Selective laser melted titanium implants play a positive role in early osseointegration in type 2 diabetes mellitus rats

Yansheng DUAN1, Xiangdong LIU1, Sijia ZHANG1, Lei WANG1, Feng DING1, Shuang SONG2, Xutao CHEN1, Banglian DENG1 and Yingliang SONG1

1 State Key Laboratory of Military Stomatology and National Clinical Research Center for Oral Diseases and Shaanxi Clinical Research Center for Oral Diseases, School of Stomatology, The Fourth Military Medical University, Xi’an, China
2 Stomatological hospital of Peking university, Beijing, China

Corresponding authors, Yingliang SONG; E-mail: songyingliang@163.com, Sijia ZHANG; E-mail: zhangsijia111@hotmail.com

Success of dental implant is associated with the surface modification. To evaluate whether the selective laser melting-superfinished titanium (Ti6Al4V) implants have a better early osseointegration in type 2 diabetes mellitus rats compare to pure titanium implants and acid-etched treated (SLA) implants, we designed a screw-shaped implant which was batch-fabricated by selective laser melting (SLM). Then the implants were randomly inserted in tibias of rats with type 2 diabetes mellitus (T2DM). After surgical operation, the SLM group showed the best bone formation around the implants with the highest bone–implant contact rate among the three groups. Removal torque tests and histomorphological analyses all revealed a stronger connection between the bone because its good surface characteristics and mechanical properties. SLM implant may be a novel implant for T2DM patients.

Keywords: Selective laser melting, Dental implant type 2 diabetes mellitus, Osseointegration

INTRODUCTION

Over the last two decades, dental implant has become an ideal treatment modality for edentulous patients1). Titanium and its alloys are the most widely used implant materials for their excellent mechanical strength, chemical inertness and high biocompatibility properties2,3). With the growing implantation demand of type 2 diabetes mellitus (T2DM) patients, an ongoing problem is that the higher failure rate of implant surgery in type 2 T2DM patients because its poor bone formation and the consequent osseointegration problems4). Given that the implant surface is a key point of successful osseointegration during the early stage of bone healing, a large number of studies have focused on increasing dental implants’ stability by managing the surface properties of the implants, to reduce the failure rate and recovery time after implantation in T2DM patients5-7). Several studies have reported that implants with a rough surface and pores were beneficial to the osseointegration between bones and implants8). An acid-etched (SLA) surface of titanium implants has been demonstrated to be a positive method to improve osteogenic induction in dental patients with normal blood glucose9).

To achieve an implant surface with excellent porous structures that are good for bone-to-implant contact, a recently developed additive manufacturing technique, selective laser melting (SLM), has been attracted considerable attention. Additive manufacturing techniques can directly fabricate physical model layer upon layer based on computer-aided design (CAD) data, resulting in savings cost and time10). Through SLM, metal frameworks produced by applying a laser beam to a pool of metal powder to selectively melt and connect the powder particles11-13). This process contributes to the rapid production of complex shapes with a high utilization of materials, a uniform distribution of density, a homogeneous structure and minimal postprocessing requirements14). With these advantages, dental implants fabricated by SLM may have strong potential in producing metal implants with optimal surfaces and proper geometry for individualized and customized implant manufacturing.

In this study, a three-dimensional dental implant was designed and manufactured by selective laser melting with Ti-6Al-4V alloy powder. The products were then implanted into a T2DM rat model by implant surgical. The aim of the study was to evaluate the effect of implants prepared by SLM on osseointegration in T2DM rats during the early bone integration stage compared to the well-known SLA treated implants and pure titanium implants.

MATERIALS AND METHODS

Materials preparation
Commercially pure titanium (grade 2) implants (maximum diameter=3 mm, minimum diameter=1 mm, total length=5.2 mm), pure titanium disks (diameter=15 mm, thickness=2 mm) and the Ti-6Al-4V alloy were purchased from Sigma-Aldrich (St Louis, MO, USA). Van Gieson was purchased from Solarbio (Beijing, China).
Designation and manufacture of porous Ti-6Al-4V implants by SLM

