Why titanium implants create silent inflammation in jawbone

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In dentistry, one of the most established methods is the replacement of lost or missing teeth with titanium (Ti) implants. However, investigators have found that Ti implants can induce inflammation in the surrounding tissue over time, leading to the expression of certain mediators known to cause chronic diseases through a constantly stimulated immune system.[1–4] These triggers lead to the activation of signalling pathways which favour a predisposition to the development of cancer and autoimmune diseases.[5] Signalling messengers like cytokines carry instructions and are received by those cells with specific receptors which are able to recognise them. In earlier publications, we defined this chronic inflammatory process as fatty-degenerative osteonecrosis in the medullary spaces of the jawbone (FDOJ).[6,7] We started a study to elucidate the transition from acute trauma during the insertion of dental implants to chronic inflammation of the jawbone. Herein, we attempt to define the role of cytokines in areas of FDOJ surrounding implants in a cohort of patients with immune system disorders. We propose the following hypothesis: Ti implants may be a possible contributor to the development of chronic inflammation of the jawbone extending beyond the local condition of peri-implantitis.

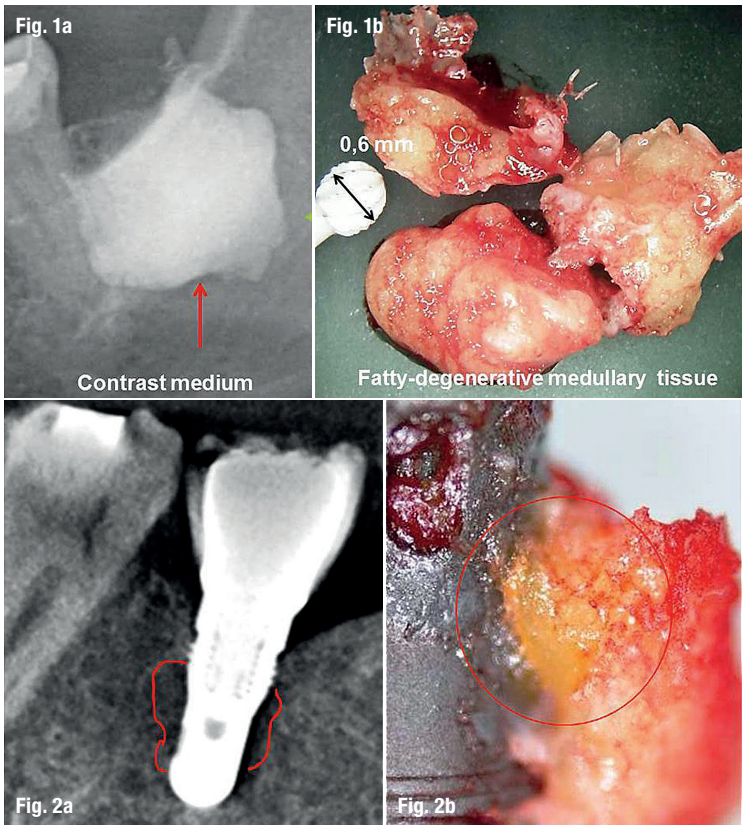


Fig. 1: Contrast medium in affected cavity after curettage **(a)** and jawbone sample of fatty and osteolytic degenerated bone marrow **(b)**. **Fig. 2:** Titanium implant in area #46 as shown in the CBCT scan **(a)**; fatty-degenerated tissue attached directly to the titanium implant **(b)**.

We selected a group of patients with well-osseointegrated Ti implants and with clinical symptoms of immune system disorders: seven with rheumatic arthritis, three with neurodegenerative diseases (including chronic fatigue syndrome and multiple sclerosis), one with ovarian cancer and three with atypical facial pain/trigeminal neuralgia. A second mandatory inclusion criterion for the Ti implant group was local diagnosis of FDOJ apically and in areas surrounding Ti implants. All patients were required to have a CBCT scan and measurement of the bone density of the jawbone using trans-alveolar ultrasound technology (TAU). TAU is useful for establishing the presence of FDOJ.[8] In a healthy control group (n = 19), samples of healthy jawbone were removed in the form of drill cores during routine dental implantation surgery. The use of bisphosphonate medication was the main exclusion criterion.

