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Formation and detection of titanium release during implant insertion

An ex-vivo study in human donor bone

Introduction: In orthopaedic wear of titanium components of endo-prosthesis is an increasing problem, especially in hip prosthesis. Inflammation and tissue degeneration make surgical revisions risky and unfavourable. As approximately one million dental implants are inserted every year in Germany alone, side-effects like multi-etiological periimplantitis become more fre-quent. This study is motivated by the need to prevent disturbance of osseointegrative healing of implants after insertion due to phagocytosis of nanoparticles. That may cause activation of prolonged tissue inflammation with subsequent higher risk of implant loss or activation of multi-etiological peri-implantitis.

Methods: Human donor bone of D1 quality (Os femoris) was cut in appropriate size and 6 Conelog implants (Camlog) of 3,8 mm diameter (3 implants with a microrough surface and 3 of machined surface) together with 6 Thommen implants of 4 mm diameter (3 implants with a microrough surface and 3 of machined surface) were inserted with a maximum torque of 20 Ncm. Afterwards the bone cavity was opened and investigated for titanium wear. Scanning electron microscopy (SEM) and energy dispersive X-ray spectroscopy (EDX) was used to perform detection of nanoparticles. Statistical analysis was performed using ANOVA.

Results: The occurence of titanium was very limited. Therefore, the size of particles could not be measured. Overall 150 sites in 12 implants have been analyzed (average of 12.5 sitesper implant). In total, the measurements of 37 sites produced positive detection of small traces of titanium (0.016–0.364 wt.%). No differences have been found regarding the surface morphology or type of manufacturer. Remarkably there are differences in the sub-groups. There is a statistically significant difference between machined and microrough surfaces in Canelog implants ($p = 0.0161$). No difference has been found in machined and microrough Thommen implants ($p = 0.696$).

Summary and Conclusion: This unpretentious investigation actually shows that wear of titanium can occur in human bone simply due to implant insertion. Though wear is extremely limited in human donor bone and of little clinical relevance. Further long-term investigations regarding aspects of bio-tribocorrosion in dental implants are needed. The risk of prolonged inflammation during osseointegration is considered to be extremely low and therefore titanium implants are a safe and predictable therapeutic option.

Keywords: titanium; wear; particles; human donor bone; bio-tribocorrosion

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Introduction

This study investigates wear of dental titanium implants after insertion in human donor bone of D1 quality. Wear particles can be phagozytosed by macrophages and therefore promote prolonged inflammation and compromise osseointegration. Nanoparticles are ubiquitous in our daily life and can be found in dental materials, too. Schmalz et al. were working on an overview of nanoparticles in dentistry [36, 37]. They found that nanoparticles can be produced through wear of restorative materials (e.g. ceramics, metals) or can be released from dental implants and that they might be able to enter the biological environment when restorations or implants are being removed from the oral cavity.

A recently published review on corrosion and wear of titanium-based dental implant connections showed that the problem of nanoparticles reached scientific evidence [2]. This scoping review of Apaza-Bedoya et al. showed that degradation at the implant-abutment connection due to wear and tribological processes are among the serious problems in dentistry. They stated that wear and corrosion debris (e.g. ions and micro- and nanoparticles) that are released into the biological surrounding tissue can stimulate peri-implantitis that in turn leads to pathologic bone resorption.

A review of the literature of titanium toxicity by Kim et al. revealed several toxic and allergic reactions

