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Effects of Delayed Release Microsphere of Exenatide on Peri-Implant Bone Response of Diabetic Rats

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Abstract

Objectives: The aim of this study is to evaluate and compare the impact of delayed release microsphere of exenatide on dental implants treatment of diabetic rats.

Materials and methods: 6 male Zucker Diabetic Fatty (ZDF) rats were divided into three groups: GroupA, diabetic rats with dental implants (controls). Group B, diabetic rats treated with exenatide and implants placed simultaneously. Group C, diabetic rats treated with exenatide until serum glucose at a constant level and then implants were placed. Implants with surrounding bone tissues were harvested and bone responses were assessed by histomorphometric analysis.

Results: Osseointegration of all implants had proceeded, bone response to implant surface of one implant in group A was similar to that in group B and C, and implants were surrounded by dense, very compact bone, osteocytes were deposited in lamellar bone in group C.

Conclusion: The present study of dental implants with Diabetes mellitus suggested that the process of osseointegration is affected by diabetes, early osseointegration can be enhanced in individuals with well-controlled diabetes, but the included samples were too small to get a statistical conclusion, further well designed comparative studies are needed to explore the exact effect of diabetes and metabolic control on bone response to dental implants.

Keywords: Dental implants; Osseointegration; Diabetes mellitus; Exenatide; Histomorphometric analysis

Introduction

Dental implant treatment has been proven to be an attractive substitute of traditional fixed or removable prosthetic appliances, which can offer good functional and aesthetic outcomes, and prevent disuse atrophy of the alveolar bone [1-3]. The success or failure rate of titanium implants is directly related to how fast and completely the surrounding tissues grow in close apposition to the implant surface, via the process of osseointegration. Diabetes mellitus (DM) which is characterized by hyperglycemia caused by insufficient insulin action or impaired insulin secretion constitute, the same as many systemic diseases, a contraindication for implant treatment because of its negative impacts on osseointegration [4].

Diabetes mellitus is characterized by hyperglycemia due to insufficient insulin action or impaired insulin secretion. It is well documented that its presence is associated not only with pathophysiological changes in the skeletal system but also impaired bone healing [5,6]. It hampers bone formation and impedes osseointegration significantly. The slower attachment of tissue to the implant surface allows a greater chance for bacterial infiltration, infection and sustained inflammation, leading to a generally poorer outcome for diabetic individuals [7].

Although the influence of Diabetes on dental implants has been widely studied in recent years, there is still controversial discussion [8-13]. According to some researchers, it may decrease the success rate of dental implants because of its pathogenic mechanisms, while some others have different point of view. They thought that implant survival rate could be enhanced when blood plasma glucose level is under control.

The objective of the present study was to evaluate and compare the impact of delayed release microsphere of exenatide on implant treatment of diabetic rats and to compare different glycemic control times on early osseointegration of dental implants. Therefore, diabetic rats with dental implants, diabetic rats treated with delayed release microsphere of exenatide and implants placed simultaneously and diabetic rats treated with exenatide until serum glucose was at a constant level and then implants were placed were compared, implants with surrounding bone tissues were harvested and bone responses were assessed by histomorphometric analysis.

Materials and Methods

Animal preparation

6 male Zucker Diabetic Fatty (ZDF) rats of 3 months old and weighing 400g at the beginning of the experiments were selected. Protocols were approved by the Ethical Board of Animal Investigations (Binzhou medical university, Yantai, China). Animals were maintained in a SPF facility (Shandong Lvye Pharmaceutical Co., Ltd, Yantai, Shandong, China) according to the Institutional Animal Use Review Board. ZDF rats were then divided into three groups and each group

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with 2 rats. GroupA, diabetic rats with 4 dental implants (controls), Group B, diabetic rats treated with Exenatide and 4 implants placed simultaneously and Group C, diabetic rats treated with exenatide until serum glucose at a constant level and then 4 implants were placed.

