

[Original publication and offprint available in German]

Translation

PULSED SIGNAL
THERAPY (PST)
FOR BONE AND
CARTILAGE FORMATION
– A POSTULATE –

Orthopädische Praxis
9/2004,
40. Jahrgang; 509-511.

Markoll, R.

On the biochemical and biophysical front...

It has long been established that bone possesses electromechanical properties and natural biopotentials that are essential in bone remodelling. These properties were first observed by Yasuda, Fukada, Bassett, Becker and others, who observed that repair and adaptive remodelling processes, occurred in response to mechanical loading, and furthermore, that such responses could be elicited by an electrical stimulus.¹ In light of this, much work has been focused on the application of exogenous electrical currents, including pulsed electromagnetic fields (PEMF's), to emulate the innate physiological and mechanical stresses evoked, and required in bone formation. Nowadays, researchers have expanded their visions, and are focusing on elucidating the mechanism of action of these fields, at the molecular level. Although several hypotheses have been proposed, the primary biochemical and biophysical effects, at the molecular, or ionic, level remain obscure.

Into the biological and biomolecular front...

Endochondral bone formation occurs through a complex series of events, whereby mesenchymal precursors committed to prechondrogenic cells, undergo a series of both morphological and biochemical modifications, in response to extrinsic factors (matrix molecules, growth factors and cytokines), modulated in an autocrine/paracrine manner, to progress from undifferentiated cells to hypertrophic chondrocytes or osteoblasts.² Differentiation therefore, depends on microenvironmental factors. Bone marrow stromal cells (BMSC) have the potential, not only to differentiate into osteoblasts, but into chondrocytes too.³ In fact, they have been extensively demonstrated to have the potential to differentiate into specialized connective tissue cells and to give rise to skeletal tissues.^{3, 4, 5, 6} Several factors, including growth factors, affect BMSC proliferation rate and osteogenic potential^{6, 7}, however, it has never been established whether these **same** factors affect BMSC chondrogenic potential too. In a study by Mastrogiacomo² and colleagues, 2001, FGF2 (fibroblast factor 2), PDGFbb (platelet derived growth factor BB), EGF (epidermal growth factor) and IGF (insulin-like growth factor), were assessed for their affect on BMSC as to affecting

both their osteogenic and chondrogenic potential. It was found that FGF2 was the most effective in maintaining BMSC in an immature state as chondro-osteoprogenitor cells, and that reconstitution of cartilage parallels that of bone.²

And now...

In having established the two scenarios above, it would seem logical to conclude that chondrocytes and osteoblasts respond to similar, and in some cases, identical extrinsic factors, and do so in a parallel manner. If this is so, then one could possibly hypothesize that both would respond to stimulation by PEMF's, and if so, in a parallel fashion (that is, both would respond either positively or negatively). The positive effects of PEMF's stimulation on osteoblasts and chondrocytes, to form bone and cartilage, respectively, are well established in the literature. Of several hypotheses made as to the exact mechanism of action of PEMF's, one suggests that they modulate the activity of primary activators, including hormones (parathyroid hormone, PGE₂, TGF-β1), growth factors (TGF-β1, FGF-2), and cytokines (IL-1), through signal transduction pathways.^{1, 8-14} PTH for example, is known to have direct effects on chondrocyte differentiation, when exposed to PEMF's (recurrent bursts, 15.4 Hz, of shorter pulses of an average of 2G).¹⁵ In the absence of PEMF's, PTH and bone morphogenetic protein (BMP), affect chondrocyte differentiation and proliferation.¹⁶ Not only have PEMF's been shown to have a reproducible osteogenic effect *in vitro*, but have simultaneously been shown to increase messenger RNA (mRNA) expression of BMP-2 and BMP-4 by reverse transcription polymerase chain reaction, in cultured rat calvarial osteoblasts.¹⁷ Hiraki and colleagues¹⁵ observed an increased expression of osteoblastic phenotypes, as a result of field-induced differentiation of rabbit chondrocytes exposed to a clinically effective healing device.

