Photomedicine and Laser Surgery
Volume 28, Number 3, 2010

Pp. 411–416
DOI: 10.1089/pho.2008.2478

Effect of Biostimulation on Healing of Bone Defects in Diabetic Rats

Utkan Kamil Akyol, Ph.D., and Metin Güngörmüş, D.D.S., Ph.D.

Abstract

Background and Objective: The aim of this study was to investigate the effects of biostimulation on healing of bone defects in diabetic rats. ***Study Design/Material and Methods:*** Twenty-eight Wistar rats weighting 250 to 300 g were used for this study. Diabetes was chemically induced with streptozotocin, and 14 nondiabetic and 14 diabetic rats were included in the study. The distal epiphysis of the right and left femurs of the diabetic rats were perforated with a surgical bone drill. This surgical procedure was performed on the left femurs of normal rats too. The wound on the right side of each diabetic rat received laser stimulation. The left femur of each nondiabetic (normal) rat served as a control. The rats were assigned to three experimental groups: (1) normal bur (control group); (2) diabetic bur; (3) diabetic bur + biostimulation. ***Results:*** There was a significant difference among all groups in substantia spongiosa formation on day 10. According to the Mann–Whitney *U* test, there was a difference between Groups 1 and 2. A significant difference was noted between Groups 2 and 3 as well as between Groups 1 and 3 and between Groups 2 and 3 in union at 20 d of healing. ***Conclusions:*** Substantia spongiosa formation was slightly more evident in Groups 1 and 3 than in Group 2. Also, there was more union in Group 3 than in the other groups on day 20. As a result, it can be concluded that low-level laser therapy (808 nm laser at 10 J/cm^2) can have a beneficial effect on spongiosa in diabetic bone repair when five treatments are administered with 2 d intervals between treatments.

Introduction

Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia and caused by the absence or inefficiency of insulin. High blood glucose may directly affect bone turnover, representing a potential mechanism by which diabetes can affect bone metabolism.[1] Many of the chronic complications of diabetes mellitus involve defects in connective tissue such as reparative bone formation and decreased linear growth.[2,3] It has been reported that the rate of osteon formation and bone mineral density are decreased in patients with diabetes compared with normal patients.[4] Evidence from observational studies suggests that decreased bone strength in diabetes contributes to fracture risk.[5,6]

In recent years, low-level laser therapy (LLLT) has gained considerable recognition and importance among treatment modalities for various medical problems including bone repair processes, musculoskeletal complications, and pain control.[7–9] Several different lasers have been identified as producing a beneficial biological effect. The use of gallium-aluminum arsenide (GaAlAs) diode laser has grown increasingly during the past 15 years. This kind of laser is known to have a high depth of penetration in comparison to other types, and several positive effects have been associated with the GaAlAs laser.[7–9] These effects, collectively called "photostimulation" or "biostimulation," nondestructively alter tissues at the cellular level.[7] Photostimulation increases the synthesis of ATP synthetase, which promotes the production of nucleic acid and accelerates cell division.[10,11] In hard tissues, low-power laser irradiation significantly increases the number of viable osteocytes in the irradiated bone by a positive effect on the bone matrix to produce highly reactive and vital bone tissue.[12] Low intensity laser can also activate repair of damaged bone tissue.[13]

The aim of this study was to investigate the effects of biostimulation on surgically created bone defects and to determine whether laser stimulation can accelerate the healing of bone defects in diabetics.

Material and Methods

Twenty-eight Wistar rats weighing 250–300 g (Ataturk University Faculty of Veterinary Animal Care Unit) were used for this study. The rats were housed two animals per cage in a room with a 12-h light–dark cycle. All animal care and surgeries were carried out in accordance with an

Ataturk University, Faculty of Dentistry, Department of Oral and Maxillofacial Surgery, Erzurum, Turkey.

Table 1. Blood Glucose Levels and Body Weights of Animals

	Blood glucose (mg/100 mL)		*Body weight (g)*	
Group	*Starting*	*Final*	*Starting*	*Final*
Normal	92 ± 1.7	98 ± 2.4	310 ± 5.3	340 ± 4.5
Diabetic	284 ± 3.7	313 ± 4.5	330 ± 5.1	260 ± 6.2

Values given as mean ± SEM.

approved protocol reviewed by Ataturk University Faculty of Veterinary Animal Care and Use Ethic Committee. Animals were given regular standard rat chow and water *ad libitum* throughout the experiment.