Clinical features of FDOJ: Definition and diagnostic criteria

FDOJ is a lesion similar to that found in long bones, also primarily defined as “bone marrow edema” and “chronic non-suppurative osteomyelitis”.[9,8] The softening of the bone marrow in FDOJ is very distinct, such that the marrow space may be suctioned out or curetted once the cortical bone has been removed. These hollow spaces, also known as “cavitations” are filled with fatty-degenerated adipocytes which have undergone dystrophic changes accompanied by demyelination of the bony sheath of the inferior alveolar nerve. Figure 1 shows a specimen of predominantly fatty transformation of the jawbone. The extent of the FDOJ lesion in the jawbone is indicated in the radiographic image with a contrast medium.

Dissolved titanium particles in the jawbone

After reports in the literature concerning dissolved Ti particles in the surrounding bone,[10–13] we analysed five of the 14 jawbone samples from the group with FDOJ and Ti implants for levels of dissolved Ti. The amount of dissolved Ti in them ranged from 3,200 to 50,600 µg/kg with a median value of 24,200 µg/kg (± 20,029 SD; Fig. 3). As we were unable to find an average maximum content of dissolved Ti which is regarded as biocompatible and acceptable in the literature, we defined the maximum dissolved Ti in healthy bone as 1,000 µg/kg of body weight, which is fourfold higher than the accepted level of all other heavy metals as described in the relevant literature (< 250 µg/kg).

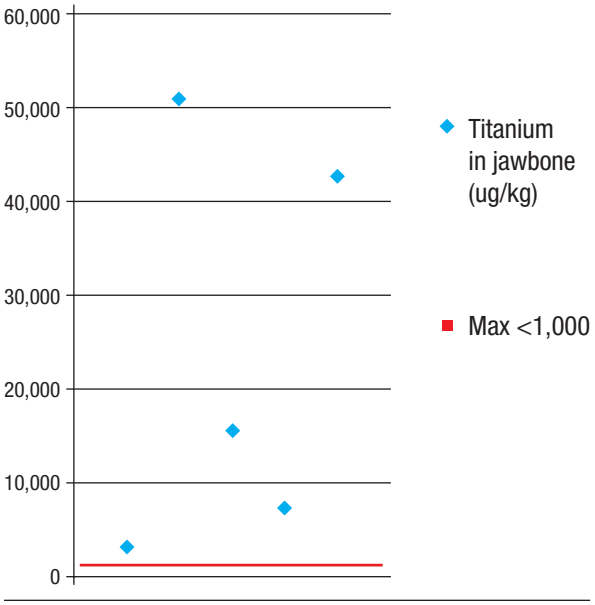


Fig. 3: Distribution of dissolved titanium in jawbone surrounding titanium implants in five cases of fatty-degenerative osteonecrosis of the jawbone.

Titanium dissolution in jawbone and TNF-α expression

Ti particles may dissolve and induce immunological reactions in the body and release systemic messengers. A study presented by Nakashima et al. elucidated the mechanisms of macrophage activation by Ti particles from implant materials and identified the cytokine-bound signalling activated by metal alloy implants via released particles.[14] Macrophages of patients were exposed to particles of Ti alloys taken from the connective tissue surrounding hip implants. Exposure of macrophages to Ti alloy particles *in vitro* over a period of 48 hours resulted in a 40-fold increase in the release of tumour necrosis factor alpha (TNF-α) and a sevenfold increase in the release of interleukin-6 (IL-6).

