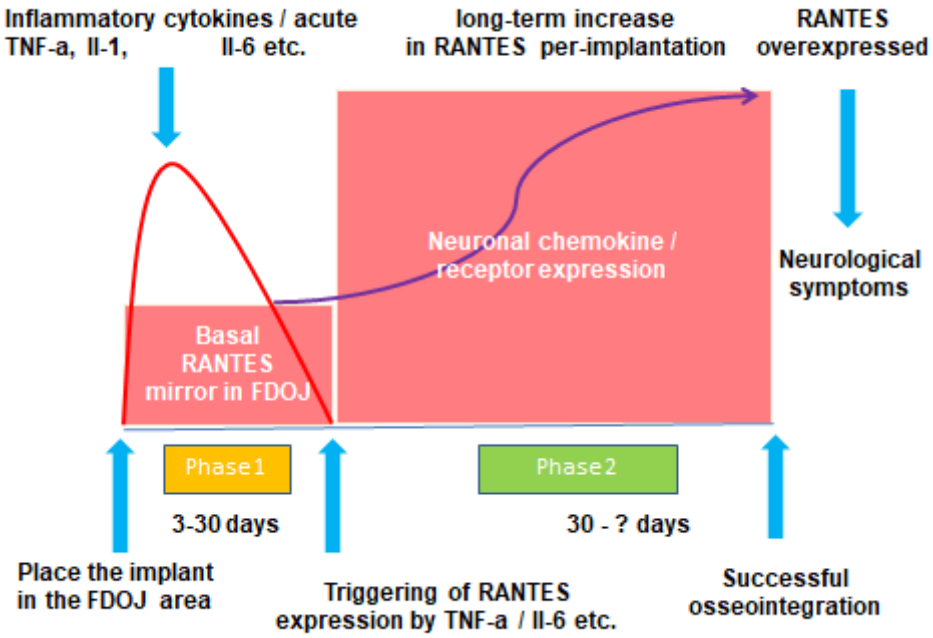

Figure 2: This figure shows schematically the sequence of cytokine expressions after wound setting by insertion of an implant into a bone compartment already preloaded by chronic inflammation. The problems for the clinician in this context include the following:

- The clinical stability of the implant leads to the misdiagnosis of an apparently inflammation-free osseointegration;
- The radiological inconspicuousness of the implant.

CAVITAU® detects focal inflammation areas around implants that cannot be identified by X-rays.

The case in Figure 3 shows that CAVITAU solves the problem by providing reliable ultrasound imaging of the circumscribed bone density.

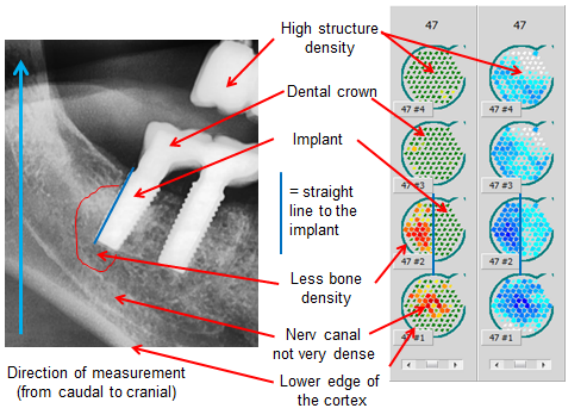

Figure 3: Left image shows two ceramic implants in area 46 and 47 in an unremarkable 2D OPG. Right image shows CaviCAVITAU® measurement in four vertical comparison steps: Bottom right measurement #1 shows caudal visualisation of the lower cortical margin of the lower jaw, as well as the less dense areas of the infra-alveolar nerve canal in red and dark blue colouring. Scan #2 shows the dense implant structure in green or light blue and white with a clearly straight delimitation to the distally located red or dark blue colouration as a sign of a reduced mineralisation density with suspected osteolysis. In a cranial and vertical direction, scan #3 shows only dense structures in green or white and light blue with suspected minor osteolysis/periimplantitis. Image # 4 shows dense structures in green or light blue with the oral cavity shown in white.