Delayed release microsphere of exenatide injection

Animals in group C received a subcutaneous injection of delayed release microsphere of Exenatide (0.74 mL/100 g, 0.1 mL/100 g of weight, Shandong Lvye Pharmaceutical Co., Ltd). This kind of microsphere releases exenatide at a steady rate, so we just need to use it every 7 days until the end of this project. 50 days later, as soon as the blood glucose was controlled at a constant level (≤16 mmol/L), dental implants were placed. Animals in group B also received a subcutaneous injection of delayed release microsphere of Exenatide (0.74 mL/100 g, 0.1 mL/100 g of weight, Shandong Lvye Pharmaceutical Co., Ltd), at the same time, dental implants were inserted simultaneously. Control animals received an injection of saline only. Blood glucose levels were detected every 7 days during the whole period by blood samples obtained from the animals tip tail.

Implantation

Rats were anaesthetized with a peritoneal injection of 4% sodium pentobarbital (0.3 ml/100 g body weight). A full-thickness incision was performed on the antero-medial portion of the femur and the implant site was prepared using a 2.3 mm diameter drill under constant irrigation with sterilized physiological saline solution. The implant was then placed (SLA coated, screw, 2.5 × 2 mm, Dentium^{R}, Korea) and confirmed its stability by passive mechanical retention. The wound was closed with conventional sutures. After the surgical procedure, the rats received a single dose of 0.06 ml/kg of penicillin via intramuscular injection for 3 days.

Sample processing and histomorphometric observation

Rats were euthanized at 30, 60 days after implant surgery in batches; there were 2 implants in each group of each time point. Femurs were placed into neutral-buffered formalin. Tissue samples were dehydrated at ascending alcohol grades and embedded in light-curing resin (Technovit 7200 VLC + BPO; Kulzer & Co., Wehrheim, Germany). Block samples were further processed using the Exakt Cutting and Grinding equipment (Exact Apparatebau, Norderstedt, Germany). Thin-ground sections were prepared along the implant axis and stained according to Levai–Laczko [14]. Slices were placed on motor-driven positioning systems (MärzhäuserWetzlar GmbH & Co KG, Wetzlar-Steindorf, Germany) andphotographedusing a digital camera (1 pixel equal to 2.21 mm;DXM 1200, Nikon, Tokyo, Japan) adapted to amicroscope (Nikon Microphot-FXA; Leitz, Germany). Histomorphometric images were analyzed.