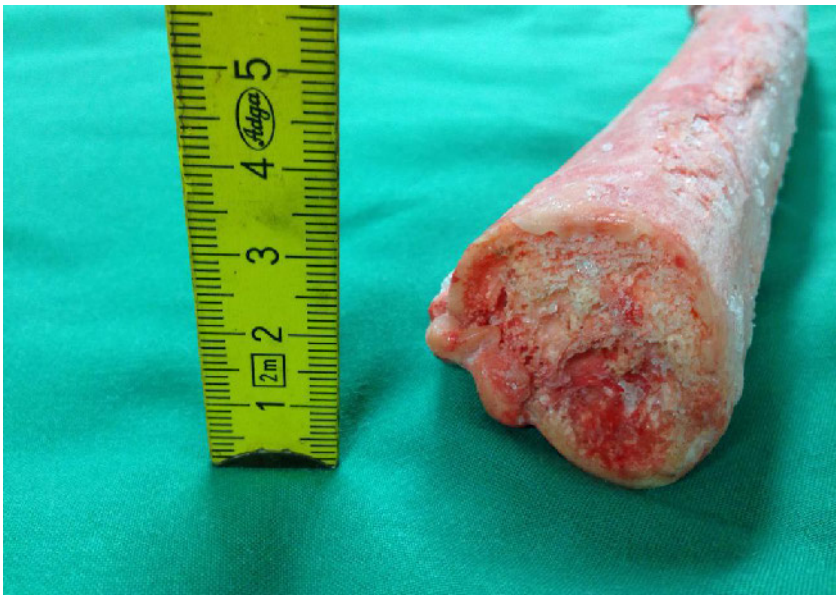


Figure 1 Deep frozen human femur shaft

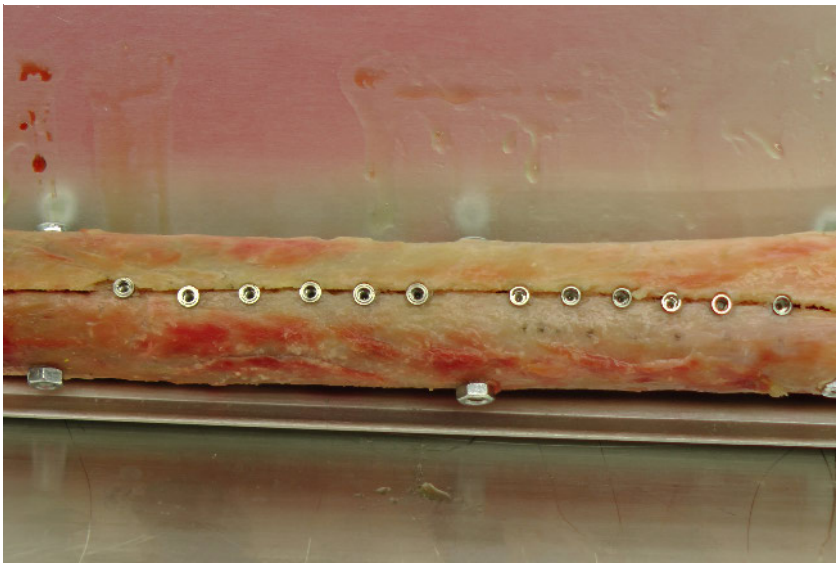


Figure 2 Human femur shaft with inserted implants

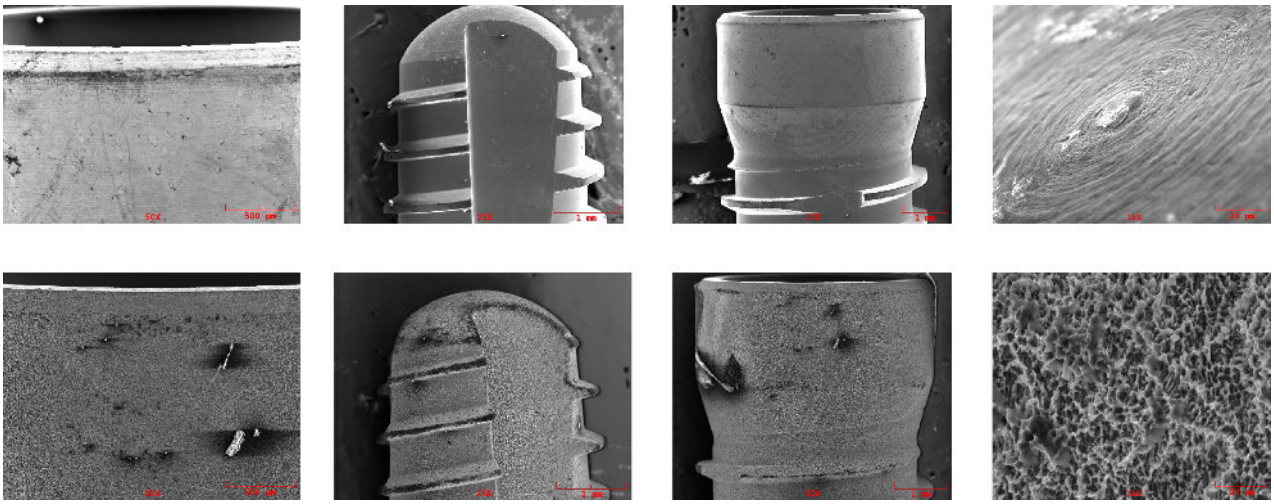


Figure 3 Canelog Implants machined (above) and microrough surface (below)

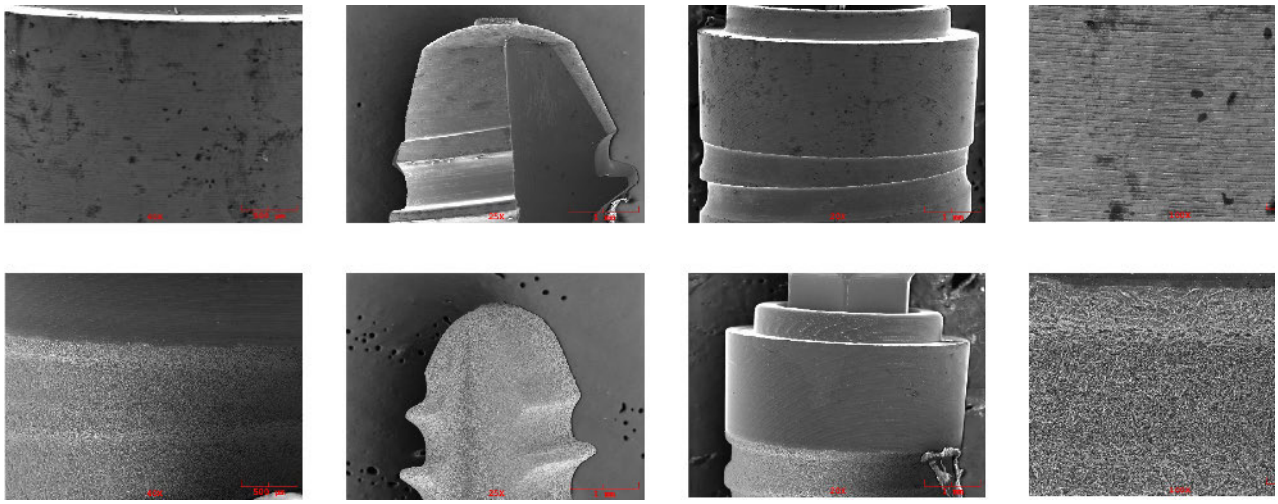


Figure 4 Thommen Implants machined (above) and microrough surface (below)

[18]. The most used titanium material is TiO2 powder that can be found in various applications such as paints, food products, drugs and cosmetics [9, 42] followed by increasing concerns of its influence on our environment and human health [3,13, 54]. Toxicity of TiO2 nanoparticles in rodents has been shown in many studies [5, 6, 8, 11, 14, 41, 48, 50, 51, 57].

Although titanium and its alloys are the most biocompatible material, wear and corrosion can still occur in extreme environment and conditions (e.g. low pH and high concentrations of fluoride) [19, 29, 44]. Schiff et al. found that fluorine ions can even destroy the titanium passive layer [35]. Wachi et al. found that titanium ions might be responsible for deteriorating effects of peri-implant mucositis [49]. Olmedo et al. found macrophages loaded with titanium particles as an indicator of corrosion processes of failed implants in human peri-implant soft tissue [27]. Using the exfoliative cytological test to observe particles inside and outside of epithelial cells and macrophages, studies from Olmedo and Penmetsa found significant higher rates of implant particles in patients with peri-implantitis [28, 30]. Wilson et al. discussed three possibilities that can cause presence of titanium particles: releasing due to friction between implant and bone during insertion, wear during debridement at maintenance procedures, and corrosion [53]. The damage of the surface of the implant due to particle release during insertion was observed by Senna et al. [40]. On the other hand Addison et al. proposed localized surface corrosion and micro-motions to be responsible for titanium particles and found wear debris unlikely to be the major contributor of particles [1].