Analysis of cytokine expression in samples of FDOJ

To discern the cytokine patterns found in the jawbone of patients from the corresponding author's dental practice, 14 patients with diagnosed FDOJ in Ti implant sites had surgery on the affected area, including the removal of existing Ti implants. All of the patients displayed FDOJ in the bone marrow adjacent to neighbouring Ti implants, which was similar to FDOJ samples as described previously in the literature[15,16]. FDOJ tissue directly attached to a Ti implant was investigated and the cytokine profiles were evaluated. The corresponding CBCT image in Figure 2 displays no, or only minor, abnormalities in contrast to the significant area of yellowish and softened cancellous bone directly attached to the Ti implant surface. At the IMD Institute for Medical Diagnostics (www.imd-berlin.de/labor), the FDOJ samples were measured for cytokine expression. As we have shown in several previous publications,[6,7] the defining characteristic of FDOJ regions is the overexpression of the pro-inflammatory messenger RANTES (regulated upon activation, normal T-cell expressed and secreted), also known as chemokine C-motif ligand 5 (CCL5). The mean values of the 19 samples of healthy jawbone (blue columns) and the results of the multiplex analysis of the seven cytokines in the FDOJ and Ti implant cohort (red columns) are shown in Figure 4. Figure 5 presents an example of the type of morphology of FDOJ samples removed from areas adjacent to Ti implants which were collected and subsequently analysed for seven cytokines.

FDOJ is similar to silent or subclinical inflammation without the typical signs of acute inflammation. In chronic inflammation, the local production of inflammatory cytokines, such as TNF-α and IL-1/6, overwhelms regulatory and compensating mechanisms, contributing to the formation of FDOJ in the bone marrow. This phenomenon of an intramedullary source of RANTES/CCL5 (R/C) overexpression appears to be more widespread than dentists and physicians previously presumed. The surgical debridement of FDOJ areas, however, may halt the induction of R/C signalling pathways and thus possibly inhibit the progression of associated symptoms.[17,7]

Why is this such an enigma in dentistry?

In previous research, we demonstrated the non-visibility and lack of obvious radiographic signs of FDOJ, which make it difficult to obtain an accurate diagnosis using common dental radiographs.[18] As a result, the existence of FDOJ and its systemic implications are largely neglected in today's dentistry. While conventional radiography is limited in its ability to properly reveal FDOJ, other means of identifying the presence of FDOJ are available. To aid the practitioner in diagnosing the bone marrow softening occurring within FDOJ lesions, a computer-assisted TAU device is available.[19] TAU has proven to be

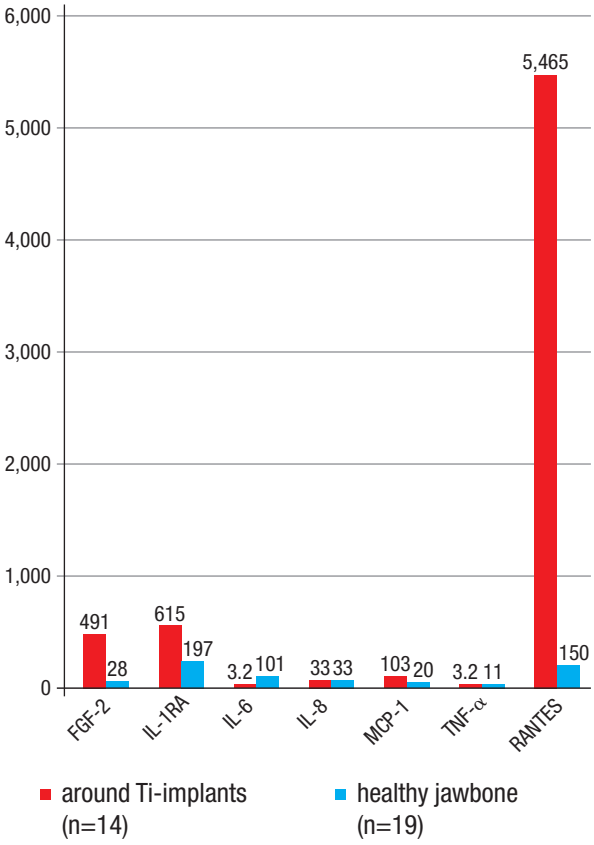


Fig. 4: Analysis of seven cytokines in the cohort with FDOJ of the jawbone and titanium implants (red columns), compared with the healthy jawbone group (blue columns). FGF-2 = fibroblast growth factor 2; IL-1RA = interleukin-1 receptor antagonist; IL-6 = interleukin-6; IL-8 = interleukin-8; TNF-α = tumour necrosis factor alpha; RANTES = regulated upon activation, normal T-cell expressed and secreted.

significantly superior to radiography for the detection of microscopically confirmed FDOJ. In numerous publications, the efficiency and reliability of TAU in the diagnosis and imaging of FDOJ has been presented.[20] Owing to these diagnostic difficulties, FDOJ is underdiagnosed by dentists in general. It should be noted that while radiographs in most cases fail to diagnose FDOJ the overexpression of pro-inflammatory signalling pathways in corresponding FDOJ areas is present and detectable as shown in Figure 4. This phenomenon is crucial in the discussion about silent inflammation.