Diabetes was chemically induced with streptozotocin (STZ; Sigma, St. Louis, MO, USA), 50 mg/kg, dissolved in citrate buffer (pH 4.5) administrated as a single intraperitoneal injection. The control rats were injected with an equivalent volume of the vehicle (citrate buffer) only. Two days after STZ injection, blood samples were collected from the saphenous vein with a 0.6 mm needle and blood glucose was measured by a glucometer and test strips (Optium Xceed Glucometer; Abbott, Abbott Park, IL, USA). All STZ-injected animals with a blood glucose of 250 mg/dL or more were included in the protocol.[14,15] The surgical procedure was postponed for 2 months until chronic complications of diabetes were evident. Specifically, high glucose levels may lead to a bone metabolism disorder such as osteopenia only when a chronic diabetic stage is reached.[16,17] Fourteen nondiabetic and 14 diabetic rats were included in the analysis.

Before surgery, the blood glucose level and body weight of each rat was checked again (starting blood glucose and body weight) (Table 1). Each rat was anesthetized with ketamine (10 mg/kg) and xylazine (3 mg/kg) intraperitoneally. The right and the left thighs of the diabetic animals were shaved and cleaned with 2% alcoholic iodine solution. Access to the femur was obtained by means of a longitudinal incision 2.0 cm long on the skin and subcutaneous tissue, and a small bone window was opened without cutting muscle tissue. After exposure, the right and the left femur distal epiphysis were perforated with a surgical bone drill (2.5 mm diameter, 3 mm depth), coupled to a micromotor (1500 rpm) under constant refrigeration with sterile 0.9% saline solution. This procedure was performed on the left femurs of normal rats as well. The incisions were then sutured with 3-0 polyglycolic acid. The wound on the right side of each diabetic rat received laser stimulation. The left femur of each nondiabetic (normal) rat served as a control. The rats were assigned to three experimental groups: (1) normal bur (control group); (2) diabetic bur; and (3) diabetic bur + biostimulation.

The Doctor Smile erbium&diode laser (Lambda Laser Products, Vicenza, Italy) was used to induce photostimulation (laser source power 20 W, laser class IV, medical class IIB, network frequency 50 Hz, input power supply 230 ± 10% VAC). The handpieces connecting to the main unit are different for the Er:YAG fiber (for cutting tissues) and for biostimulation (for LLLT). A system of programs allows the

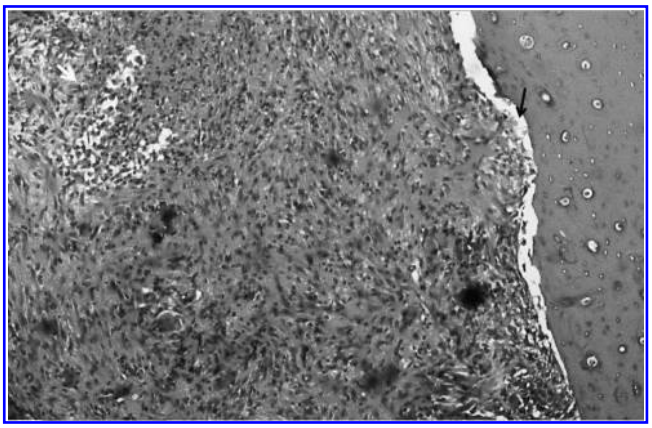

FIG. 2. Photomicrograph of a tissue sample from an animal in the diabetic bur group at day 10. Cavity border (black arrow) and fibrinous material (white arrow) can be seen (H&E, original magnification ×100).

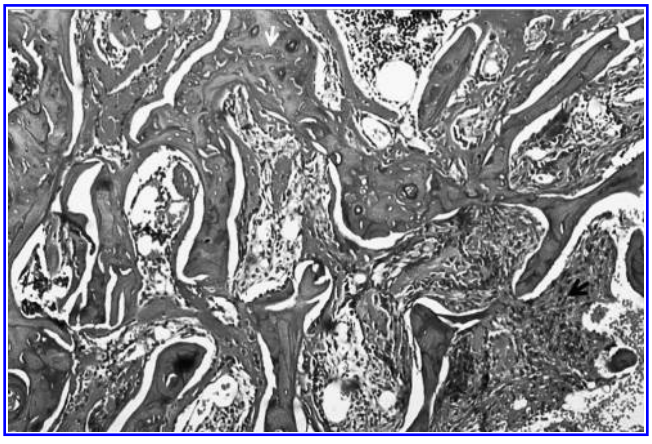

FIG. 1. Photomicrograph of a tissue sample from an animal in the normal bur group at day 10. New bone formation (white arrow) and fibrinous material (black arrow) can be seen (hematoxylin and eosin [H&E], original magnification ×100).