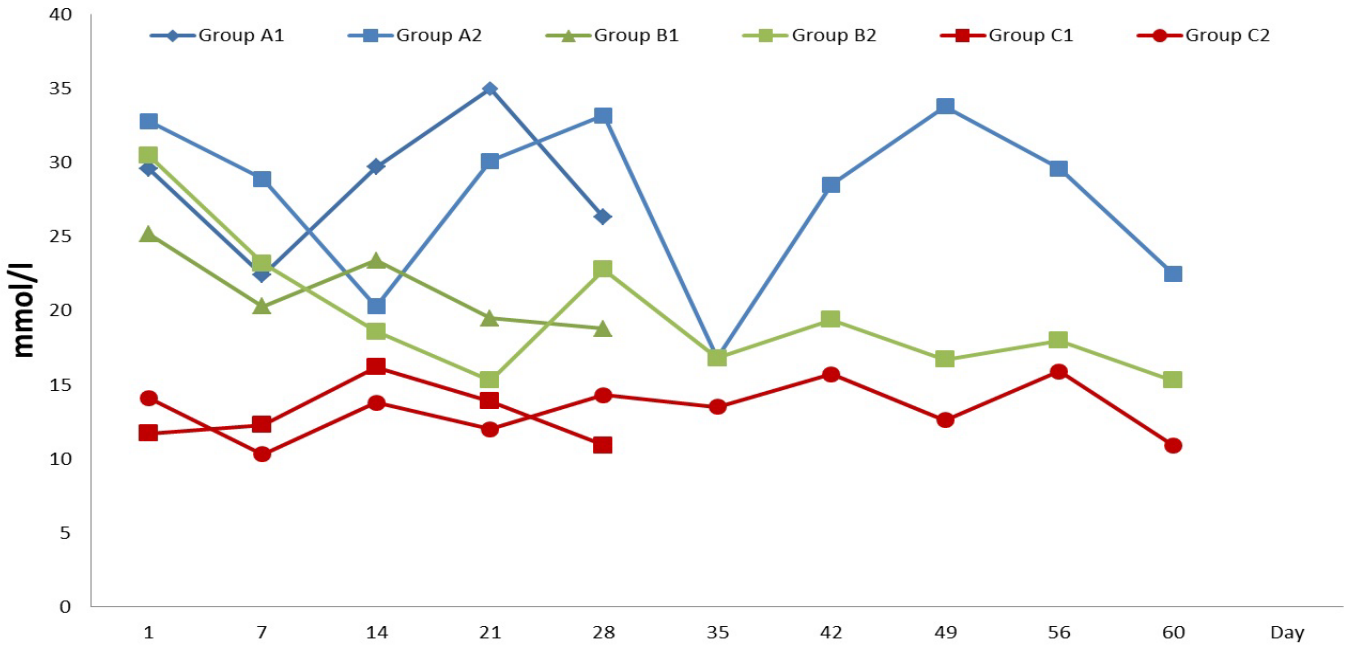
Results

Clinical findings

All of these 6 animals were in good conditions and did not present any disturbance on soft tissue healing or tibiae fractures. No implant was lost during the whole study period. Blood glucose levels of each rat were shown in Figure 1, glucose of animals treated with exenatide was controlled at a constant level in group Band C, while glucose of animals in group A was at very unstable levels.

Histomorphometric observations

30 days after implantation: The light microscopic analysis showed that the bone did not fill the entire space of the threads in group A (Figure 2a), whereas the gap between the pre-existing bone and the implant was filled with a scaffold of newly formed woven bone in group B and C (Figure 2b and 2c). In areas where bone was present, a direct bone-implant contact was seen without presence of intervening fibrous tissues, the implant of group B was surrounded by woven bone, whereas bone in Group C seems more compact and regular, bone close to the implant surface began to remodeling and osteoid was deposited.



Glucose of animals treated with exenatide was controlled at a constant level in group B and C, while glucose of animals in group A was at very unstable levels.

Figure 1: Blood glucose levels of all animals.

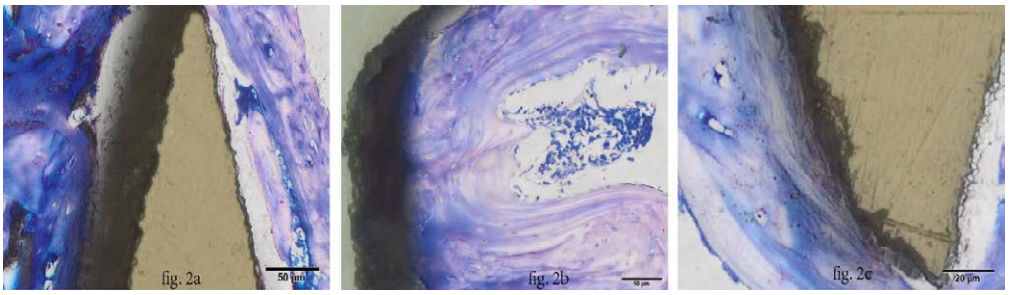


Figure 2: Histomorphometric observations of all groups, 30 days after implantation.