Case study of high titanium dissolution in jawbone

This case study highlights the problem of the deceptive reassurance that radiographs appear to provide in relation to the fact that there is possible release of Ti particles to the peri-implant environment. The radiograph of a Ti implant in area #15 showed no suspicious reactions and the implant could be viewed radiographically and mechanically as a successful one. In contrast, Figure 6 shows, after explantation of the Ti implant, a blackish metallic precipitate in the alveolus along the bony grooves formed by the threads of the removed Ti implant. When the jawbone containing this precipitate was analysed by spectral analysis for heavy metal content (Figs. 6 & 7), the value for Ti was increased by a factor of 50, with an assumed limit value of < 1,000 µg/kg of body weight. The osseous tissue surrounding the implant thus contained 50 times the acceptable limit of Ti.

Sensitisation of immune system by titanium implants

TNF-α, a pro-inflammatory cytokine, is released at the beginning of almost every immune response based on individual sensitisation to Ti. Thus, TNF-α plays a key role in the failure of many implants in the case of genetic incompatibility.[1,21,22] In addition to the particles released from implant wear, Ti sensitisation is the result of increased pro-inflammatory reactivity of non-specific immune cells (tissue macrophages and monocytes), which in some patients occurs after contact with particulate debris, that is, Ti particles. Such particles (diameter of 1–10 µm) are consistently released into the environment surrounding implants through mechanical abrasion and chemical, bacterial and galvanic corrosion,[23] resulting in hyper-inflammatory conditions.[24] Sterner et al. investigated the effects of alumina ceramic, zirconia ceramic and Ti particles of varying size and concentration on TNF release in a human macrophage system.[25] It was found that in a direct comparison of alumina and Ti particles of the same size and concentration, Ti stimulated significantly higher TNF-α distributions. Zirconia did not induce significant TNF-α secretion.

Earlier, we demonstrated the solubility of Ti particles in the jawbone with reference to several images: after contact with such Ti particles, tissue macrophages release pro-inflammatory cytokines as part of an inflammatory reaction.[24] The extent of the release of pro-inflammatory cytokines is determined by polymorphisms in the genes of the respective cytokines and thus varies individually. Jacobi-Gresser et al. found that patients with implant loss or peri-implantitis showed significantly more pronounced genetic predisposition to inflammation, as well as markedly elevated positive immunological test results with overactivation of TNF-α and IL-1β.[22] Thus, the two cytokines TNF-α and IL-1 are the key mediators of a local but also systemic inflammatory response.[26] The extent to which the pro-inflammatory cytokines are released after contact with Ti oxide particles differs individually. The basis for supernatant reactions is found in individually occurring polymorphisms in the genes for the pro-inflammatory cytokines TNF-α and IL-1 and the anti-inflammatory counterpart IL-1 receptor antagonist.[27]

Secondary RANTES/CCL5 expression driven by TNF-α in FDOJ

The question arises as to whether there is an induced or synergistic interaction between the inflammatory TNF-α mediators secreted around Ti implants and the highly

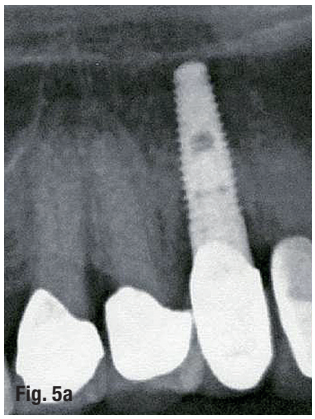
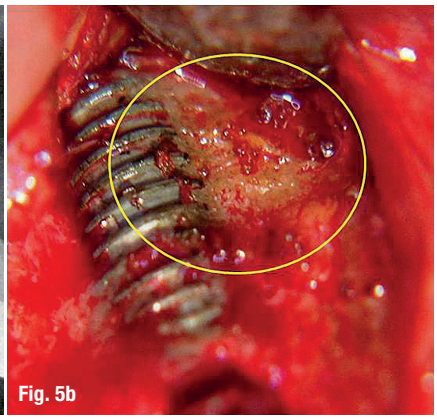