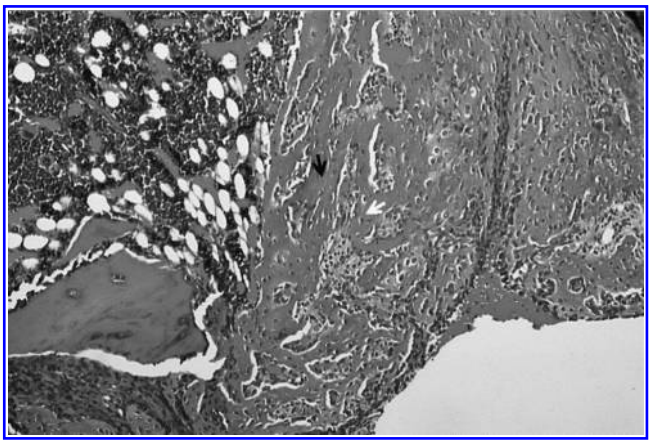

FIG. 3. Photomicrograph of a tissue sample from an animal in the diabetic bur + biostimulation group at day 10. New bone formation (black arrow) and osteoblasts (white arrow) can be seen (H&E, original magnification ×100).

Table 2. The Effect of Biostimulation in Diabetic and Nondiabetic Rats at 10 Days of Healing

	Groups	*Mean*	*SD*	p
Union	Normal bur	1.00	0.00	
	Diabetic bur	1.14	0.37	>0.05
	Diabetic bur + biostimulation	1.14	0.37	
Spongiosa	Normal bur	1.85	0.89	
	Diabetic bur	0.57	0.53	0.012[a]
	Diabetic bur + biostimulation	1.85	0.53	
Bone marrow	Normal bur	1.28	0.48	
	Diabetic bur	1.00	0.00	>0.05
	Diabetic bur + biostimulation	1.00	0.00	
Sum of histologic scores	Normal bur	4.14	1.34	
	Diabetic bur	2.71	0.75	[a]0.033
	Diabetic bur + biostimulation	3.71	0.48	

[a]Statistically significant.

user to choose from preset treatment parameters such as the level of power and type of pulse. Continuous irradiation with a GaAlAs laser (808 nm wavelength) was applied with a power density of 0.1 W/cm^2. Laser irradiation was maintained within a 1 cm^2 biostimulation spot. LLLT was started immediately after surgery and was repeated on days 2, 4, 6, and 8 (five sessions) after surgery with 10 J/cm^2 (total dose, 2 J/cm^2×5). Laser energy was applied for 20 sec (2 J/cm^2) (0.1 W×20 sec/1 cm^2) per session and approximately 1 cm from the surface (hind limbs) of the wound (total 100 sec).

In all rats, fracture of the femur during the preparation of the defects, infection, or death did not occur as a result of high glucose levels. After blood glucose levels and body weights of the rats were measured again (final blood glucose and body weight) (Table 1), the diabetic and nondiabetic rats were killed at days 10 and 20 to compare the bone healing of each group.

Histopathologic study

The femurs were fixed with 10% neutral buffered formalin and they were decalcified in 10% EDTA (ethylenediaminetetraacetic acid). The specimens were embedded in paraffin and sectioned to 5 μm thickness. Histological sections were stained with hematoxylin and eosin (H&E) and examined at a magnification of ×100. The histologic analysis was performed using the histological scoring system developed by Heiple et al.[18] A maximum total score of 20 is possible with this system, considering the proximal as well as distal bone formation in fractures. Because our study had only one-sided bone formation (bone cavity) instead of two-sided, one value for distal or proximal spongiosa was deleted from the scoring system. Therefore scores were obtained up to 16, then statistical analyses of the data were done according to this scoring system. Scoring was carried out by two experts in histology, who were blinded to the treatments.