The screw-shaped implant model (maximum diameter=3 mm, minimum diameter=1 mm, total length=5.2 mm) was designed into a cone form by a 3D design software (pro engineer 5.0 (SolidWorks, Concord, MA, USA) with 3-mm strut max diameters and 4.4-mm strut axis lengths and saved as an STL format (Figs. 1A, B). Disk-shaped models with diameters of 15 mm and thicknesses of 2 mm were designed and managed in the same way. These models were then fabricated by a metal printer (EP-M250, Yijia, Beijing, China) using commercial grade IV Ti6Al4V powders with particle sizes ranging from 15 to 53 μm (apparent density 2.60 g/cm³, tap density 2.87 g/cm³). The manufacturing process was carried out according to a previous work with some modifications and the schematic diagram is shown in the supplementary material (Fig. 2)15. The STL format model was passed into a slice software (Eplus3D printing software system, Yijia) and exported as an epa format to enter into the control system of the printer. The model was then sliced into 20-μm layers with a defined laser path. The machine was equipped with 160 W power using an 80-μm diameter laser beam and 30-μm layer thickness, 500-mm/s laser scan speed and 20-μm hatch distance. Several hours were taken to fuse the slices layer-by-layer, and the components of porous and dense metal parts were formed. To avoid oxidation and contamination, the SLM procedure was run under 99.999 wt% purity argon. After vacuum heat treatment, the printed specimens were cleaned up and dried for use. A total of 32 implants and 8 disks were produced using the above method.

Preparation of control implants

The pure titanium implants and disks with the same sizes as the SLM products were divided into two groups based on the surface treatment: no treatment and acid-etched (SLA) treatment. The SLA procedure was performed based on previous procedure16. Briefly, specimens were sandblasted with large grits of 0.25 to 0.50 mm and were acid etched in 67% H₂SO₄ at 120°C for 10 min to produce the SLA surface.

Surface characterization analysis

The surface morphology of the specimens from the three groups were observed by emission scanning electron microscope (SEM; JSM-6700F, JEOL, Tokyo, Japan) under ×1,000 and ×5,000 magnification. The images were analyzed by PC-SEM 6700 software. The surface wettability was measured by a contact angle measuring system (EasyDrop, Standard, KRÜSS, Hamburg, Germany). The element analysis of the implant surfaces was performed by an energy dispersive X-ray spectrometer and analyzed using Jade software. The surface roughness was evaluated by a scanning probe microscope (SPI13800-SPA-400, Seiko Instruments, Chiba, Japan) and three typical parameters, including
the mean roughness (Ra), quadratic average roughness (Rq) and the peak-to-valley roughness (Rz) were calculated. Ten random sites were selected on each implant to obtain an average value.

Mechanical properties measurement
Yield strength of the implants was measured by uniaxial compression tests using an electronic universal testing machine (Instron 5985, maximal load 50 kN, 2.5 kHz sample rate, Boston, MA, USA) at room temperature. The samples were clamped in the chucks of the machine with a compression speed of 1 mm/min, and a digital camera was used to record the real-time stress-strain behavior of the implants during the tests. The force and displacement were then analyzed by a static test software (Bluehill Universal, Boston, MA, USA).

Animal model of T2DM
A total of 60 male Sprague-Dawley rats (8-week old) were purchased from Air Force Medical University. The animal experiment protocol was approved by the Animal Care and Experiment Committee of the Air Force Medical University (SCXK2014-0002). The rats were housed under standardized conditions (12 h light/dark cycle, 22±2°C, relative humidity 55±10%) throughout the study. After a week of normal diet feeding, the rats were then fed with a high-fat diet for four weeks, and a single low-dose (30 mg/kg) of streptozotocin was administered through intraperitoneal injection to induce T2DM as previously reported17). One week later, random plasma glucose levels (PGLs) were measured via the caudal vein using a glucometer. The rats with PGL>16.7 mmol/L were considered to be successful T2DM models and used in the subsequent experiments. During the entire experiment, the rats were kept on the high-fat diet. The PGL and body weight of each rat was recorded before and after the surgery.

Implant surgical procedure
A total of 48 T2DM rats were randomly chosen and divided into three groups (n=16). The surgical procedures and all dental implants were under sterile conditions. The rats were anaesthetized with 2% pentobarbital sodium via intraperitoneal injection. The surgical procedures were carried out according to those described in a previous study18) (Figs. 3A–D). Each group of animals received one kind of implant inserted on bilateral tibia in the sagittal plane of the head, one for micro CT and histomorphologic analysis, the other was measured by removal torque measurement.

Micro CT: scanning
After four and eight weeks of recovery, a micro-CT scanner (Y. Fox, YXLON, Hamburg, Germany) was used to evaluate bone formation at a scanning resolution of 12 mm in the rat models. Three-dimensional images (3D) were constructed and analyzed by 3D modeling software (VGStudio MAX, Volume Graphics, Heidelberg, Germany). The volume of interest was selected as 0.2 mm around the implant and the bone volume/total volume (BV/TV), bone surface/bone volume (BS/BV), trabecular thickness (Th.Th), trabecular number (Th.N) and trabecular spacing (Th.Sp) were calculated.