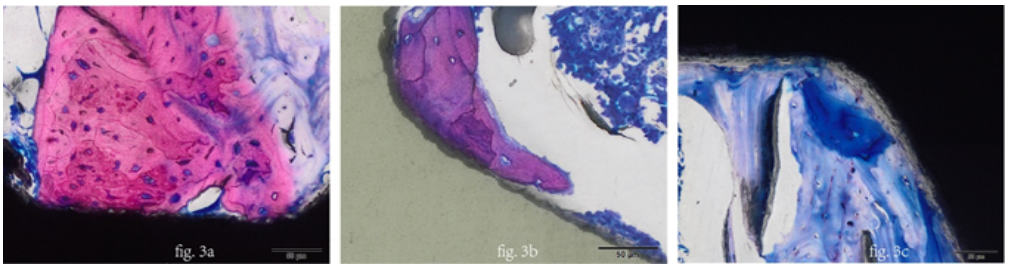


Figure 3: Histomorphometric observations of all groups, 60 days after implantation.

60 days after implantation: Osseointegration of all implants had proceeded, bone response to implant surface of one implant in group A was similar to that in group B and C, and implants were surrounded by dense, very compact bone, osteocytes were deposited in lamellar bone in group C. Cement lines were seen to delineate pre-existing bone and newly formed bone (Figure 3).

Discussion

Diabetes is an increasingly common endocrine disorder characterized by chronic hyperglycemia and tissue compartment abnormalities, including macrovascular and microvascular complications [15]. Previous studies on systemic treatment with insulin have reported controversial results; some studies reported that insulin therapy reversed impaired bone healing through regulating the formation and resorption of bone [16], while some other literatures concluded that traditional method of insulin administration cannot control the release rate and need to be administrated frequently [17-19]. Recently, exenatide was introduced (and has recently been approved in the USA) and reported as a therapy in patients with type 2 diabetes mellitus [20], sustained release microsphere can enhance the convenience, reduce the frequency of injection and can improve compliance and control of hyperglycemia.

In the present study, a delayed release microsphere of exenatide was administrated, animals in groups B and C received a subcutaneous injection of delayed release microsphere of exenatide every 7 days until the end of this project, the results revealed that this kind of microsphere released exenatide at a steady rate, blood glucose in treated groups was controlled at a constant level by once a week of injection of this kind of microsphere.

The influence of diabetes mellitus and metabolic control on dental implants osseointegration has been widely studied in recent years. A systematic literature review summarized the effects of diabetes on dental implant therapy [9], the included studies reported that poorly controlled diabetes negatively affects implant osseointegration, however, under optimal serum glycemic control, osseointegration can successfully occur in patients with diabetes, finally the author concluded that a successful dental implant osseointegration can be accomplished in subjects with diabetes with good metabolic control in a similar manner as in subjects without diabetes. Molon et al. evaluated bone healing around dental implants with established osseointegration in experimental Diabetes mellitus and insulin therapy by histomorphometric and removal torque analysis in a rat model, and found that Diabetes mellitus impaired the bone healing around implants and insulin therapy can prevent the occurrence of bone abnormalities [21].

The histomorphometric observation of this study suggested that exenatide therapy can also improve bone response to dental implants. After 30 days of implant surgery, diabetic rats treated with delayed release microsphere of exenatide revealed a better bone-implant contact and bone formation than diabetic subjects, diabetic rats with well controlled glucose seemed to have a better organized and compact bone than rats with controlling glucose. 60 days after implantation, there was complete bone-implant contact in all groups, newly formed bone was well organized, and bone response in group A was similar to the other two groups or even better.

Conclusion

The present study of dental implants with DM suggested that the process of osseointegration is affected by diabetes, early osseointegration can be enhanced in individuals with well-controlled diabetes, but the included samples were too small to get a statistical conclusion, further well designed comparative studies are needed to explore the exact effect of diabetes and metabolic control on bone response to dental implants.