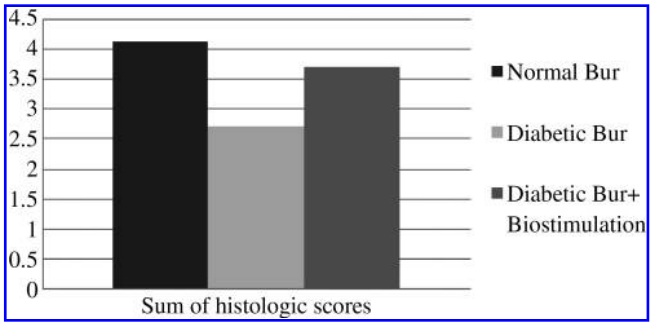

FIG. 4. Sum of histologic scores on day 10.

Statistical analysis

Data were analyzed using Microsoft SPSS 11.0 for Windows (SPSS Inc., Chicago, IL, USA). The differences between the groups were analyzed with the Kruskal–Wallis test. The Mann–Whitney *U* test for pair-wise comparisons was performed when the Kruskal–Wallis test indicated significant differences.

Results

Histological results on day 10

There was fibrous union in Group 1, and in the histological preparation series, there were areas where the development of early and active new bone formation in the substantia spongiosa (internal medullary region of bone) was slightly more evident. There was fibrinous material, identified

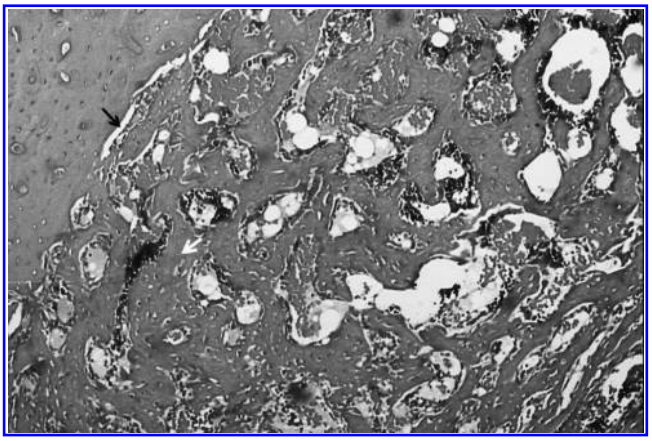

FIG. 5. Photomicrograph of a tissue sample from an animal in the normal bur group at day 20. Cavity border (black arrow) and new bone formation (white arrow) can be seen (H&E, original magnification ×100).

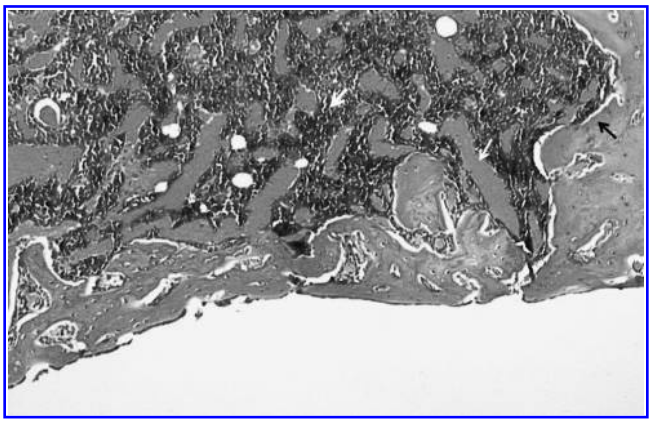

FIG. 6. Photomicrograph of a tissue sample from an animal in the diabetic bur group at day 20. Cavity border (black arrow), fibrinous material (white arrow), and new bone formation (white arrow) can be seen (H&E, original magnification ×100).

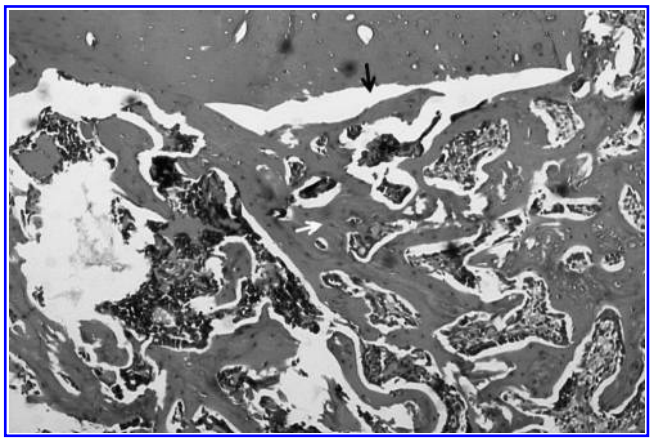

FIG. 7. Photomicrograph of a tissue sample from an animal in the diabetic bur + biostimulation group at day 20. Cavity border (black arrow) and new bone formation (white arrow) can be seen (H&E, original magnification ×100).

as fibrin with many tissue fragments, in most of the cavities of the group (Fig. 1).

