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PRE-PRESS

Titanium Particle Exfoliation from Different Dental Implants after Insertion

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ABSTRACT

The titanium exfoliation level during dental implant installation has not yet been available. The present study aims to confirm the presence of titanium exfoliation in different implant surfaces throughout the installation and identify the association between insertion torque and surface abrasion. Three different implant surfaces were assigned to low and high insertion torque groups. The implants were installed into porcine bone blocks. Then, the surrounding bone at the ostomy site was analysed for the titanium exfoliation using an inductively coupled plasma mass spectrometry. The low and high insertion torques were 30 and 58 Ncm respectively. The average titanium content from all samples was 4.9±2.7 µg. Anodized implant released significantly less titanium compared to others (p<0.05). All implants released titanium indifferently compared to low and high insertion torques (p>0.05). Within the limitation of the present study, anodized implant released the least amount of titanium exfoliation. The insertion torque was not associated with titanium exfoliation.

Keywords: dental implant; post insertion; surface damage; titanium exfoliation; titanium particle.

INTRODUCTION

Titanium has been used as material in dental implants for over fifty years (Buser *et al*., 2017). Mechanical properties such as high strength and excellent resistance to corrosion make titanium the most proper substance for an oral implant (Mombelli *et al*., 2018). However, the failures of dental implants are still present. The potential cause of implant loss usually is bone resorption. Researchers are always looking for an answer to why early and late bone loss happens. Several causes of progressive bone loss are suspected, including infection, overloading force, systemic diseases, and inflammatory response (Oh *et al*., 2002; Mombelli *et al*., 2018).

Recently, titanium particle and ion have been regarded as responsible for the surrounding implant bone loss. The particle might play roles in inducing inflammatory reaction and hypersensitivity (Fretwurst *et al*., 2018). A high amount of titanium particles was identified around soft and hard tissue in a peri-implantitis case. Such findings might give a clue that the titanium particle could be a possible contributing factor for the bone resorption (Olmedo *et al*., 2013).

Several mechanisms for titanium release have been suspected, including a titanium exfoliation during installation and cleaning, micromovement between abutment-fixture connection, and biocorrosion (Fretwurst *et al*., 2018). Titanium particles were found around a bone-implant junction immediately after the implant was placed (Franchi *et al*., 2004). Previous study also found that the movement between the abutment-fixture interfaces released the particle to peri-implant tissue (Blum *et al*., 2015). Although titanium is believed to be well tolerated by the human body, the biocorrosion persisted under an inflammatory environment (Ishii *et al*., 2003).

Studies on titanium release during the installation are not adequately available. Therefore, the present study aimed to confirm the presence of titanium exfoliation in different implant surfaces throughout the implant installation. Also, the study intended to identify the association between insertion torque and surface abrasion.

MATERIALS AND METHODS

Experiment model

Experimental model was approved by Mahidol University-Institute Animal Care and Use Committee (Ref. No.: MU-IACUC 2019/005). The experiment was carried out on an ex vivo porcine pelvis model. Implants were installed into bone blocks, then they were removed. The amount of titanium around osteotomy site was assessed.

Implant selection

Three commercial brands of implants were selected including 4.0x10 mm sandblasted large-grit acid-etched (SLA, Superline, Dentium, Seoul, Korea), 4.0x10 mm laser-treated (LAS, Biomate Plus, Biomate, Kaohsiung, Taiwan), and 4.3x10 mm anodized surface (ANO, Nobel CC, Nobel Biocare, Karlskoga, Sweden) implants (Fig. 1). All implants shared a similar configuration which was the tapered and self-tapping design. The sample size was five implants in each group. The micro-surface morphology of the implants were also investigated.

Bone block preparation

The blocks were cut into 2 cm size, and bone density was investigated using computed tomography scan (Revolution frontier, GE Health Care Co., Inc., Chicago, USA). The bone density of the blocks was allowed between 500-600 Hounsfield units (Fig. 2). The bone blocks were also cut into halves and clamped together before implant osteotomy and installation. Unclamping the block allowed the easy removal of implant and caused the least harmful to the implant surface during removal.