Own investigations regarding torque dependent insertion depth of dental titanium implants in artificial bone showed that implants are stressed during insertion with up to 70 Ncm of torque [24]. Wear of dental titanium implants in artificial bone was subsequently investigated [25]. It has been shown that in artificial bone of D1 quality wear was very limited with only 0.17 to 0.47 atomic percent and with particles of 100 to 150 nm in size. This present study was aimed to re-check the previous findings under more clinically relevant conditions in human donor bone of D1 quality.

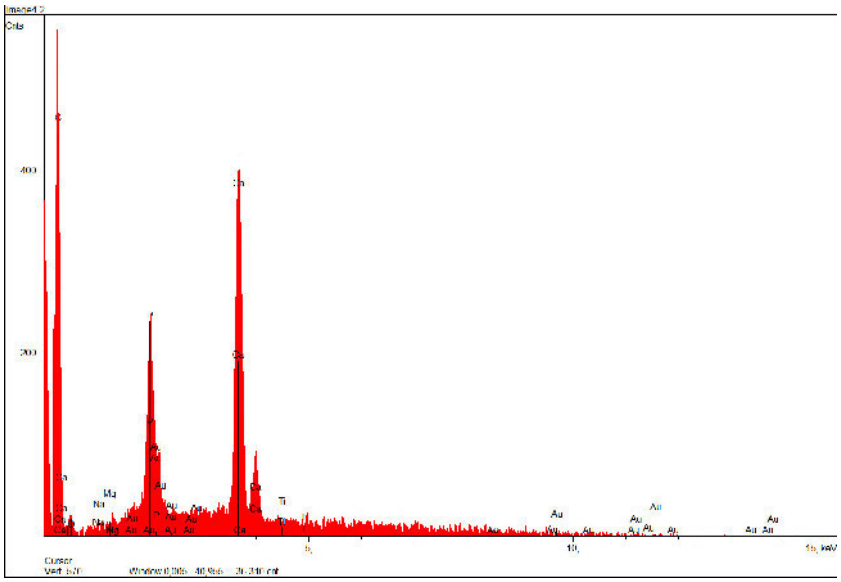


Figure 5 EDX-spectrum of sample 7

Methods

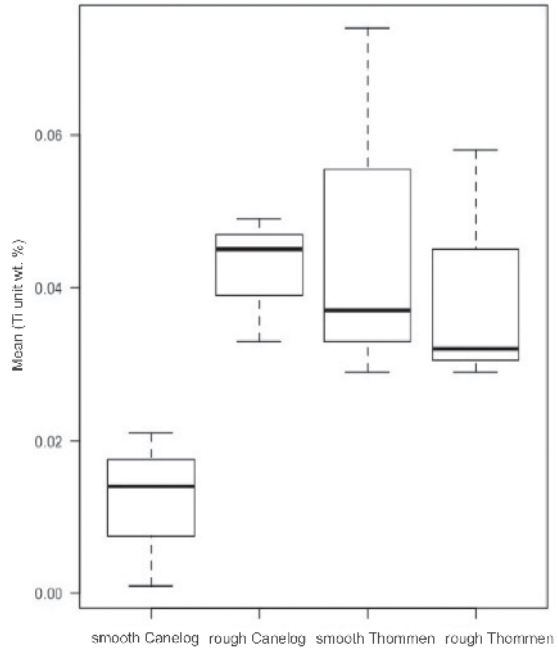
Human donor bone was provided by the Dr. Senckenberg Anatomical Institute of the University Hospital of the Goethe University Frankfurt (No. 65300308–2018–01). The donor bone encompassed a deep frozen femur bone shaft (Os femoris) of 25 cm in length and 3.5 cm in width (Fig. 1).