Case reports on chronic inflammation around implants and CaviTAU® visualisation

In these case reports, we confirm the reduced bone densities shown by CaviTAU® - where the practice procedures allow - with the postoperative findings of RANTES/CCL5 expression measured by the multiplex procedure of light microscopy.

Generally speaking, OPG scans do not show any findings of reduced bone density and are not sufficient for the diagnosis of osteolysis [Lechner, J. Validation of dental X-ray by cytokine RANTES – comparison of X-ray findings with cytokine overexpression in jawbone. Clinical, Cosmetic and Investigational Dentistry 2014:6 71–79.] The focus of the here documented case reports is on the metrological evaluation of bone density with ultrasonogaphy device CaviTAU® from a diagnostic and a preventive perspective:

Case #1: History: The 35-year-old patient comes to our practice with pressure complaints at two titanium implants at 24 and 25. Previously, after several root fillings and unsuccessful apicectomies, the teeth were finally removed and replaced by titanium implants. The patient brings a DVT with her on which the implanting dentist cannot see any abnormalities at 24, 25 that could explain the pressure complaints and pulling pain in the implant area. As the patient does not want to have the two implants fitted due to this chronic feeling of pain, she comes to us with the request for a more detailed ultrasound diagnosis of her bone situation in the area of 24,25.

Our diagnostics: We carried out a measurement of the bone density in the implant area 24/25 with CaviTAU®. The healthy neighbouring teeth 23 and 26 were also measured, as recommended in the CaviTAU® application as a lateral comparison measurement (Figure 4).

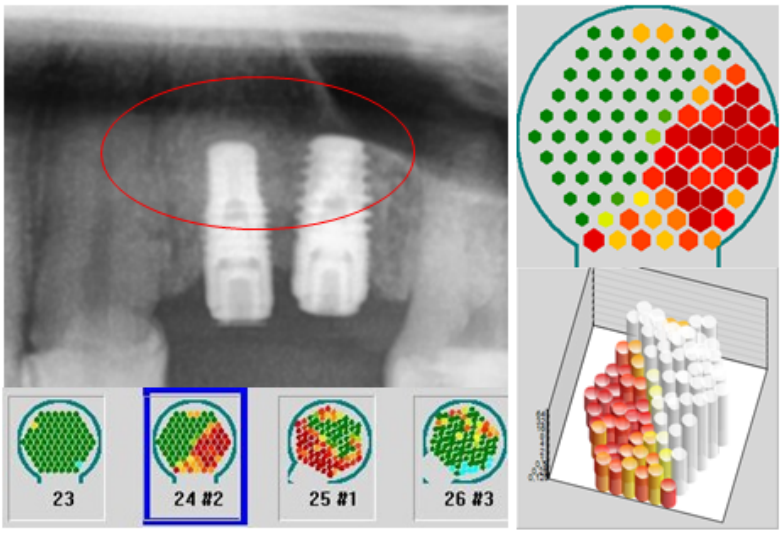

Figure 4: Left window: The 2D-OPG shows implants in area 24 and 25; inconspicuous bone around the implants. Left lower: In contrast to the X-ray the measurement of the bone density adjacent to the implants by CAVITAU displays in red diminished bone density. Right upper: Very clear displays the straight line where the implant (in green) gets in contact with the obvious osteolytic neighbouring jawbone in red. Right lower: White columns display the implant, while directly adjacent jawbone displays diminished bone density.