Insertion protocol

The study group was divided into high (>35 Ncm) and low (≤35 Ncm) insertion torque. All implants were installed by a single highly experienced practitioner who was familiar with the study implants. A pilot study was performed to identify a proper osteotomy for achieving the intended insertion

torque. All implants were installed into porcine bone blocks at the crestal level, then removed immediately by unclamping the block.

Titanium exfoliation analysis

After the implants were removed from the blocks, the blocks were re-clamped. Then, a trephine drill of diameter 8 mm was used to harvest the surrounding bone from the socket. The samples were weighted to be between 100 mg and 200 mg. Based on the recommended protocol, microwave digestion (Titan MPS, PerkinElmer, Germany) was used to digest samples before the quantification of titanium. The samples were digested in 7 millilitres (mL) of HNO3, then the solution was filtrated with a filter paper and diluted to 50 mL with type I water. The condition of running a program is shown in Table 1. After the digestion, an inductively coupled plasma mass spectrometry (ICP-MS) (NexION 350x, PerkinElmer, USA) was used to quantify the released titanium particles and the data was processed using Software Syngistix™ for ICP-MS version 1.0 (Shelton, CT, USA). Internal (1,000 µg/mL Scandium, PerkinElmer, USA) and external (Instrument calibration standard 2, PerkinElmer, USA) standards were also used.

Statistical analysis

Statistical analyses were performed using the commercially available software, SPSS version 18.0 (Chicago, IL, USA). The data normality was proved using the Kolmogorov-Smirnov test. The torque values and amount of released titanium particles were expressed as the mean ± standard deviation (SD). Differences between groups were analysed by one-way analysis of variance (ANOVA) and least significant difference (LSD) test. The independent *t*-test was used to compare high and low insertion torque groups. Pearson correlation test was used to identify the association between the insertion torque value and the amount of titanium exfoliation. The statistical significance level was set to $p<0.05$.

RESULTS

The differences in the torque values between different implants within the low (30.0±1.7 Ncm) and high (57.5±8.8 Ncm) insertion torque groups were not statistically different (p=0.496 and p=0.902, respectively). The level of titanium exfoliation is shown in Fig. 3. The average titanium content from all samples was 37.7±11.5 mg/kg or 4.9±2.7 µg. The ANO surface exhibited significantly less amount of released titanium at both low and high insertion torques compared to others (p=0.042 and p=0.001, respectively). The comparison within the same implant showed that the level of released titanium between low and high insertion torque was not different (p-values are shown in Fig. 3). In addition, the association between the insertion torque and released titanium was not found (p=0.379).

DISCUSSION

Titanium has been widely used for medical implants such as the oral implant, orthopaedic prosthesis, and arterial stent. It is also regularly contained in daily products, for example, cosmetics, food additives, and toothpastes (Kim *et al*., 2019). Recently, the concern of local and systemic titanium toxicity has risen. Titanium dioxide is the most common form found in the human body (Grande and Tucci, 2016). Many studies reported uptake of the titanium dioxide particle by both the animal and human cells. All metallic forms pose some biologic risks such as cytotoxicity, metal hypersensitivity, chronic inflammation, tissue necrosis, and bone resorption (Sarmiento-González *et al*., 2009; Mombelli *et al*., 2018). Titanium in both colloidal and ionic forms can be transferred through the human circulatory system and get accumulated in specific organs such as lymph nodes, spleen, liver, or specific immune cells (Grande and Tucci, 2016). Fibrosis in the alveolar tissue, necrosis of hepatocyte, and the central nervous system damage has been reported in animal models (Bermudez *et al*., 2004; Wang *et al*., 2007; Valentini *et al*., 2018). In addition, the titanium level in human blood was used as a biomarker for orthopaedic implant failure. Increased titanium level around orthopaedic prostheses and in blood indicated increased local and systemic inflammation indicating the ailing prostheses (Lalor *et al*., 1991; Thomas *et al*., 2006).