In Group 2, there was fibrous union in most of the cavities. In specimens, there was active new bone formation in the substantia spongiosa, and there was fibrinous material in all of the cavities of the group (Fig. 2).

There was fibrous union in all of the specimens of Group 3. Early and active new bone formation in the substantia spongiosa was more evident. There was fibrinous material in all of the cavities of the group (Fig. 3).

Statistically, it was determined that there were significant differences between the three groups in substantia spongiosa formation ($p = 0.012$) (Table 2) and in sum of histologic scores on days 10 ($p = 0.033$) (Table 2, Fig. 4). *Post hoc*, as shown by results of the Mann–Whitney *U* test, there was a difference between Groups 1 and 2 ($p = 0.011$) and Groups 2 and 3 ($p = 0.01$) in substantia spongiosa formation. Also, there was a difference between Groups 1 and 2 ($p = 0.031$) and Groups 2 and 3 ($p = 0.02$) in the sum of histologic scores.

On the other hand, there were no differences between the groups regarding the other parameters such as union and bone marrow ($p > 0.05$) at 10 d of healing. No cortex development was observed in any of the groups at 10 d of healing; therefore, this parameter is not included in the statistical analysis.

Histological results on day 20

In Group 1, there was fibrous union in all of the cavities of the group. The area of early and active new bone formation in the substantia spongiosa was slightly more evident. There was fibrinous material in most of the cavities. Bone marrow occupied more than half of the defect in a few specimens (Fig. 5).

Fibrous union was observed in all of the cavities of Group 2. The area of active new bone formation in the substantia spongiosa was slightly more evident. Fibrinous material was observed in cavities (Fig. 6).

In Group 3, there was osteochondral union in most of the cavities. There were areas of active new bone formation in the substantia spongiosa. Also, reorganized substantia spongiosa formation was observed in a few specimens. There was fibrinous material in Group 3 in most of the cavities (Fig. 7).

Table 3. The Effect of Biostimulation in Diabetic and Nondiabetic Rats at 20 Days of Healing

	Groups	*Mean*	*SD*	p
Union	Normal bur	1.00	0.00	0.001[a]
	Diabetic bur	1.00	0.00	
	Diabetic bur + biostimulation	2.00	0.00	
Spongiosa	Normal bur	1.85	0.89	>0.05
	Diabetic bur	2.14	0.37	
	Diabetic bur + biostimulation	2.42	0.53	
Bone marrow	Normal bur	1.28	0.48	>0.05
	Diabetic bur	1.00	0.00	
	Diabetic bur + biostimulation	1.00	0.00	
Sum of histologic scores	Normal bur	4.14	1.06	0.008[a]
	Diabetic bur	4.00	0.57	
	Diabetic bur + biostimulation	5.42	0.53	

[a]Statistically significant.

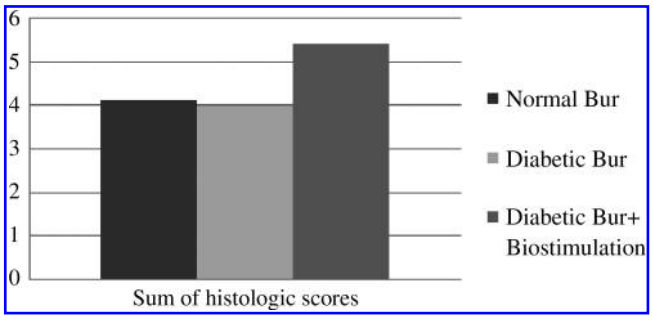

FIG. 8. Sum of histologic scores on day 20.

There was a significant difference between Groups 1 and 3 ($p = 0.0001$) and Groups 2 and 3 ($p = 0.0001$) in union at 20 d of healing (Table 3). Also, it was determined that there was a significant difference between Groups 1 and 3 ($p = 0.024$) and Groups 2 and 3 ($p = 0.002$) in the sums of histologic scores on day 20 (Fig. 8). There were no differences between the groups in substantia spongiosa formation and in bone marrow ($p > 0.05$) at 20 d of healing (Table 3). No cortex development was observed in all of the groups at day 20 and this parameter was not included in the statistical analysis.