The shaft was split longitudinally and afterwards fixated by screws crossways. By this, the bone cavity could be opened after implant setting without bringing stress to the implant surface or the cavity walls (Fig. 2). Afterwards implants have been inserted into the cut of the lengthwise separation. Due to the restricted length of the bone shaft the limited number of only 12 implants could be inserted with sufficient space between the implants. This fact enabled the placement of only 3 implants of each group. Six Conelog implants (Camlog) of 3,8 mm diameter (3 implants with microrough surface and 3 with machined surface) together with 6 Thommen implants of 4 mm diameter (3 implants with microrough surface and 3 with machined surface) were inserted with a maximum torque of 20 Ncm and sufficient water cooling to prevent heat exhaustion. In both systems standard stainless steel drills were used meeting the recommendations of the drilling protocols. A previous analysis of an unused stainless steel drill for possible titanium sources showed a very homogeneous composition of the drill surface. The spectra gave a slight indication of the presence of titanium on the drill surface, but the titanium signal of the EDX analysis was not greater than its statistical error. Therefore, titanium was only present in traces in the drill material. To obtain sample size small enough for the SEM vacuum chamber each implant cavity was cut into 1.5 cm pieces (Fig. 3 and 4). Implant and bone units have been dried in an exsiccator for 14 days to ensure SEM imaging. To obtain suitable electrical conductivity of the donor bone, sputtering of these samples was necessary. The device used was Edwards S150B Sputter Coater. Sputter gas was Argon to provide a suitable source of ions for efficient target bombardment. Target material was gold (negative cathode) having favourable electrical conduction features. Samples have been sputtered for one minute at 1kV voltage and 100 mbar pressure. Additional advantages of sputtering was reduction of scanning electron microscope beam damage to the bone, reduction of sample charging, improvement of secondary electron emission as well as improvement of edge resolution. Energy dispersive X-ray spectroscopy (EDX) is a measurement method in the field of material testing and analytics. The electron beam of specific energy is used to stimulate atoms of a certain sample that thereupon emit a characteristic X-ray radiation. Each element emits its specific and distinct X-ray spectrum. In this way the elementary composition of the samples surface can be analyzed. Statistical analysis was performed using one- and two-factor analysis of variance (ANOVA).

The output of the EDX-software of a concentration value of a specific element cannot be mistaken with a positive detection of the analyzed element even if the nominal value is non-zero. In fact the interpretation of the value is based on statistical tests. That means that with a certain probability the real and unknown result of titanium is located around the given value. For this reason the software also shows the standard deviation (SD) in addition to the measured nominal count. If one chooses the single standard deviation the probability that the real and unknown value of titanium lies within the standard deviation is 68.3 %. If one doubles the standard deviation (2SD) the probability raises to 95.5 %. Nominal values less than the single or double standard deviation indicate a corresponding high probability that the real and unknown titanium value is zero (even the value itself is not

Sample	Description	Sites per sample	Mean (Ti unit wt.%)	SD	min	max
1	Canelog osseointegrative	20 (4 positive)	0.045	0.077	0.006	0.364
2	Canelog osseointegrative	12 (4 positive)	0.049	0.041	0.009	0.142
3	Canelog osseointegrative	16 (1 positive)	0.033	0.024	0.000	0.097
4	Canelog machined	6 (0 positive)	0.014	0.010	0.003	0.029
5	Canelog machined	4 (2 positive)	0.021	0.023	0.005	0.055
6	Canelog machined	2 (0 positive)	0.001	0.001	0.001	0.002
7	Thommen osseointegrative	15 (6 positive)	0.058	0,025	0.031	0.116
8	Thommen osseointegrative	15 (5 positive)	0.032	0.025	0.004	0.094
9	Thommen osseointegrative	15 (2 positive)	0.029	0.019	0.000	0.059
10	Thommen machined	15 (6 positive)	0.037	0.016	0.004	0.064
11	Thommen machined	15 (3 positive)	0.074	0.064	0.000	0.252
12	Thommen machined	15 (4 positive)	0.029	0.018	0.002	0.060

Table 1 Detection of traces of titanium on Canelog and Thommen implants (unit weight %)



(Fig. 1–6, Tab. 1: F. Müller)

Figure 6 Box-Plot

zero). Actually in analytical practice this in turn means that titanium could not be detected seriously.