Studies employing different electric field frequencies have demonstrated that bone cells are dependent on frequency in responding to electric fields¹⁸, and that the most effective frequencies lie in the range 10-30Hz - closely resembling the frequencies most often observed in living animal bones.¹⁴ PST unique energy parameters - low biological frequencies (10-20Hz), quasi-rectangular waveform,

measured field strengths (intensity) predominantly in the 0.5 to 1.5 mT range (or 5-15 Gauss) - lie within this effective range, which explains its success in the treatment of chronic pain associated with connective tissue (cartilage, tendon, ligaments and bone) injury, osteoarthritis (OA or Arthrosis) and also in the treatment of joint-associated soft tissue injury (traumatic, including soft tissue injury). Not only has PST been cited in world renown journals, but was patented in the US and Europe, on 25 February 2003, patent number US 6,524,233, for the Electromagnetic Stimulation of Cartilage Tissue.

Meanwhile...

In accordance with the arguments presented here, the use of PST for the treatment of post-menopausal women with osteoporosis is indeed justified. Moreover, PST has been medically approved and certified, as a therapeutic modality for the treatment of Musculoskeletal, and therefore, Connective Tissue, Disorders, – under which Osteoporosis is classified – and is currently employed in 600 Therapy Centers worldwide. Indeed, pilot studies on postmenopausal women with osteoporosis have been met with promising success, as PST appears to stimulate bone formation – an effect parallel to that observed in cartilage regeneration.

Osteoporosis is present in most elderly individuals and is a particular problem in postmenopausal women because it leads to frequent fractures. Weight bearing exercises and increased calcium intake can help, and while several medications are available, improvement is not dramatic and adverse side effects limit their use. In early controlled clinical studies, between 1978 and 1980, of over 100 women, between the ages of 55 and 75 years, with evidence of moderate to advanced osteoporosis, it was observed that PST resulted in a statistically significant increase in mean bone density, of greater than 25 percent, in a randomly selected sample group.

Currently, further studies on postmenopausal women with Osteoporosis, are underway. Corroborating data at the Osteoporose Diagnostik- und

Therapiezentrum München, clearly demonstrate a beneficial and significant trend in improvement, as evidenced by the increase in volumetric bone mineral density (vBMD), after treatment with PST. In addition, patients have reported an associated decrease in pain. The benefits of PST in this regard, are not surprising, owing to its established and documented success in pain management.^{19, 20, 21, 22}

References

1. Spadaro JA. Mechanical and electrical interactions in bone remodeling. *Bioelectromagnetics*. 1997; 18(3): 193-202.
2. Mastrogiacomo M, Cancedda R and Quarto R. Effect of different growth factors on the chondrogenic potential of human bone marrow stromal cells. *Osteoarthritis and Cartilage*, 2001; 9, Supplement A, S36–S40.
3. Johnstone B, Hering TM, Caplan AI, Goldberg VM, Yoo JU. In vitro chondrogenesis of bone marrow-derived mesenchymal progenitor cells. *Exp Cell Res* 1998; 238:265–272.
4. Beresford JN, Bennett JH, Devlin C, Leboy PS, Owen ME. Evidence for an inverse relationship between the differentiation of adipocytic and osteogenic cells in rat marrow stromal cell cultures. *J Cell Sci*. 1992; 102(Pt 2): 341–351
5. Caplan AI, Bruder SP. Mesenchymal stem cells: building blocks for molecular medicine in the 21st century. *Review-Trends in Molecular Medicine*, 2001; 7(6): 259-264.
6. Martin I, Muraglia A, Campanile G, Cancedda R, Quarto R. Fibroblast growth factor-2 supports ex vivo expansion and maintenance of osteogenic precursors from human bone marrow. *Endocrinology* 1997; 138:4456–4462.
7. Muraglia A, Martin I, Cancedda R, Quarto R. A nude mouse model for human bone formation. *Bone* May, 1998; 22(5): (suppl) 131S-134S.
8. Luben RA. Effects of low-energy electromagnetic fields (pulsed and DC) on membrane signal transduction processes in biological systems. *Health Physics* July, 1991; 61(1): 15-28.