Discussion

LLLT is a light source treatment that generates light of a single wavelength. LLLT, when used appropriately, can stimulate the healing of injured tissues.[19] Numerous experimental and clinical trials using LLLT have shown impressive bone healing outcomes, and LLLT has consequently been used extensively in wound management of soft and hard tissue injuries.[20] Although LLLT has previously been used on bone repair,[21] surgically created bony defects,[22] and autogenous bone grafts,[23] its use is not as well documented with regard to bone healing in diabetics. In the present study, it was observed that bone healing was delayed in diabetic rats compared with controls. This might be explained by prospective results of diabetic complication. Mishima et al.[24] demonstrated that STZ-induced diabetes mellitus in the rat results in reduced bone formation rates as well as a reduced number of osteoclasts on the alveolar wall, suggesting that the early stage of diabetes mellitus produces low bone turnover in that wall. Their results agree well with histological descriptions of the changes in the long bones of rats with STZ-induced diabetes.[25] Our findings demonstrated that LLLT has a positive effect on bone healing in diabetic rats. Substantia spongiosa formation was faster in Group 3 than Group 2 at day 10. It should be emphasized that bones in the diabetic group with laser stimulation (Group 3) healed more rapidly than the diabetic group in which a bur alone was used (Group 2).

However, there was a difference between all of the groups in union at 20 d of healing. Bones of the diabetic group with laser stimulation (Group 3) healed more rapidly than those of Groups 1 and 2. This outcome, regarding union, may be explained by LLLT inducing fibrilogenesis, maturation and organization of collagen fibers, osteoblast activity, and organic matrix formation and mineralization, which lead to bone tissue formation.[21,26] Previous investigations support our observations. In an experimental study, Pretel et al.[21] investigated the effects of LLLT on bone repair in rats. They found that the laser group had an advanced tissue response compared to the control group, shortening the initial inflammatory reaction and promoting rapid new bone matrix formation at 15 and 45 d. Khadra et al.[27] examined enhanced bone formation in rat calvarial bone defects using LLLT. This research reported that histological analyses disclosed more pronounced angiogenesis and connective tissue formation, and more advanced bone formation in the biostimulation group than in the controls. Da Silva and Camilli[23] evaluated the effect of laser treatment with at a fluence of 10.2 J/cm^2 on autogenous bone grafts in rats, and the investigators concluded that laser irradiation at the grafted site stimulated osteogenesis during the initial stages of the healing process in a skull defect and that this effect was dose dependent. In our study the energy of the laser employed was in accordance with the average fluence of these studies (10 J/cm^2). The main outcome from these studies is that LLLT has a positive effect on bone healing. Our findings demonstrated that LLLT has a positive effect on bone healing in diabetic rats too. However, there are currently no additional studies that associate laser therapy as a stimulator for bone healing in diabetics.

Conclusion

In the histological preparation series, there were areas where the development of early and active new bone formation in the substantia spongiosa was slightly more evident in Groups 1 and 3 (normal bur and diabetic bur + biostimulation) than in Group 2 (diabetic bur). There were no differences between the groups with regard to the other parameters such as union, bone marrow, and cortex at 10 d of healing.

It was also determined that there was more union in Group 3 (diabetic bur + biostimulation) than the other groups on day 20. There were no differences between the groups regarding the other parameters at 20 d of healing.

As a result, we conclude that LLLT (808 nm laser at 10 J/cm^2) has a beneficial effect on the spongiosa in diabetic bone repair, when used for five treatments at 2 d intervals between treatments. We believe that a 808 nm laser at 10 J/cm^2 can be confidently used in bone healing in diabetic patients.

Acknowledgments

This study was supported by Ataturk University Scientific Research Projects Fund. The authors thank Dr. Havva Erdem and Dr. Cemal Gundogdu (Department of Pathology, Medical Faculty, Ataturk University, Erzurum, Turkey) for their evaluation of the histology slides.

Author Disclosure Statement

No competing financial interests exist.

References

1. Vestergaard, P. (2009). Bone metabolism in type 2 diabetes and role of thiazolidinediones. Curr. Opin. Endocrinol. Diabetes Obes. 16, 125–131.
2. Vestergaard, P., Rejnmark, L., and Mosekilde, L. (2005). Relative fracture risk in patients with diabetes mellitus, and the impact of insulin and oral antidiabetic medication on relative fracture risk. Diabetologia 48, 1292–1299.