Results

In total 12 implants were inserted into human donor bone, 6 Conelog implants and 6 Thommen implants of which 3 of each manufacturer have had a microrough osseointegrative surface and 3 of each group a machined surface. SEM investigation and EDX analyses have been performed on various sites of the crestal parts of each implant. Overall 150 sites in 12 implants have been analyzed (average of 12.5 sites per implant). In total the measurements of 37 sites (24.55 %) produced positive detection of little traces of titanium (0.016–0.364 wt.%).

Canelog implants with microrough surface produced 9 of 48 positive sites (18.75 % of 48 sites) and Canelog machined surface implants produced 2 of 12 positive sites (16.66 % of 12 sites). Thommen implants with microrough and machined surface produced 13 of 45 positive sites each (28.88 % of 45 sites) (Tab. 1 and Fig. 5).

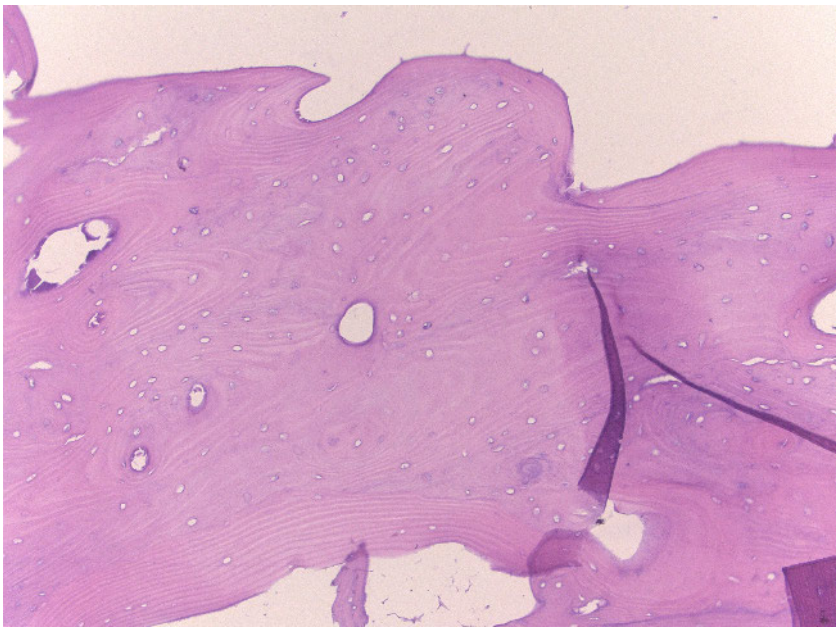
Univariate statistical analyses showed no differences regarding the surface morphology ($p = 0.326$) or type of implant manufacturer ($p = 0.167$). Bivariate testing including both factors (surface and manufacturer) showed a marginal significant difference ($p = 0.0755$) indicating that there are differences in the sub-groups. There is a statistically significant difference between machined and microrough surface in Canelog implants ($p = 0.0161$) as well as a difference between machined surface implants of Thommen and Canelog ($p = 0.0826$). No difference has been found in machined and microrough Thommen implants ($p = 0.696$). Also no statistical significant difference has been found between microrough surface implants of Thommen and Camlog ($p = 0.81$) (Fig. 6).

