Titanium Nanotube Surfaces Improve Osseointegration in a Diabetic Rat Model

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Background

Diabetes is highly prevalent in the United States and around the world. In the United States, there are an estimated 38.4 million people (11.6%) with diabetes and 97.6 million people (38%) with pre-diabetes[1]. For those people 65 years or older, 48.8% have pre-diabetes[1]. Diabetes is a chronic progressive inflammatory disease with effects on multiple systems including vasculature, nervous and skeletal systems[2,3]. The inflammatory state increases bone resorption while limiting bone deposition, leading to osteoporosis over time[2,3]. Bone loss can lead to fractures that require orthopedic implants[4]. Impaired healing due to diabetes can lead to complications such as implant loosening, device failure, and infections[4].

Titanium nanotubes have shown the ability to improve outcomes in osteoporotic models due to hormone dysregulation[5]. In this paper, Zhang et al. explored the effect of titanium nanotubes on osseointegration under diabetic conditions using a rat model, where diabetes-associated inflammatory and impaired vascularization typically inhibit implant integration[6].

Methods

Machined titanium screws were used as the control group, while the experimental group (TNTs) consisted of machined titanium screws that were further anodized to create the nanotube surface. The diabetic animal model was created by injecting the 9-week-old rats with streptozotocin to kill off the beta-islet cells in the pancreas. The rats' body weight, intraperitoneal glucose tolerance test (IPGTT), and insulin tolerance test (ITT) were evaluated to confirm the development of type 2 diabetes mellitus (T2DM).

Screws with and without nanotubes were placed into the distal femur of the rats. The study also included control rats and T2DM rats without implants. Micro-CT scanning was performed to record bone growth around the implants at 4-, 8-, and 12-week timepoints to generate data on bone volume/total volume (BV/TV), trabecular thickness (Tb.Th), trabecular number (Tb.N), bone surface/bone volume (BS/BV), and trabecular separation (Tb.Sp).

Results and Discussion

Micro-CT imaging showed obvious osteoporosis in the distal femurs of the T2DM rats compared with the control rats, as shown in Figure 1. Consistent with these findings, the T2DM rats resulted in significant bone loss in the distal femur and dramatically reduced weight gain compared with the control rats (weight data are not shown here but are reported in the original publication).

At 4-, 8-, and 12-week timepoints, micro-CT images showed increased bone growth around the nanotube surface relative to the control surface, as shown in Figure 2.

Quantification of the bone structure at 12 weeks showed greater bone volume/total volume (BV/TV), thicker trabecular structures (Tb.Th), and a higher trabecular number (Tb.N) for the nanotube surface than for the control surface, as listed in Table 1. In contrast, bone surface/bone volume (BS/BV) and trabecular separation (Tb.Sp) were lower for the nanotube surface. Due to the increased trabecular number and thickness, the spacing between trabeculae on the nanotube implants was lower, resulting in higher bone volume.

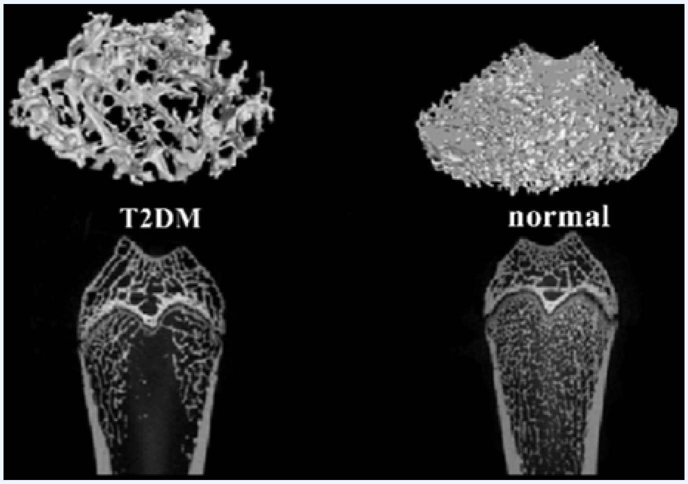

Figure 1: Micro-CT images of distal rat femur with bone loss due to T2DM and normal control at 12-weeks post injection. This image is modified from the work of Zhang et al[6].

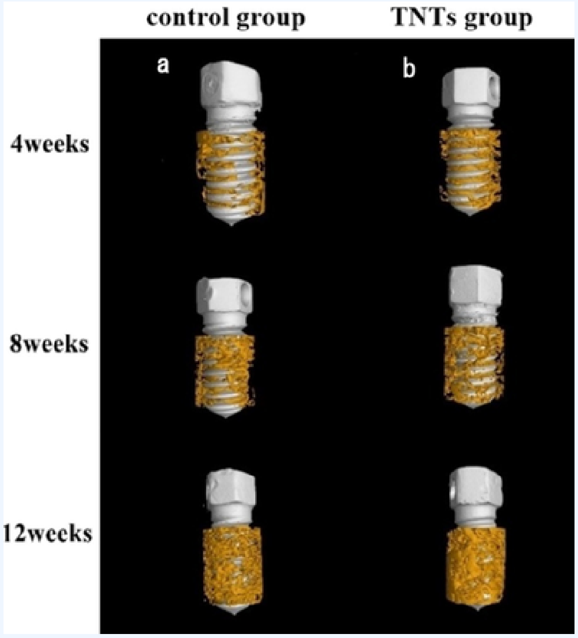

Figure 2: Micro-CT images of bone around control titanium and titanium nanotube surfaces screws at 4-, 8-, and 12-weeks after implantation. This image is modified from the work of Zhang et al[6].

Table 1: Micro-CT quantification of bone around implants at 12 weeks after implantation. This table is modified from the work of Zhang et al[6].

Group	BV/TV	Tb.Th	Tb.N	BS/BV	TB.Sp
Control	21.7 ± 2.6	28.3 ± 4.7	2.1 ± 0.2	9.6 ± 0.4	423.2 ± 23.5
TNTs	25.2 ± 4.1	46.7 ± 6.6**	3.5 ± 0.2**	8.9 ± 1.2	354.1 ± 21.3**

**$p < 0.01$

Conclusion

Diabetes is a pervasive, chronic and progressive disease state that inherently causes bone loss, leading to vascular, neurological and skeletal complications[1-3]. Fractures are common as the disease progresses into osteoporosis, requiring orthopedic implants or amputation if the implants fail to achieve proper healing[1-3]. Titanium nanotubes present a technology upgrade for the orthopedic implants that doesn't rely on drugs or supplements but rather works with the host biology to lower inflammation, recruit vasculature, improve stem cell differentiation to heal and retain bone around the implant[7-9]. In this study, the combination of higher BV/TV, Tb.Th, and Tb.N, together with lower BS/BV and Tb.Sp, indicated more robust bone formation for the nanotube surface than for the control surface under diabatic conditions in the rat model.

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