Interpretation of the CaviTAU® measurement: The green colouring of the healthy teeth 23 and 26 serves as a check. The extensive red colouration with clear demarcation to the hard implant proves the patient's complaint pattern: Both implants were implanted in a bone area that had not healed; the remaining fatty-degenerative osteonecrosis of the jawbone (FDOJ) leads to the patient's neuralgic complaint pattern after implantation.[Lechner J, von Baehr V. Peripheral Neuropathic Facial/Trigeminal Pain and RANTES/CCL5 in Jawbone Cavitation, Evidence-Based Complementary and Alternative Medicine, vol. 2015, Article ID 582520, 9 pages,

2015. doi:10.1155/2015/582520] These FDOJ areas remain in a silent or subclinical inflammation without the typical signs of an acute inflammation ("silent inflammation").[Lechner J, Schmidt M, von Baehr V, Schick F. Undetected Jawbone Marrow Defects as Inflammatory and Degenerative Signaling Pathways: Chemokine RANTES/CCL5 as a Possible Link Between the Jawbone and Systemic Interactions?. *J Inflamm Res*. 2021;14:1603-1612 https://doi.org/10.2147/JIR.S307635] This case represents the importance of the question:

- Were the implants inserted into healthy bone?
- Digitally we have in our modern X-ray technology a digital determination of the **bone quantity** (is the bone big enough for implantation?),
- but no digital determination of **bone quality** (is the bone healthy enough for implantation?).

Therapeutic conclusion: The implanting dentist has already tried antibiotics for several weeks without success. Therefore, the only way out is to remove the implants, clear out the ostitic areas and build up the bone to enable further implantations in the young patient. The cost aspect: The financial expenditure of the preceding implantation is thus just as free as the preceding root fillings and root tip resections. A short documentation of the bone density in the area 24 and 25 with a low-cost CaviTAU® measurement would have led to a considerable cost saving and a medically safe procedure.

Case #2: Female patient, 57 years old; chronic facial pain after implantation. Medical history: After extraction root-filled tooth 16 immediate ceramic implant with internal

sinus lift 9 months ago. Implant fixed, not sensitive to biting, but chronic pain in the right upper jaw for 6 months with as yet unclear cause.

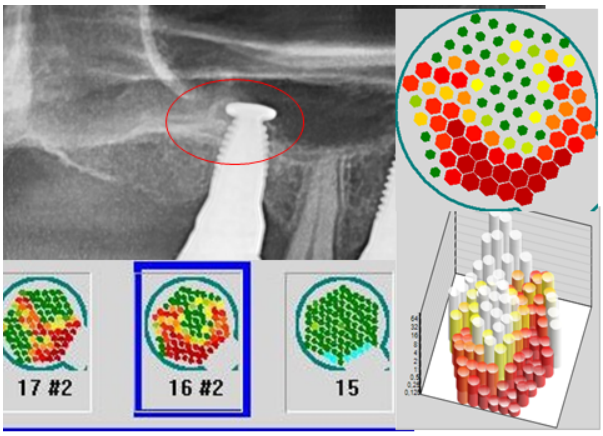

Figure 5: 2D-OPG shows ceramic implant, placed about 9 months ago. The X-ray does not give any indication of a possible cause for atypical facial pain since insertion. Bottom left image shows the overview measurement with CaviTAU®: According to the CaviTAU® measurement, the conspicuous areas with possible osteolysis indicated by red colouration are towards to the apical area of implant 16, with clear osteolysis. Right image: Relatively high degree of bone loss around the implant indicated by red color codes. The 3D-CaviTAU® image shows the implant in white and the surrounding diminished bone density in red.

The 3D representation of X-ray imaging in implantology is not without its challenges either. Typical hardening artifacts in the digital volume tomogram as a result of titanium implants: The regions between the implants and the implant-bone interface cannot be visually reconstructed correctly for technical reasons" [Schulze RKW, Berndt D, d'Hoedt B. On cone-beam computed tomography artifacts induced by titanium implants. Clin Oral Impl Res 2009 (Online-Vorabpublikation am 21.10. 2009.] These hardening artefacts are amplified further by ceramic implants in DVT.