Histomorphological analyses
Four and eight weeks after implantation, the implants were entirely removed from the rats followed by 48 h' formalin fixation, decalcification and insertion into resin. Ground sections of 300-μm thickness were then made using high precision diamond disc slicing (Leica SP 1600, Leica, Wetzlar, Germany). Decalcified sections of approximately 100 μm thickness were then made using a grinder (Rotopol-35, Streuers, FL, USA). The specimens were stained by Van Gieson (VG) using the standard method. A stereoscopic microscope (DMI6000B, Leica Microsystems, Shanghai, China) was used to observe the prepared specimens to analyze the morphologic features of the bone tissue around the implant and the interface of the implant. Images were taken at 20× magnification and analyzed by an imaging system (Leica Imaging System, Cambridge, UK). The bone-implant contact rate (BIC%) was obtained by calculating the ratio of the entire length of the implant and the bone-implant contact area using ImageJ software.

Removal torque measurements
Four and eight weeks after recovery, the rats were sacrificed and the soft tissues were elevated to expose the implantation sites. The implant was fixed with a removal tool that was connected with a digital torque gauge (MGT-12, Mark-10, Copiague, NY, USA). As the torque gradually increased, the critical torque value to destroy the implant-tissue adherence was recorded as the maximum removal torque.

Fig. 3 Implant surgical procedures in T2DM rats.
A skin incision was made on the proximal tibia of the rat, muscular dissection and periosteum detachment were followed to expose the bone surface (A). The implant was then inserted on tibia in the sagittal plane (B). Wound suture was performed after implantation (C). The rat was in a stable condition after the operation (D). The femur.
Statistical analyses

Statistical analyses were performed using SPSS 13.0 and the data were expressed as the means±standard deviations (SD). One-way analysis of variance (ANOVA) was applied to compare the outcomes of the three groups. Differences with \( p<0.05 \) were considered to be significant.

RESULTS

Surface characterizations

SEM images of implant surfaces of the experimental and control groups were taken at \( \times 1,000 \) and \( \times 5,000 \) magnification (Figs. 4A, B). Porous structures can be observed on the surface of all three types of implants. However, the SLM surface showed a honeycomb-like structure with irregular and multilevel pores and peak and valley shapes, while the porous structures of the SLA surface and pure titanium surface were regular and flat. The SLM implants had a higher degree of roughness than the control surfaces. The mean Ra, RMS and Rz values are shown in Table 1. The SLM implant surface Rz was approximately two times larger than the SLA implant.

The element analysis showed that elements including Ti, C, O, P, Ca, Na, Cl, Mg, Al, Si, and Cr were found on the SLM and the SLA implant. The Ti content was higher in the SLM implant (72.93\% weight) than the SLA implant (62.97\% weight). The pure titanium implants only include five elements, such as Ti, C, O, P, Ca, and Ti content is lowest (41.97\% by weight) (Figs. 5A–C). This result revealed a higher degree of Ti purity on the SLM implant surface compared to the controls.

It was observed in contact angle measurements that regular drops were formed on the control samples when demineralized water was applied; The mean contact angles were 99.7° and 79.3° on the pure titanium surface and the SLA surface, respectively. However, the water spread over a larger area of the SLM surface and the contact angle was 0° (Figs. 6A, B), indicating that the SLM surface presents a more favorable wettability.

Mechanical properties

The mean yield strengths were 480, 460 and 440 N/mm² for the pure titanium, SLA and the SLM implant, respectively. The low yield strength of the SLM implant indicated a low elastic modulus.

Animal models

Weight and PGLs of the rats were recorded and showed in Figs. 7A, B. The PGLs of rats in T2DM group increased rapidly to 28 mmol/L during the second month’s induction, and stabilized at 27–28.5 mmol/L in next four months. While the PGLs of rats in control groups were gradually increased but maintained below 10 mmol/L in the whole course. The body weight of experimental

| Roughness/nm | Pure titanium | SLA | SLM |
|--------------|---------------|-----|-----|
| Ra           | 333.8±11.2    | 396.9±13.2 | 508.9±15.8 |
| Rq           | 420.0±18.4    | 475.2±21.6 | 602.0±26.5 |
| Rz           | 2,782.0±121.7 | 1,049.0±97.8 | 2,589.0±160.3 |
rats rapidly increased to over 500 g within two months’ induction, but subsequently decreased to 330 g in the next three months. The weight of control rats increased gradually from 260 to 520 g during the course.

**Micro CT- scanning**

The 3D reconstructed Micro-CT images of the SLM implants and the control implants are shown in Fig. 8. The implants and cancellous bone are respectively marked in white and yellow. Bone volume around the implant surface of the SLM implant was obviously larger than other two groups. The morphometric index of the bones summarized in Table 2. Compared to the control groups, BV/TV and Tb.Th were significantly higher in the SLM group at 4 weeks and 8 weeks, while Tb.N was lower, which indicated a more compact bone formation around the SLM implant.

