The Effect of Pulsed Electromagnetic Field (PEMF) upon Diabetic Fracture Healing

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INTRODUCTION:

Type I diabetes mellitus (DM) is an autoimmune disease that disrupts the body's ability to produce insulin and thus cannot regulate glucose levels. DM has been associated with impaired fracture healing including cellular proliferation resulting in inferior mechanical properties. Pulsed electromagnetic fields (PEMF) have been used in the clinical setting to enhance fracture healing since the 1970s. However, the precise mechanism by which PEMF works to promote fracture healing is still not known. Animal studies on PEMF used to treat nonunion are scant in the literature, probably because clinical application of the technology moved quickly due to its safety and limited, rare side-effects. Sarker et al concluded that healing of rat tibia was enhanced by the application of PEMF as demonstrated by an increase in rat callus quantity. Therefore, this purpose of this study was to evaluate the role of PEMF upon DM fracture healing. To our knowledge, no studies have tested PEMF for the treatment of fracture on compromised patient populations or animal models with systemic diseases such as DM.

METHODS:

Animals: All animals were used in compliance with the New Jersey Medical School Animal Care and Use Committee. BB Wistar non-diabetic (non-DM) and diabetic (DM) animals were used for this study. DM animals and non-DM animals were monitored for glycosuria and hyperglycemia (blood glucose (BG)). DM animals were implanted with a subcutaneous implant (LINPLANT ®) that contained insulin and palmitic acid. Surgical procedure: A 4mm incision was made over the patella and a 1.1mm 40 gauge Kirschner wire was inserted into the femur. After an intramedullary fixation, a closed, mid-diaphyseal transverse fracture was created with a three-point bending machine which was confirmed by x-ray and the appropriate treatment applied. Rats were free to ambulate freely. One day following surgery, animals were placed for up to 8 hours a day in cages and PEMF treatment applied. Experimental Animal Groups: The animal groups consisted of a non-DM group without PEMF, an insulin treated, poorly controlled diabetic animals with an insulin LINPLANT® without PEMF, and the last group consisted of an insulin treated, poorly controlled diabetic animals with PEMF. Six weeks post-surgery, 2ml of whole blood was collected and glycosylated hemoglobin (HbA1c) levels were determined using the Glyc-AffinGHb kit (Perkin-Elmer Life Sciences, Norton, OH). HbA1c is a time-averaged measure of blood glucose control when compared to normal patients. Local levels of growth factors were measured on day 7 and determined using ELISA assays specific for rat PDGF-AB, TGF-β1,IGF-1 and VEGF. At 6 weeks animals were sacrificed for mechanical testing. Statistical Analysis: Samples were analyzed using Minitab-15. A P value <0.05 was considered significant.

RESULTS:

General health: The blood glucose and HbA1c levels for the non-DM group were significantly lower compared to the DM and DM treated with PEMF groups (Table 1). The BG levels between the DM and DM treated with PEMF groups were not significantly different indicating that PEMF did not alter systemic blood glucose or HbA1c levels. Protein levels: At day 7 PDGF, VEGF, and IGF-1 levels were significantly higher in the DM animals that received PEMF compared to those that did not receive PEMF treatment. Mechanical testing: Six weeks post fracture, the healing femurs of DM, PEMF+ failed at a torque that was significantly greater than that of the DM, PEMF- rats (p=0.035). A significant increase was observed in the stiffness of the healing fractures of DM, PEMF+ compared to DM, PEMF- animals (p=0.013).

Figure 1. (A-C). 6 week radiographs. (A) Non-DM without PEMF (B) DM, PEMF-, and (C) DM, PEMF+

	General Health		
N=6 per group	Average BG	HbA1c	Glycosuria
non-DM PEMF-	82±17[a,b]	7.2±2.2[a,b]	-
DM, PEMF-	340±33	13.3±2.8	+
DM, PEMF+	372±26	13.8±3.4	+

Table 1. General health of animals. The data represent averages ± SD
[a] Represents values statistically lower than DM values, P<0.001.
[b] Represents values statistically lower than DM treated with PEMF values, P<0.05.

	Local Growth Factor Level of Fracture Callus			
N=6 per group	PDGF (pg/mg)	TGF-β1 (pg/mg)	IGF-1 (pg/mg)	VEGF (pg/mg)
non-DM PEMF-	3.1±1.0	17.3±3.5	6.5±1.4	0.68±0.14
DM, PEMF-	1.7±0.6[a,b]	8.7±1.2 [a]	3.1±0.9 [a,b]	0.31±0.1[a, b]
DM, PEMF+	3.0±0.7	6.7±0.2	6.0±0.1	0.57±0.01

Table 2. Protein level of local factors at day 7.
The data represents averages ± SD. These values are normalized to BCA total protein
[a] Represents values statistically lower than non-DM values, P<0.001.
[b] Represents values statistically lower than DM, PEMF+ values, P<0.05.

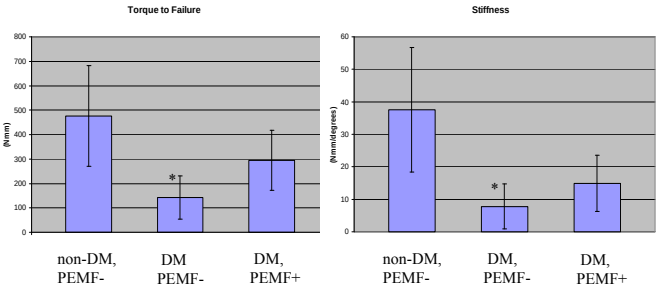

Figure 2. Mechanical Testing. The data represents averages ± SD.* Represents values statistically lower than non-DM, and DM+ PEMF values, P<0.05.

CONCLUSION:

Diabetes impairs the fracture healing process through a series of events, however the mechanism through which diabetes impairs bone healing is currently unknown. Recent studies have demonstrated that PEMF can facilitate fracture healing. The exact method by which endogenous and therapeutic electric fields affect bone formation is not clear. In the present study, local growth factor expression in the fracture callus treated with PEMF was investigated in rats that spontaneously develop insulin-dependent DM. Significant reduction of PDGF, TGFβ-1, IGF and VEGF level occur in the DM, PEMF- fracture callus compared to the non-DM, PEMF-. Rats treated with PEMF significantly increased PDGF,IGF-1, and VEGF levels in the fracture callus as well as an increased stiffness and torque to failure compared to those that did not receive PEMF. To our knowledge, this is the first study looking at the effect of PEMF in diabetic animals. This study confirms the importance of local growth factors, such as PDGF-AB, which play an integral role in the early bone healing.

REFERENCES: Gebauer et al. 2002. *Low-intensity pulsed ultrasound increases the fracture callus strength in diabetic BB Wistar rats but does not affect cellular proliferation.* Gandhi et al. 2005. *The effect of local insulin delivery on diabetic fracture healing.* Gandhi et al. 2006. *The effects of local platelet rich plasma delivery on diabetic fracture healing.* Sarker, et al. 1993. *Effect of PEMF on fresh fracture-healing in rat tibia.*
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