In orthopaedics, the titanium exfoliation from the prostheses disrupted the balance of bone remodelling (Marshall *et al*., 2008). Direct activation of macrophage has been identified as a possible cause. Also, the simulation of the surrounding cells to release various cytokines promoted a negative impact on the surrounding tissue (Wang *et al*., 2007; Wachi *et al*., 2015). *In vitro* studies have shown that the osteoblasts responded to the titanium particle by losing viability, decreased adhesion, and decreased proliferation. The titanium particle also provoked human osteoclast precursor to a mature osteoclast by activation of nuclear factor-kB ligand and osteoprotegerin (Pioletti *et al*., 1999; Koide *et al*., 2003; Cadosch *et al*., 2010).

Recently, studies are linking the failure of the dental implant to titanium toxicity. Although the titanium used in the dental implant has high corrosion resistance and excellent mechanical properties, released titanium particles still could escape from a surface modification layer (Martini *et al*., 2003; Xuereb *et al*., 2015). Peri-implant inflammation has been connected to the titanium particles. A high concentration of titanium was found in peri-implantitis soft and hard tissues. Inflammatory granuloma lesions associated with the dental implant presented a metal-like particle in a histological study. Moreover, inflammatory cells containing titanium particles were also discovered around failed implants (Olmedo *et al*., 2010; Wachi *et al*., 2015).

Another cause of implant failure may be attributed to a metal allergy. Hypersensitivity reaction was repeatedly reported. The local symptoms of inflammation such as pain, swelling, erythema, and bone resorption, which ensued after dental implant placement subsided after removing the implant. Allergic eczema associated with the dental implant was also reported (Lim *et al*., 2012; Hosoki *et al*., 2016; Albrektsson *et al*., 2018).

A plausible mechanism of titanium exfoliation consisted of mechanical wear and biocorrosion. Friction and stress between implant and bone during the installation mechanically cause the stripping of titanium particles from the surface (Schliephake *et al*., 1993; Sridhar *et al*., 2016). However, the amount of titanium content has not yet been identified or related to clinical implications. Several studies demonstrated wear debris at the implant-abutment interface because of micromovement upon function (Blum *et al*., 2015). Moreover, disinfection titanium surface and implantoplasty caused the exfoliation of titanium (John *et al*., 2014). Despite high corrosion resistance, the titanium implant still corroded under an oral environment, especially under an inflammatory circumstance (Mombelli *et al*., 2018).

The bone surrounding the implant undergoes a remodelling process from the first to last day. Trauma from surgery and function triggers a bone turn over. Mild trauma promotes successful osseointegration meanwhile more trauma could lead to a bone or implant loss. Peri-

implantitis is usually a cause for implant loss. However, it is not responsible for an early bone loss. The causes of early bone loss are low primary stability, premature loading, excessive trauma, infection, and patient behaviours or systemic diseases (Qian *et al*., 2012; Albrektsson *et al*., 2017). Also, individual immunological reactions to a foreign body could be a possible cause (Trindade *et al*., 2016).

The reaction between the titanium particle and immune cells clearly showed a negative impact. A specific genotype of interleukin was found in association with the early bone loss (Shimpuku *et al*., 2003). Therefore, an excessive immune reaction between the titanium exfoliation and immune cells should not be overlooked. The early bone loss might relate to the particle in some specific patients. As mentioned above, the previous publication confirmed the presence of titanium exfoliation during the installation. This study was the first to report the titanium levels in three common commercial implant surfaces after installation. Further clinical studies on the adverse effects of oral implant titanium exfoliation could identify or rule out the potential bone destruction attributed to titanium particles.

High insertion torque has been a controversial issue due to its detrimental effect (Berardini *et al*., 2016). The high insertion torque improved primary stability by reducing micromobility, which was important in an immediate loading (Trisi *et al*., 2011). However, a concept of compressive necrosis was against the high insertion torque protocol. Duyck *et al*. (2015) reported greater marginal bone resorption when placing an implant with high torque (>50 Ncm) while many authors found no harmful effects from high torque protocol. The present study also found the increased level of titanium content when the fixture was installed with high torque. However, the statistical analysis showed insignificant differences. A study in denser bone type or increasing torque might show a more significant outcome.