9. Chang K, Hong-Shong Chang W. Pulsed electromagnetic fields prevent osteoporosis in an ovariectomized female rat model: A prostaglandin E₂-associated process. *Bioelectromagnetics*. 2003; 24(3): 189-198, 2003.
10. Luben RA, Cain CD, Chen MC, Rosen DM, Adey WR. Effects of electromagnetic stimuli on bone and bone cells in vitro: Inhibition responses to parathyroid hormone by low-energy low-frequency fields. *Proc Natl Acad Sci USA*, July, 1982; 79:4180-4184.
11. Guerkov HH, Lohmann CH, Liu Y, Dean DD, Simon BJ, Heckman JD, Schwartz Z, Boyan BD. Pulsed electromagnetic fields increase growth factor release by nonunion cells. *Clinical Orthopaedics & Related Research*. 2001; (384):265-279.
12. McLeod KJ, Donahue HJ, Levin PE, Rubin CT. Low-frequency sinusoidal electric fields alter calcium fluctuations in osteoblast-like cells. In: Brighton CT, Pollack SR, eds. *Electromagnetics in Biology and Medicine*. San Francisco, CA: San Francisco Press, Inc; 1991:chap 19.
13. Ryaby JT, Fitzsimmons RJ, Khin NA, Culley PL, Magee FP, Baylink DJ, et al. A growth factor-dependent model for magnetic field regulation of bone formation. Presented at the Thirteenth Annual Meeting of the Bioelectrical Repair and Growth Society; October 10-13, 1993; Dana Point, CA. BRAGS; 1993:42.
14. <http://books.nap.edu/books/0309054478/html>
Possible Health Effects of Exposure to Residential Electric and Magnetic Fields (1997), Commission on Life Sciences (CLS)
15. Hiraki Y, Endo N, Takigawa M, Asada A, Takahashi H, Suzuki F. Enhanced responsiveness to parathyroid hormone and induction of functional differentiation of cultured rabbit costal chondrocytes by a pulsed electromagnetic field. *Biochim Biophys Acta*.; Oct 22, 1987; 931(1):94-100.
16. Minina E, Wenzel HM, Kreschel C, Karp S, Gaffield W, McMahon AP, Vortkamp A. BMP and Ihh/PTHrP signaling interact to coordinate chondrocyte proliferation and differentiation. *Development*. 2001 Nov; 128(22): 4523-4534.

17. Bodamyali T, Bhatt B, Hughes FJ, Winrow VR, Kanczler JM, Simon B, Abbott J, Blake DR, Stevens CR. Pulsed Electromagnetic Fields Simultaneously Induce Osteogenesis and Upregulate Transcription of Bone Morphogenetic Proteins 2 and 4 in Rat Osteoblasts in vitro. *Biochemical and Biophysical Research Communications*. 1998; 250:458–461 (ARTICLE NO. RC989243)
18. McLeod KJ and Rubin CJ. Frequency specific modulation of bone adaptation by induced electric fields. *J. Theor. Biol.* 1990; 145: 385-396.
19. Markoll R. Pulsed Signal Therapy: a practical guide for clinicians. In: *Weiner RS, ed. A Practical Guide for Clinicians*. CRC Press. 2001: 715-728.
20. Perrot S, Marty M, Kahan A, Menkés C-J, et al. Efficacy of Pulsed Electromagnetic Therapy in Painful Knee Osteoarthritis (abstract). *Arthritis Rheum.* 1998; 41(3) (suppl): S357
21. Kornhauser SH. Pulsed Signal Therapy: Powerful Pain Relief and Promising Potential: Interview with Dr. Richard Markoll. *Medical Electronics*. 1999; 30(3): pp.44-49.
22. Hershler C, Sjaus A. Pulsed Signal Therapy: Treatment of Chronic Pain due to Traumatic Soft Tissue injury. *International Medical Journal*. 1999; 6(3): 167-173.