Discussion

This present study indicates that the investigated titanium implants are only very little abrasive. The most abrasive resistant surface was found in Canelog implants with machined surfaces. Nearly similar abrasive behavior was found in both Thommen surfaces together with microrough Canelog implants. Results of a previously published investigation of Canelog implants have shown a ten times higher abrasion behavior in artificial bone compared to human donor bone (up to 0.46 wt.% of titanium particles) [25]. This difference might be determined due to the properties of the artificial bone blocks (Sawbone, 40 pcf) that were used previously. These solid blocks were completely of compacta bone quality while human donor bone was of spongious medullary consistency in the center of the sample with an outer rim of compacta structure of only 2–3 mm. This compacta structure was found to be strong enough to obtain primary stability for all implants but lacks standardization (Fig. 7). On the one hand this standardization was given sufficiently in the artificial bone model that was lacking clinical needs on the other hand. The results show that microrough surfaces are more abrasive than machined surfaces due to the micro-retentive pattern after sand blasting and acid etching to ensure osseointegration. Therefore, it is no wonder that Canelog's machined surface is clearly less abrasive than its microrough. Remarkably this difference cannot be found in Thommen's surface where machined is comparable abrasive to microrough. Another interesting fact is that both Canelog and Thommen microrough surfaces are similar in abrasive behavior. So no superiority of one manufacturer over the other can be concluded.

In comparison Sridhar et al. did not found traces of titanium of 16 Straumann implants in artificial bone of 10, 20, 30 and 40 pcf Sawbone blocks [43]. The examination method used by Sridhar et al. (light microscopy and X-ray diffractometry) can be regarded as a potential cause for the failure to successfully detect titanium nanoparticles, since light microscopy does not achieve magnifications as high as those with a scanning electron microscope and therefore titanium particles that are scattered cannot be reliably detected in the nanometer range. In contrast another in-vitro study found reduced oxide layer of dental implants after insertion and pullout tests using microstructural analysis [47]. Deppe et al. found that the mean surface roughness, mean maximal roughness and the developed surface area ratio were highly modified after implant placement into bone using an in-

vitro study model [10]. Three different implant systems with different surface roughness have been inserted into Class I porcine bone. It was found that in the acid-etched implant surface the mean surface roughness decreased especially in the apical region (-10.4 %) compared to large-grit-blasted implant surface. In anodized implants the mean surface roughness increased (+5.7 %) indicating a destruction of the surface. Meyer et al. confirmed contamination of peri-implant bone in minipigs after placement of titanium implants by using scanning electron microscopy [20]. Results revealed titanium particles especially in the crestal part of the bone and around implants with rough surfaces. Wear was found to be less important on surfaces with a roughness of 1.5 µm and 0.4 µm. Recently, these findings have been confirmed by Suarez-Lopez del Amo et al. [45]. The authors tested 5 different implant surfaces (dual-acid etched, fluoride-modified, sandblasted large-grit acid-etched/hydrophilic sandblasted large-grit acid-etched, phosphate-enriched titanium oxide, and large grit). Results showed round or small angular elongated titanium debris in the crestal part of the osteotomy site. In contrast these findings could not have been confirmed by another group of researchers [52]. After insertion of implants in rabbit tibia Wennerberg et al. did not find an association between implant roughness and ion release. Surgical interventions of advanced peri-implantitis often require the removement of macroscopic implant threads for surface smoothening [39]. Various instruments have been tested to achieve a new plain implant surface [7, 32]. Schwarz et al. clearly demonstrated titanium contamination of neighboring bone and connective tissue after this implantoplasty resulting in a localized mixed chronic inflammatory cell infiltrate dominated by plasma cells and lymphocytes [38]. Actually, the authors did not report any clinical adverse effects related to the presence of those titanium particles. Peri-implantitis treatment in all its aspects is yet insufficiently predictable [16] compared



(Fig. 7: Dr. Manuel Niederhagen, OptiPath Frankfurt/M.)