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References

1. Listgarten MA, Lang NP, Schroeder HE, Schroeder A (1991) Periodontal tissues and their counterparts around endosseous implants. Clin Oral Implants Res 2: 1-19.
2. Higaki N, Goto T, Ishida Y, Watanabe M, Tomotake Y, et al. (2014) Do sensation differences exist between dental implants and natural teeth?: a meta-analysis. Clin Oral Implants Res 25: 1307-1310.
3. Monteiro DR, Silva EV, Pellizzer EP, Filho OM, Goiato MC (2015) Posterior partially edentulous jaws, planning a rehabilitation with dental implants. World J Clin Cases 3: 65-76.
4. Mombelli A, Cionca N (2006) Systemic diseases affecting osseointegration therapy. Clin Oral Implants Res17: 97-103.
5. Delamaire M, Maugendre D, Moreno M, Le Goff MC, Allannic H, et al. (1997) Impaired leucocyte functions in diabetic patients. Diabet Med 14: 29-34.
6. Geerlings SE, Hoepelman AI (1999) Immune dysfunction in patients with diabetes mellitus (DM). FEMS Immunol Med Microbiol 26: 259-265.
7. Retzepi M, Donos N (2010) The effect of diabetes mellitus on osseous healing. Clin Oral Impl Res 21: 673-681.
8. Kotsovilis S, Karoussis IK, Fourmousis I (2006) A comprehensive and critical review of dental implant placement in diabetic animals and patients. Clin Oral Implants Res. 17: 587-599.
9. Javed F, Romanos GE (2009) Impact of diabetes mellitus and glycemic control on the osseointegration of dental implants: a systematic literature review. J Periodontal 80: 1719-1730.
10. Wang F, Song YL, Li DH, Li CX, Wang Y, et al. (2010) Type 2 diabetes mellitus impairs bone healing of dental implants in GK rats. Diabetes Res Clin Pract 88: e7-e9.
11. Courtney MW Jr, Snider TN, Cottrell DA (2010) Dental implant placement in type II diabetes: A review of the literature. J Mass Dent Soc 59: 12-14.
12. Wang B, Song Y, Wang F, Li D, Zhang H, et al. (2011) Effects of local infiltration of insulin around titanium implants in diabetic rats. Br J Oral Maxillofac Surg 49: 225-229.
13. Marchand F, Raskin A, Dionnes-Hornes A, Barry T, Dubois N, et al. (2012) Dental implants and diabetes: conditions for success. Diabetes Metab 38: 14-19.
14. Donath K (1988) The cutting-grinding technique for producing histological preparations of non-cuttable tissue and materials. The Taxidermist 34: 197-206.
15. Kuritzky L, Umpierrez G, Ekoé JM, Mancillas-Adame L, Landó LF (2014) Safety and efficacy of dulaglutide, a once weekly GLP-1 receptor agonist, for the management of type 2 diabetes. Postgrad Med 126: 60-72.
16. Beam HA, Parsons JR, Lin SS (2002) The effects of blood glucose control upon fracture healing in the BB Wistar rat with diabetes mellitus. J Orthop Res 20: 1210-1216.
17. Siqueira JT, Cavalher-Machado SC, Arana-Chavez VE, Sannomiya P (2003) Bone formation around titanium implants in the rat tibia: role of insulin. Implant Dent 12: 242-251.
18. de Morais JA, Trindade-Suedam IK, Pepato MT, Marcantonio E Jr, Wenzel A, et al. (2009) Effect of diabetes mellitus and insulin therapy on bone density around osseointegrated dental implants: a digital subtraction radiography study in rats. Clin Oral Implants Res 20: 796-801.
19. Oates TW, Dowell S, Robinson M, McMahan CA (2009) Glycemic control and implant stabilization in type 2 diabetes mellitus. J Dent Res 88: 367-371.
20. Nielsen LL, Young AA, Parkes DG (2004) Pharmacology of exenatide (synthetic exendin-4): a potential therapeutic for improved glycemic control of type 2 diabetes. Regul Pept 117: 77-88.
21. de Molon RS, Morais-Camilo JA, Verzola MH, Faeda RS, Pepato MT, et al. (2013) Impact of diabetes mellitus and metabolic control on bone healing around osseointegratedimplants: removal torque and histomorphometric analysis in rats. Clin Oral Implants Res 24: 831-837.