Following figure 6 documents in this case the fact of hardening artifacts in DVT/CBCT radiography:

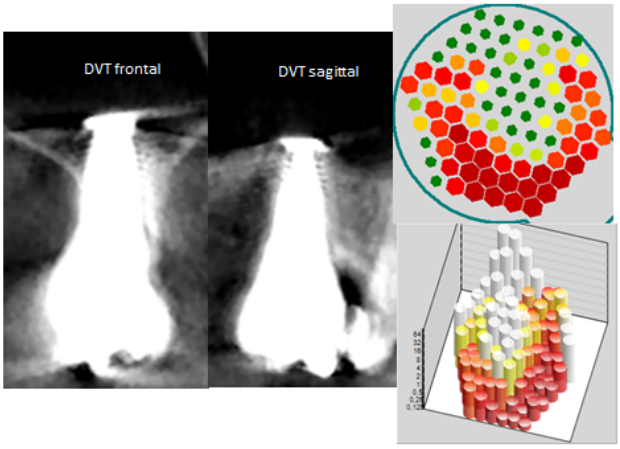

Figure 6: Left and mid window show DVT/CBCT frontal and sagittal images of implant 16 without any conspicuous signs of inflammation. Right upper 2D.CAVITAU image displays in green apical part of implant (green = hard substance), surrounded by red signs of suspected osteolysis or osteonecrosis (red = low bone density). Right lower 3D-CAVITAU image displays in white hard substance of implant, surrounded by red signs of suspected osteolysis or osteonecrosis.

Will the histology and the RANTES multiplex measurement of the apical peri-implant tissue confirm the accuracy of the ultrasound measurement and the lack of visualisation of the inflammatory area with OPG and DVT?

“0.5 cm sample material (apical region 16) with an older ***scarring apical granuloma*** *with* ***foreign body granulomas*** *around partially birefringent foreign material. Sample material consisting predominantly of* ***fibrous connective tissue with foreign body giant cells*** *partly around birefringent foreign material. Only minimal chronic inflammatory cell infiltration.”*

Here we also discuss the inducing or synergistic interaction between the messenger substances secreted around implants and the highly overexpressed R/C levels in the bony area that the implants are in. Have further inflammatory signalling cascades - primarily based on RANTES/CCL5 messenger substances - been provoked by the insertion of the implant and the directly associated wound healing?

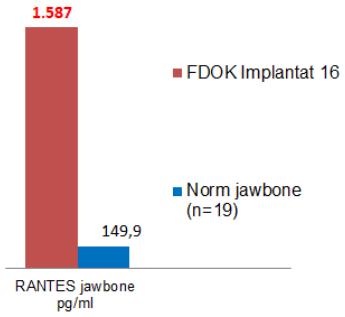

Figure 7: In addition to the histology, the peri-implant tissue shows not only the typical FDOK softening (see Figure 6 above), but also the overexpression of the proinflammatory chemokine RANTES/CCL5 . This further validates the pathological imaging by CaviTAU®.

Case #3: Female patient, 57 years old: Migraines on right side only; atypical facial pain since implant placement, in upper right jaw only.

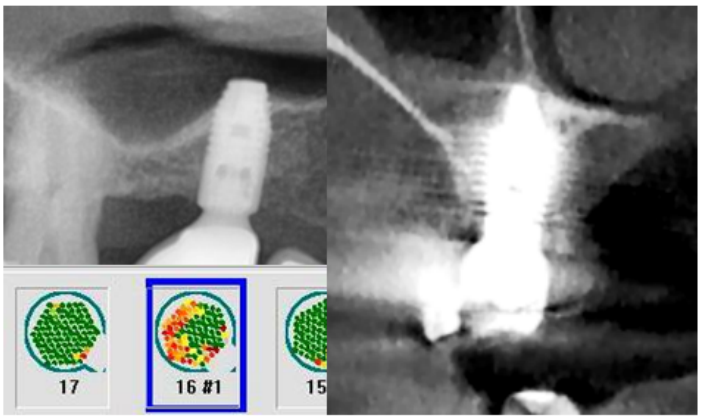

Figure 8: Top left 2D-OPG shows completely unremarkable bone tissue around the implant at 16. The right image should show the degree of mineralisation of the peri-implant bone environment in DVT; however, the brightening artifacts caused by the implant prevent this analysis. Only the CaviTAU® scan in the lower left image clearly shows red colouration around implant 16, indicating an area of reduced mineralisation density.