Figure 7 Histological verification of compacta

to periodontitis treatment [22] and therefore scientific evidence is heterogeneous [23]. That's why knowledge of every part of the etiology of peri-implantitis is mandatory. A contrary assessment was recently done by Petterson at al. [31]. In order to investigate the influence of titanium on peri-implant inflammation, 13 patients with peri-implantitis (test group) and 11 patients with periodontitis (control group) have been included in this study. In patients with peri-implantitis, significantly higher titanium values have been measured than in the control group. They concluded that titanium can potentially worsen inflammation symptoms and make treatment prognosis worse. In order to investigate the possible influence of released components of dental implants as a result of peri-implant therapy or the corrosion of the titanium surface, Noronha Oliveira et al. carried out a systematic literature search in the Pubmed database [26]. 79 articles have been included in the analysis. It has been observed that metal ions and metal particles activate osteoclasts, pro-inflammatory cells and cytokines in the peri-implant tissues. Degenerative changes have been found in macrophages and neutrophils after the phagocytosis of titanium microparticles. Degradation products that result from the degradation of dental implants have a cytotoxic and genotoxic potential for peri-implant tissues. The quantity and the physicochemical properties of the degradation products determine the extent and damage to the peri-implant tissues. Safioti et al. performed a cross-sectional study on peri-implantitis and bacterial load [34]. They believe that in peri-implantitis bacteria not only trigger an immune response from the host, but also lead to electrochemical changes and corrosion of the titanium surface, which can result in an increased inflammatory process. In order to investigate the influence of the released titanium on the peri-implant inflammation, 20 plaque samples of 30 patients have been taken and analyzed. Significantly higher titanium values have been measured in implants with peri-implantitis than in healthy peri-implant conditions.

Investigations on orthopedic prosthesis revealed the underlying patho-physiologic mechanism resulting in bone and implant loss [12, 15]. Titanium alloy increases the release of inflammation-inducing mediators (Prostaglandin E2, Interleukin-1, Interleukin-6, TNF) [15]. Human monocytes released more inflammatory mediators due to Ti-Al-V in comparison to titanium-aluminum-niobium

(Ti-Al-Nb) [33]. Yu et al. investigated synergistic effects of H_2O_2 and albumin on corrosion behavior of titanium alloy (Ti6Al4V) in physiological saline [56]. A much higher rate of metal release was observed in both media (albumin and H_2O_2) compared to the presence of H_2O_2 and albumin alone. Furthermore Zhang et al. showed that albumin suppressed the dissolution of Ti6Al4V in the presence of H_2O_2 at short periods (< 24 h), but after longer periods the dissolution rate increased. That might be attributed to the reduction of the oxide film of titanium [58].

Allergic reactions against titanium are supposed to be impossible and mostly intolerance or hypersensitive reactions against titanium are wrongly diagnosed as allergy. There are reports of hypersensitive reactions like erythema, eczema, pain, necrosis and bone loss after insertion of titanium implants [18] but allergic reactions were reported by Hosoki et al. in 2016 [17] and Thomas et al. [46]. Berglund and Carlmark performed a study on systemic disease of titanium (known as "yellow nail syndrome") using energy-dispersive X-ray fluorescence (EDXRF) in the nails of 30 patients and found high concentrations of titanium [4].

A recently published comprehensive critical review concluded that titanium particles are being released from titanium surfaces because of mechanical wear, contact to chemical agents, and interaction with substances produced by adherent biofilm and inflammatory cells [21]. The authors found that wear, corrosion, titanium particles, inflammation, and microorganisms take part in a complex host response to foreign bodies. Environmental factors together with corrosion and wear lead to material degradation called tribocorrosion. Released titanium particles disturb cell function, surface disruption changes protein absorption, bacterial load causes inflammation, inflammation changes pH that in turn alters the composition of biofilms that in turn causes again corrosion. So multiple feedback loops compromise the peri-implant hard and soft tissue. Mombelli et al. finally concluded nicely that "biofilms cause inflammation, and biofilms cause corrosion". In summary this conclusion can be broadened to the full aspect of the scientific field of bio-tribocorrosion "insertion causes wear, wear causes inflammation, wear causes corrosion, corrosion causes wear, corrosion causes inflammation, inflammation causes corrosion, biofilms cause inflammation, biofilms cause corrosion" [55].

Nevertheless, the fact that implant insertion causes very limited wear as shown is only a small aspect in the etiology of multifactorial peri-implantitis and its clinical relevance compared to bacterial issues and immune response might be inferior. Still clinicians should keep this aspect in mind to promote and augment adequate options for their patients during primary (implant insertion) and secondary (peri-implantitis treatment) implant surgery.

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Conflicts of interest

The authors declare that there is no conflict of interest as defined by the guidelines of the International Committee of Medical Journal Editors.

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