Fig. 5a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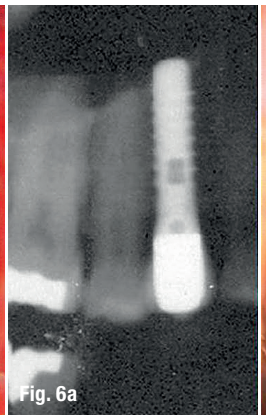
Fig. 6a

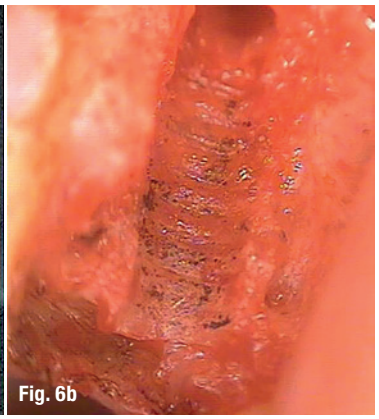
Fig. 6b

Fig. 5: Attachment of fatty-degenerative bone to titanium implant (area #13; **b**); radiograph does not indicate inflammatory bone loss or significant peri-implantitis **(a)**. **Fig. 6:** Radiographic image prior to removal of titanium implant from area #15 **(a)**; alveolar bone with precipitation of titanium particles **(b)**.

overexpressed R/C levels found in our previous research. Secretion of inflammatory cytokines mediates the systemic effects of adipose tissue inflammation. R/C expression dramatically increases in inflammatory sites.[28] Studies show the ability of Ti wear particles in a human bone marrow cell culture to induce a significantly higher release of pro-inflammatory and osteolytic mediators, which are responsible for the aseptic loosening of implants.[29] Beyond these findings based on TNF-α, our previous research points towards the next step of the process, namely the possibility of mediator cascades by R/C overexpression as found in FDOJ. Reduced blood flow and capillary density followed by ischemia in the medullary spaces of jawbone may lead to a hypoxic situation.[30] Adipocytes and the necrotic parts of fat cells are considered to be immunologically active. In understanding FDOJ, R/C and immune system disorders, the role of these immune effects is relevant. While pro-inflammatory cytokines such as TNF-α and IL-6 are distributed early on during the acute stage of an injury or tissue infection, chemokines like R/C may be activated at a later time. They may play a crucial role in the transition of acute pain into a more chronic phenomenon. In conjunction with tissue damage or infection, ischemia-induced chemokine expression causes an increase in inflammatory cytokines.[31] R/C expression was spontaneous and continuous in most samples of mature adipocytes from omental and subcutaneous deposits, and hypoxia and ischemia caused an approximately 36 % increase in R/C. Human adipocytes express R/C and can thus be identified as a new cellular source of this messenger.[32,33] The network of cytokine effects between TNF-α and the hyperactivated R/C cascades found in FDOJ (Fig. 8) has not yet been fully investigated.

Why is RANTES/CCL5 overexpression possibly connected to systemic diseases?