**Histomorphological analyses**

Histological images and the BIC% results within the three groups are shown in Fig. 9. In the SLM and SLA group, newly formed bone tissue stained by Van Gieson was observed around the implants at four weeks, and the BIC value was higher in the SLM group than the SLA group, while little bone connection was found around the pure Ti implants at this stage. After eight weeks of recovery, a good bone connection was seen on both the SLM and the SLA surface and the BIC value of the
two groups showed no significant difference, while the bone-implant connection of the pure Ti group remained weak.

**Removal torque measurements**

The removal torque of the three groups at four and eight weeks are summarized in Fig. 10, including mean values and SD. The SLM group showed statistically significantly higher removal torque than that of the SLA and pure titanium groups before recovery of four and eight weeks.
Table 2  Morphometric indexes for bone formation of the three groups at 4 and 8 weeks

| Groups      | Recovery time (weeks) | BV/TV   | Tb.Th (mm)  | BS/BV(1/mm) | Tb.N (1/mm) | Tb.Sp (mm) |
|-------------|-----------------------|---------|-------------|-------------|-------------|------------|
| Pure titanium  | 4                     | 0.207125| 0.066248    | 30.1898     | 3.12625     | 0.253597   |
|             | 8                     | 0.309800| 0.061143*   | 33.2699     | 5.15351     | 0.133928   |
| SLA         | 4                     | 0.387093| 0.056972    | 35.1048     | 6.79442     | 0.090207   |
|             | 8                     | 0.334652| 0.061634    | 32.4494     | 5.42964     | 0.12254    |
| SLM         | 4                     | 0.618582*| 0.134188*   | 14.9045     | 4.60982     | 0.082740*  |
|             | 8                     | 0.577618*| 0.103698*   | 19.2867     | 5.57017     | 0.075829*  |

DISCUSSION

As a technique that can produce customized metal products, the emerging SLM technique is believed to have great application potential for dental implant. Dental implants prepared by SLM had already achieved satisfying osseointegration in beagles19). In this study, T2DM rats were used as models to further demonstrate that the SLM implants may also present better osseointegration than other implants in the case of T2DM.

Because of osseointegration defects from T2DM patients, the early stage integration of the bone implant is a key point for the success of dental implant. A fibrin clot extends rapidly around the implant’s screw and osseointegration starts as soon as the insertion of implants, and osteoblasts-implant attachment subsequently occurs20). Di Iorio et al. reported that surface roughness influences fibrin clot retention and thereby influences the early stages of osseointegration21). Other studies further demonstrated that higher implant surface roughness contributed to better interface strength and larger surface coverage by bone22,23). A porous structure that allows new bone ingrowth is beneficial to the mechanical interlocking of bone-to-implant interfaces24). In our study, such surface characteristics were observed on both the SLM and SLA implants, but the SLM implants with a higher roughness and controllable pore structure may achieve better outcomes.

The purity of the titanium surface also influences the mechanical stability and osteo-induction ability of implants25). This property raises the question whether the surface treatment process induce surface contamination. An implant produced by SLM technology may avoid this risk26). As shown in our study, the pure titanium implant had the pure surface with fewer elements other than Ti, however, the osseointegration around it was still weak because its surface was smooth and its Ti proportion was low. The SLM surface possessed the highest proportion at 72.93% of Ti among the three groups. These results showed that the SLM implants combined two advantages for dental implant, with both a high degree of surface roughness and high pureness.

Moreover, Ferguson et al. reported that implants with an extremely hydrophilic surface have better clinical outcomes27). In this study, the SLM implants had the smallest contact angle of the three groups, which represented good wetting and caused successful osseointegration.

Dental implants also require proper mechanical properties. Among titanium alloys, the Ti-6Al-4V alloy has been demonstrated to have a relatively low Young’s modulus, and this characteristic helps to avoid the stress shielding effect after implantation28). The SLM implants in our study using Ti-6Al-4V alloy as a raw material with a feedback low elastic modulus, which was verified by the yield strength results. In addition, the low elastic modulus may also be influenced by the porous structure of the SLM products.

With all of these advantages in SLM implants, were carried out to verify our hypothesis in vivo. Histomorphometrical analysis revealed that the SLM surface had a higher percentage of BIC than the control surfaces at 4 weeks’ recovery, which indicates that the early osseointegration of SLM implants was better than controls. While no significant difference was observed at 8-week between the SLA and SLM implants. The degree of osseointegration of implants was then further measured by removal torque tests, and the Rz value of the SLM implants was also the highest at 4-week and 8-week. These results directly confirmed that the SLM implants have a favorable effect on osseointegration in T2DM rats during the early stage of bone healing.

CONCLUSIONS

Compared to SLA and pure titanium implants, the SLM implants showed both higher mechanical properties and appropriate surface characteristics such as high roughness, high purity, good wettability and polylaminate porosity structure. And these advantages are likely to contribute to early osseointegration of SLM implants in T2DM rats than the SLA implants.

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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