3. He, H., Liu, R., Desta, T., et al. (2004). Diabetes causes decreased osteoclastogenesis, reduced bone formation, and enhanced apoptosis of osteoblastic cells in bacteria stimulated bone loss. Endocrinology 145, 447–452.
4. Bechtold, S., Putzker, S., Bonfig, W., et al. (2007). Bone size normalizes with age in children and adolescents with type 1 diabetes. Diabetes Care 30, 2046–2050.
5. Vestergaard, P., Rejnmark, L., and Mosekilde, L. (2009). Diabetes and its complications and their relationship with risk of fractures in type 1 and 2 diabetes. Calcif. Tissue Int. 84, 45–55.
6. Schwartz, A.V. (2003). Diabetes mellitus: does it affect bone? Calcif. Tissue Int. 73, 515–519.
7. Kawalec, J.S., Pfennigwerth, T.C., Hetherington, V.J., et al. (2004). A review of lasers in healing diabetic ulcers. The Foot 14, 68–71.
8. Pires Oliveira, D.A., de Oliveira, R.F., Zangaro, R.A., and Soares, C.P. (2008). Evaluation of low-level laser therapy of osteoblastic cells. Photomed. Laser Surg. 26, 401–404.
9. Torres, C.S., dos Santos, J.N., Monteiro, J.S., et al. (2008). Does the use of laser photobiomodulation, bone morphogenetic proteins, and guided bone regeneration improve the outcome of autologous bone grafts? An in vivo study in a rodent model. Photomed. Laser Surg. 26, 371–377.
10. Ueda, Y., and Shimizu, N. (2003). Effects of pulse frequency of low-level laser therapy (LLLT) on bone nodule formation in rat calvarial cells. J. Clin. Laser Med. Surg. 21, 271–277.
11. Yaakobi, T., Maltz, L., and Oron, U. (1996). Promotion of bone repair in the cortical bone of the tibia in rats by low energy laser (He-Ne) irradiation. Calcif. Tiss. Int. 59, 297–300.
12. Dörtbudak, O., Haas, R., and Mailath-Pokorny, G. (2002). Effect of low power laser irradiation on bony implant sites. Clin. Oral Implants Res. 13, 288–292.
13. Garavello-Freitas, I., Baranauskas, V., Joazeiro, P.P., et al. (2003). Low-power laser irradiation improves histomorphometrical parameters and bone matrix organization during tibia wound healing in rats. J. Photochem. Photobiol. B. 70, 81–89.
14. Karasu, C. (1999). Increased activity of H_2O_2 in aorta isolated from chronically streptozotocin-diabetic rats: effects of antioxidant enzymes and enzyme inhibitors. Free Radic. Biol. Med. 27, 16.
15. Karasu, C., Dewhurst, M., Stevens, E.J., et al. (1995). Effects of anti-oxidant treatment on sciatic nerve dysfunction in streptozotocin-diabetic rats: comparison with essential fatty acids. Diabetologia 38, 129.
16. Frykberg, R.G. (1999). Epidemiology of the diabetic foot: ulcerations and amputations. Adv. Wound Care. 12, 139–141.
17. Alkan, A., Erdem, E., Günhan, O., and Karasu, C. (2002). Histomorphometric evaluation of the effect of doxycycline on the healing of bone defects in experimental diabetes mellitus: a pilot study. J. Oral Maxillofac. Surg. 60, 898–904.
18. Heiple, K.G., Goldberg, V.M., Powell, A.E., et al. (1987). Biology of cancellous bone grafts. Orthop. Clin. North Am. 18, 179–185.
19. Hawkins, D., Houreld, N., and Abrahamse, H. (2005). Low level laser therapy (LLLT) as an effective therapeutic modality for delayed wound healing. Ann. N. Y. Acad. Sci. 1056, 486–493.
20. Bergman, S.A. (2007). Perioperative management of the diabetic patient. Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod. 103, 731–737.
21. Pretel, H., Lizarelli, R.F., and Ramalho, L.T. (2007). Effect of low-level laser therapy on bone repair: histological study in rats. Lasers Surg. Med. 39, 788–796.
22. Nissan, J., Assif, D., Gross, M.D., Yaffe, A., and Binderman, I. (2006). Effect of low intensity laser irradiation on surgically created bony defects in rats. J. Oral Rehabil. 33, 619–624.
23. da Silva, R.V., and Camilli, J.A. (2006). Repair of bone defects treated with autogenous bone graft and low-power laser. J. Craniofac. Surg. 17, 297–301.
24. Mishima, N., Sahara, N., Shirakawa, M., and Ozawa, H. (2002). Effect of streptozotocin-induced diabetes mellitus on alveolar bone deposition in the rat. Arch. Oral Biol. 47, 843–849.
25. Shires, R., Teitelbaum, S.L., Bergfeld, M.A., et al. (1981). The effect of streptozotocin-induced chronic diabetes mellitus on bone and mineral homeostasis in the rat. J. Lab. Clin. Med. 97, 231–240.
26. Nicola, R.A., Jorgetti, V., Rigau, J., et al. (2003). Effect of low-power GaAlAs laser (660 nm) on bone structure and cell activity: an experimental animal study. Lasers Med. Sci. 18, 89–94.
27. Khadra, M., Kasem, N., Haanaes, H.R., Ellingsen, J.E., and Lyngstadaas, S.P. (2004). Enhancement of bone formation in rat calvarial bone defects using low-level laser therapy. Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod. 97, 693–700.