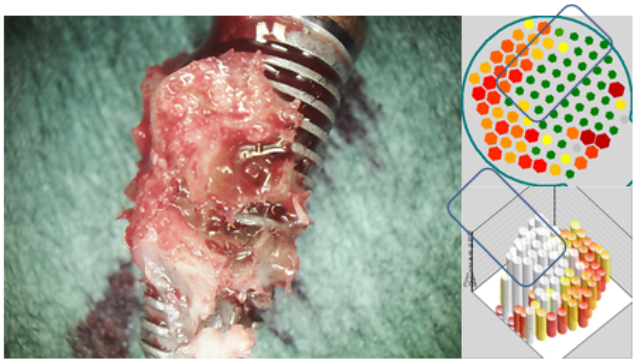

Figure 9: The postoperative scan of the bone situation around the implant clearly shows the FDOJ tissue attached to the implant in the left part of the image. Corresponding to this in the right part of the image is the 2D view of the hard implant shown in green in CaviTAU® with a rectangular outline of the implant and a

visualisation of the osteolytic dissolved tissue around the implant bed in red. The lower left part of the image shows the 3D-representation of the osteolytic dissolved tissue around the implant bed in red with clear borderlines to the implant shown in white.

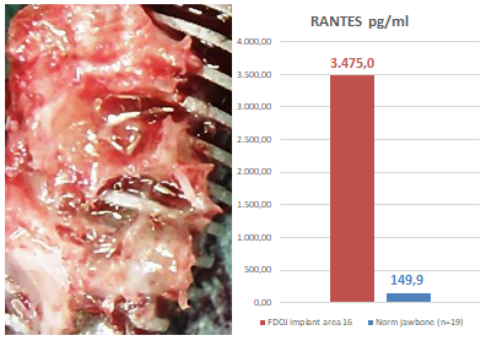

Figure 10: The left part of the image shows an enlargement of the dissolved bone areas directly around implant. The right part of the image shows the local overexpression of R/C with around 30 times the standard value of the multiplex analysis of the fatty parts shown directly in the left part of the image. In addition to the R/C overexpression, the histology also confirms the FDOJ and the particularly interesting “formation of oil cysts” in the affected medullary region. The term “oil cysts” is mentioned independently by Bouquot and Sollmann.

Histology: “*Excidat region 16: Medullary tissue from region 16 with exclusively fatty marrow as well as necrobiotic changes and areas of mucinous degeneration as well as small “oil cysts”. Lastly, small areas of fibrosis, altogether consistent with changes related to fatty degenerative osteolysis of the jawbone (FDOJ).”*

Conclusions

Our case studies demonstrate the immunological relationship between implants and FDOJ. The extent to which increased expression of R/C derived from FDOJ areas contributes to immune-mediated disease is difficult to determine. Our cases provide evidence for the possible interaction between implants, R/C signalling and general health. A comprehensive understanding of the complex networks described in our cases requires further research. Removal of implants and surgical removal of surrounding FDOJ areas can reduce R/C overexpressed signalling pathways, potentially reducing inflammatory input and associated symptoms.

- Due to the insufficient imaging of the mineralisation levels in the bony implant environment in 2D-OPGs and the unavoidable hardening artefacts in DVTs, a decisive part of the bone marrow in the jaw cannot be correctly immunologically assessed.
- These assessment criteria in implantology are offered by CaviTAU® measurement.
- After extraction "silent inflammation" remains in the jawbone. This situation is then also often responsible for a failure of the subsequent implantation, or even an immediate implantation. For the future procedure in such cases, a prior measurement of the bone density and thus a determination of the metabolic situation in the jawbone is therefore essential by itself for the safety of the patient and the treatment success of the dentist.
- For “unexplained pain" as in case reports, the easy-to-use and radiation-free CaviTAU is available to detect radiographically undetectable "silent inflammations".