The anodized implant produced the least titanium exfoliation. This might be due to the low surface roughness of the anodized implant. With a smaller surface area, the anodized titanium surface had less chance to physically contact to the surrounding bone. A previous study found

1,940 µg/kg of titanium particles around the implant site in the human jaw which was considered as the titanium quantity during function (He *et al*., 2016). The amount was around 300 times less than our result. A similar study in the animal model assessed titanium in surrounding bone 1 year after placement found around 200 ng of titanium which was 2.5 times less than our result (Wennerberg *et al*., 2004). The concentration of titanium in submucosal plaque (48.73 ng/µL) and gingival fluid (2.02 to 2.44 ppb) was also found immensely less than our result (Olmedo *et al*., 2013; Safioti *et al*., 2017). Therefore, the amount of titanium immediately after the installation is greater than during the function.

Titanium exfoliation after the installation was quantified in the present study. The amount immediately after the installation was surprisingly greater than during function. This high amount of titanium should be considered for further studies to identify the clinical risk and immunological response which may explain early implant failure or marginal bone loss in a specific circumstance. However, this study did not identify the biological risk of the titanium particle which could be future goal.

CONCLUSION

Within the limitation of the present study, anodized implant released the least amount of titanium exfoliation in both low and high insertion torque experiments. The insertion torque was not related to amount of released titanium particle after the installation.

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Table 1 Microwave digestion condition

Step	Temperature (°C)	Ramp time (minutes)	Holding time (minutes)
1	160	5	10
2	190	3	25
3	50	1	15

Figure

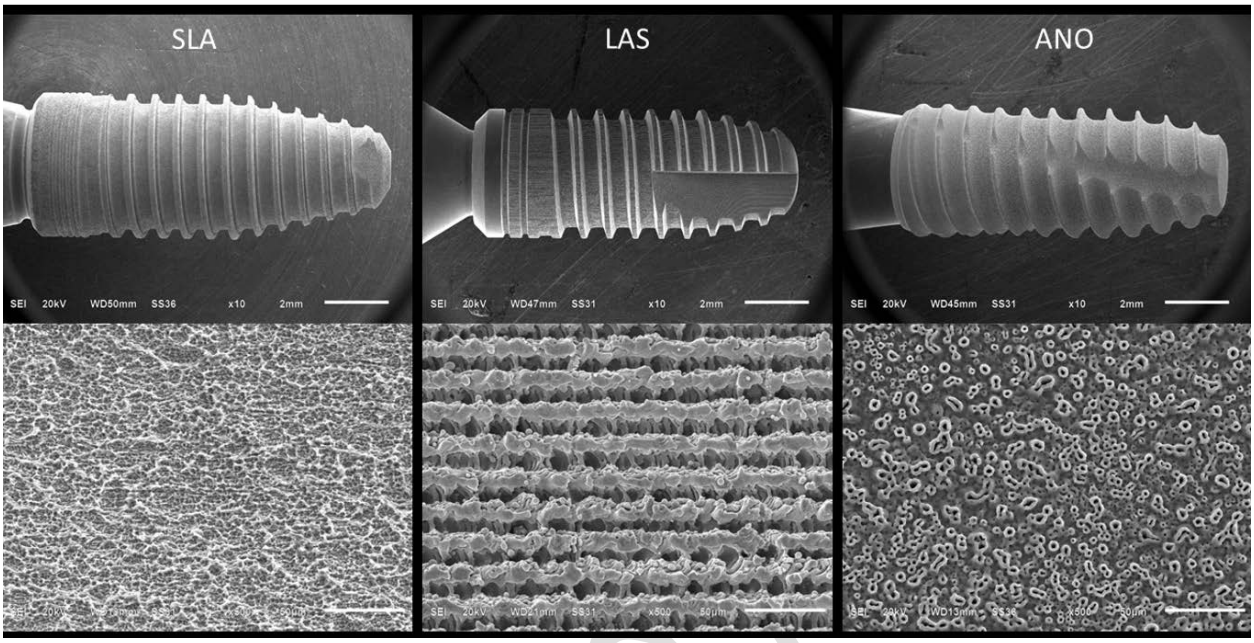

Fig. 1 Scanning electron microscope illustration showing gross and micromorphology; SLA: sandblast large-grit acid etch surface, LAS: laser-treated surface, ANO: anodized surface.