Pro-inflammatory signalling mediators such as R/C in particular affect the organism systemically and may result in chronic inflammatory processes or provoke further pathophysiological mechanisms. It is generally accepted that an imbalance between cytokines and their specific inhibitors is characteristic of chronic inflammatory conditions.[34] FDOJ represents a new inflammatory cellular response phenomenon in that the cytokines are not triggered by the presence of bacteria or viruses. This is supported by the fact that levels of typical acute pro-inflammatory cytokines such as TNF-α and IL-6 are not found to increase in this process. These acute cytokines are found to be absent in the FDOJ samples. Accordingly, we have hypothesised that R/C signalling is a chronic disturbance that may contribute to the development of chronic inflammation. The absence of acute inflammation in FDOJ denotes the subclinical and hidden proliferation of chronic immunological processes driven by R/C. High levels of the inflammatory cytokine R/C are found in the ageing stem cell milieu.[35] In the case of breast cancer, there is evidence of a synergistic osteo-immunological reaction to Ti implants, as TNF-α is an activator of the R/C promoter for mesenchymal stem cells in the tumoural environment of breast cancer via its signal transduction pathway.[36] The TNF-α stimulation of the mesenchymal stem cells led to a dose-dependent increase in the expression of R/C in the tumour.[37] Research on R/C and rheumatoid arthritis shows the same mechanism: in non-stimulated synovial fibroblasts, the expression of mRNA was not detectable for R/C.[38] R/C-activated chondrocyte functions are associated with joint inflammation and cartilage degradation in rheumatoid arthritis. IL-1β and TNF-α also induce the production of R/C, which is overexpressed in arthritic joints.[39,37] The stimulatory chain from TNF-α and IL-1β to R/C can also have a patho-genomic effect in cardiovascular diseases.[40]

Implantation and possible cytokine cascades

Perala demonstrated the induction of TNF-α *in vitro* after co-incubation of native implant material, which ensures that immunogenic particles are released from the materials.[41] Concerning cytokine expression in the context of an implant and the associated phases of healing, the analysis during different stages of implantation reveals several new phases of cytokine-triggered signalling pathways:

1. The Ti implant is placed in an ischemic area of subclinical FDOJ owing to the radiographically inconspicuous nature of FDOJ and the absence of alternative methods of measuring bone density. The systemic effect hitherto is subclinical and therefore free of symptoms.

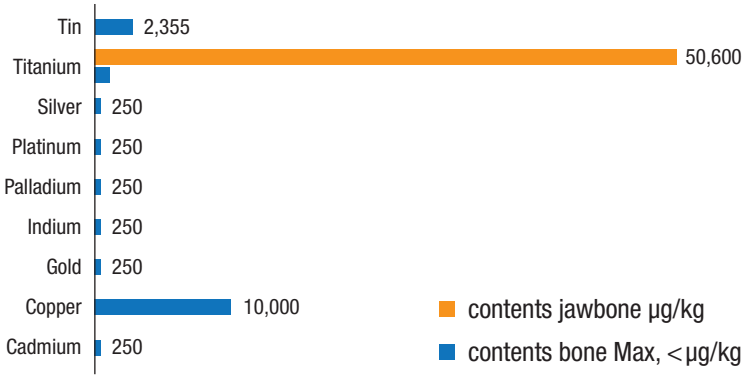

Fig. 7: Titanium content in the jawbone (area #15) as determined by spectral analysis.