Address correspondence to:
Utkan Kamil Akyol, Ph.D.
Ataturk University, Faculty of Dentistry
Department of Oral and Maxillofacial Surgery
Erzurum, Turkey
Ataturk Universitesi Dis Hekimligi Fakultesi
Cerrahi A.D 25240
Erzurum
Turkey

E-mail: utkanakyol@yahoo.com

This article has been cited by:

1. Tatiane Lopes Patrocínio-Silva, André Moreira Fogaça de Souza, Raul Loppi Goulart, Carolina Fuirini Pegorari, Jussan Rodrigues Oliveira, Kelly Fernandes, Angela Magri, Rosa Maria Rodrigues Pereira, Daniel Ribeiro Araki, Márcia Regina Nagaoka, Nivaldo Antônio Parizotto, Ana Cláudia Muniz Rennó. 2014. The effects of low-level laser irradiation on bone tissue in diabetic rats. *Lasers in Medical Science* **29**, 1357-1364. [CrossRef]
2. Jonas D. Batista, Darceny Zanetta-Barbosa, Sérgio V. Cardoso, Paula Dechichi, Flaviana S. Rocha, Rogério M. Pagnoncelli. 2014. Effect of low-level laser therapy on repair of the bone compromised by radiotherapy. *Lasers in Medical Science* . [CrossRef]
3. Kathrin H. Beckmann, Gesa Meyer-Hamme, Sven Schröder. 2014. Low Level Laser Therapy for the Treatment of Diabetic Foot Ulcers: A Critical Survey. *Evidence-Based Complementary and Alternative Medicine* **2014**, 1-9. [CrossRef]
4. Rodrigo Carvalho Pinto Coelho, Lívia Prates Soares Zerbinati, Marília Gerhardt Oliveira, João Batista Blessmann Weber. 2013. Systemic effects of LLLT on bone repair around PLLA–PGA screws in the rabbit tibia. *Lasers in Medical Science* . [CrossRef]
5. HyukIl Kwon, WonBong Lim, JiSun Kim, SangMi Jeon, SangWoo Kim, Sandeep Karna, HyunRok Cha, OkJoon Kim, HongRan Choi. 2013. Effect of 635 nm irradiation on high glucose-boosted inflammatory responses in LPS-induced MC3T3-E1 cells. *Lasers in Medical Science* **28**, 717-724. [CrossRef]
6. Luciana Batista Pereira, Daniela Thomazatti Chimello, Maidy Rehder Wimmers Ferreira, Luciano Bachmann, Adalberto Luiz Rosa, Karina Fittipaldi Bombonato-Prado. 2012. Low-Level Laser Therapy Influences Mouse Odontoblast-Like Cell Response in Vitro. *Photomedicine and Laser Surgery* **30**:4, 206-213. [Abstract] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links]
7. Daniela Cervelle Zancanela, Fernando Lucas Primo, Adalberto Luiz Rosa, Pietro Ciancaglini, Antonio Claudio Tedesco. 2011. The Effect of Photosensitizer Drugs and Light Stimulation on Osteoblast Growth. *Photomedicine and Laser Surgery* **29**:10, 699-705. [Abstract] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links]