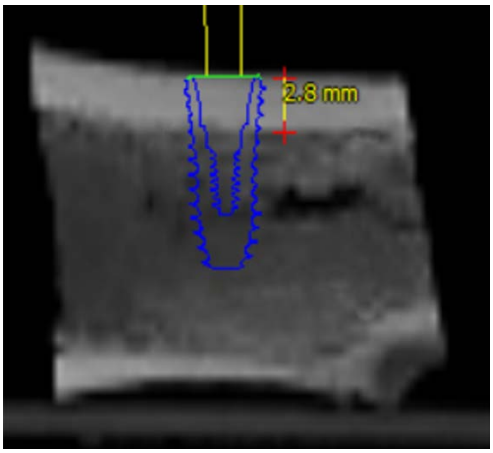

Fig. 2 Radiographic image of the porcine bone block.

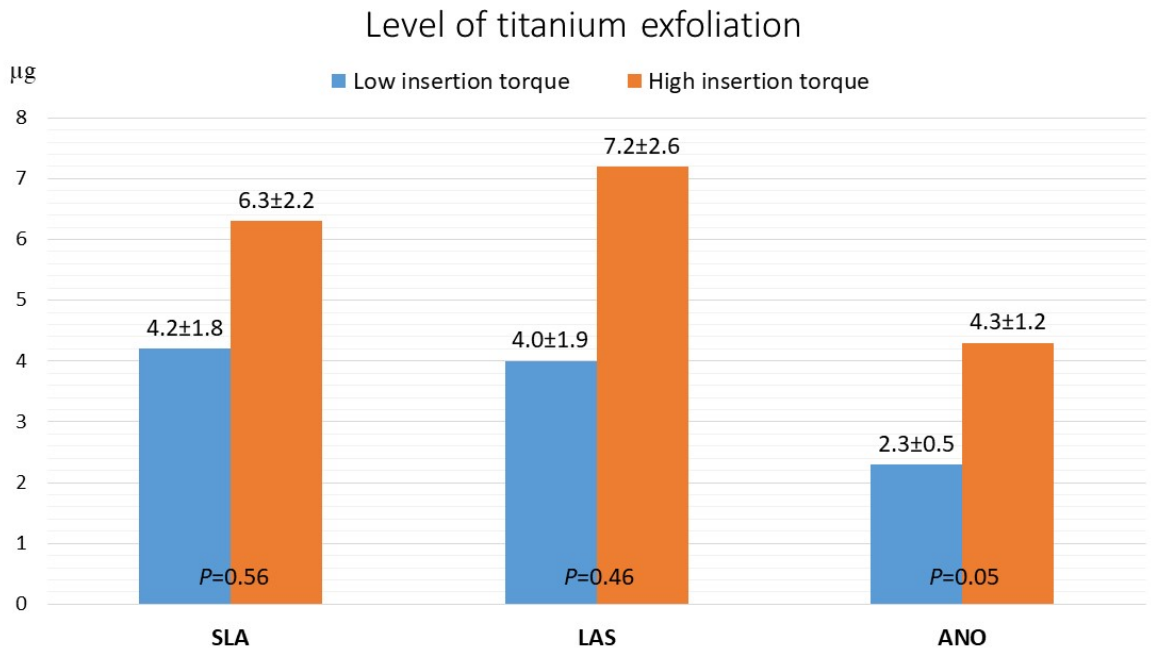

Fig. 3 Level of titanium exfoliation.