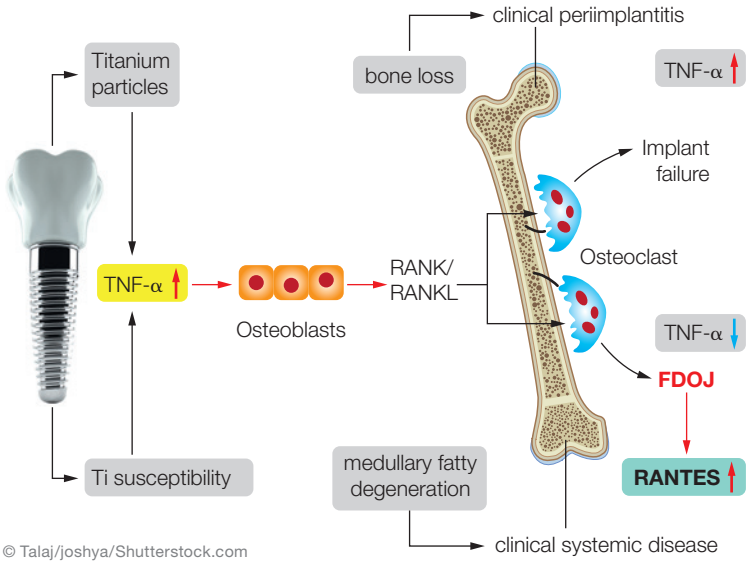

Fig. 8: Possible side effects of titanium implants, resulting either in bone loss and implant failure (shown in the upper pathway: TNF-α up) or in medullary fatty-degenerative osteonecrosis with no implant loss but systemic interference by RANTES/CCL5 overexpression (shown in the lower pathway: TNF-α down and RANTES up). TNF-α = tumour necrosis factor alpha; RANK = receptor activator of nuclear factor κB; RANKL = RANK ligand; FDOJ = fatty-degenerative osteonecrosis of the jawbone; RANTES = regulated upon activation, normal T-cell expressed and secreted.

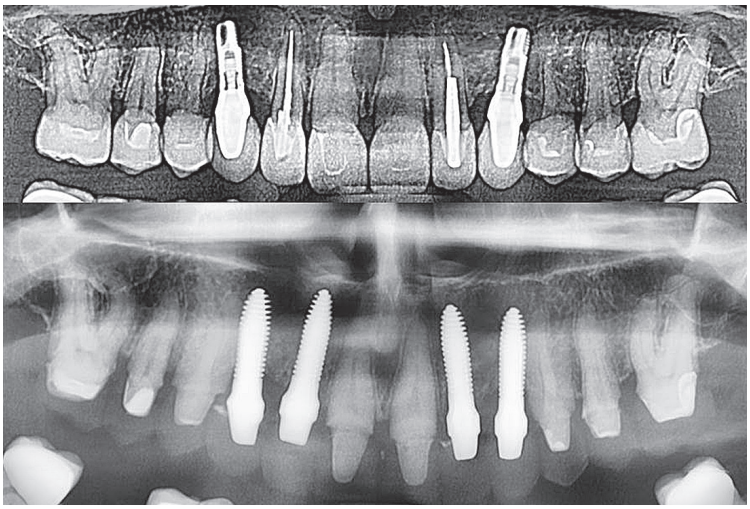

Fig. 9: In this case, replacement of titanium implants and root fillings with ceramic implants all in one session cured the female patient (38 years old) of Alopecia areata (spotty balding).

2. The acute wound setting initiated by the insertion of an implant in which the surgical trauma induces the release of acute cytokines creates inflammatory cascades via TNF-α, IL-6 and IL-1β expression.
3. Ti particles provoke expression of TNF-α at a later stage of wound healing.
4. In the medium to long term, TNF-α expression provokes increased secretion of R/C.

Here, the problems for clinicians include the following: (a) the clinical stability of the Ti implant leads to the misdiagnosis of an apparently inflammation-free osseointegration; (b) the radiographic and clinical inconspicuousness of Ti implant; and (c) the systemic symptoms of an immune system disorder are not directly related to the Ti implant because they occur only after a certain amount of time. As a result, an osteo-immunological scenario in the case of implantation is conceivable, as shown in Figure 8. Immediate replacement of Ti implants by non-dissolving ceramic implants gives a perspective for the integrative treatment of patients with chronic immunological diseases (for an example, see Figure 9).

Conclusion

Our data provides some evidence for the immunological relationship between Ti implants and FDOJ. A purely clinical assessment of Ti implants is insufficient. Radiographs also fail to indicate the derailed mediator process (cytokines and interleukins) triggered by Ti implants. Consequently, the evaluation and indication of Ti implants must also be viewed from a systemic perspective. In failing to recognise this, detrimental local and systemic health consequences may occur in the host that are concealed by the apparent success of a "stable implant". As far as we know, this study is the first to describe clinically the possible connection between Ti implants and FDOJ as a vector or cause of so-called silent inflammation. Removal of Ti implants and surgical debridement of surrounding FDOJ areas may diminish R/C-overexpressed signalling pathways and thus possibly reduce inflammatory input.

Editorial note: This article is a shortened version of the following open-access publication: Lechner J, Noumbissi S, von Baehr V. Ti implants and silent inflammation in jawbone—a critical interplay of dissolved Ti particles and cytokines TNF-α and RANTES/CCL5 on overall health? EPMA J. 2018 Jun 8;9(3):331–43.

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Literature

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