



Non-pharmacological treatment of osteoporosis with Nuclear Magnetic Resonance Therapy (NMR-Therapy)

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Summary

Objectives: To demonstrate the long-term effects of the therapeutic use of nuclear magnetic resonance (NMR) on bone mineral density (BMD) parameters in patients with osteoporosis.

Methods: We enrolled 103 patients aged between 45 and 89 years who had osteoporosis with a T-score of bone mineral density less than -2.5. All patients received an osteoporosis treatment with low field nuclear magnetic resonance using a special NMR device (MBST, MedTec, Germany) for one hour per day on 10 consecutive days. At baseline and 12 months after NMR treatment the BMD was measured by DEXA. Additionally, the levels of the bone turnover markers osteocalcin and bone crosslaps (β -CTX; crosslinked telopeptides of collagen 1) were measured by immunoassays.

Results: BMD and serum levels of osteocalcin increased significantly from baseline to 12 months. β -CTX remained stable.

Conclusions: Under therapeutically use of NMR-Therapy, BMD-parameters increased during 12 months after a treatment block (10 x 1h). Therefore, NMR-Therapy can be considered a useful alternative or supplement to medical therapy in patients with osteoporosis.

INTRODUCTION

The bone is metabolically active and constantly being repaired and remodelled.

The disorder osteoporosis is characterised by poor bone strength and increased risk of fractures due to structural deterioration of the bone.

Osteoporosis is getting more and more relevance in health policy.

Based on demographic changes (increase in older population) the amount of people with osteoporosis and its complications like vertebral body or femoral neck fracture will multiply, too. In addition to effective drug therapy non-pharmaceutical treatments with only few or even no side effects are interesting.

Osteoporosis can be prevented and treated. However, it remains underestimated, underdiagnosed and undertreated (1).

Today bisphosphonates are the preferred drug therapy of osteoporosis. The use of bisphosphonates for the treatment of osteoporosis is described as a first-line therapy before any other treatment regime (2, 3). All bisphosphonates are associated with at least partially very harmful side effects, primarily gastrointestinal and kidney diseases are not uncommon in long-term treatment.

TABLE 1

Effect of NMRT on Bone mineral density (DEXA).

T-score		baseline			12 months		significance
area	mean	± SD	median	mean	± SD	median	
L1	-2.0	± 1.23	-2.4	-1.9	± 1.22	-2.1	p < 0.005
L2	-2.2	± 1.07	-2.6	-2.1	± 1.22	-2.2	p < 0.005
L3	-2.3	± 1.30	-2.5	-2.0	± 1.32	-2.0	p < 0.001
L4	-2.1	± 1.48	-2.2	-1.9	± 1.63	-2.3	p < 0.005
neck	-2.1	± 0.87	-2.2	-2.1	± 1.51	-2.0	p < 0.001
troch	-1.4	± 0.91	-1.5	-1.4	± 0.91	-1.4	n.s.
inter	-1.3	± 0.82	-1.3	-1.3	± 0.77	-1.3	n.s.
ward	-2.1	± 0.95	-2.2	-2.1	± 0.91	-1.9	p < 0.05

Result of the BMD measurement by DEXA at baseline and 12 months after NMRT.

L1 – L4 = lumbar spine zone (L1, L2, L3, L4); neck = femoral neck; troch = trochanter; inter = intertrochanteric area; ward = Ward's triangle; mean plus standard deviation and median of T-scores, p indicates significant difference between baseline and 1 year

Latest osteoporosis treatment is done by RANK ligand inhibitors – specific antibodies against signal transduction by „Receptor Activator of Nuclear factor Kappa B Ligand” (RANKL) of osteocytes – which support bone degeneration.

Along with an increase in proliferation of osteoblasts and the associated bone formation a simultaneous decrease in bone degeneration would be desirable.

The development of a noninvasive, nonpharmacological therapy which can provoke positive effects on bone cells, improve function and movement and reduce pain would be valuable. Nuclear Magnetic Resonance (NMR) as a therapeutic form of treatment has already been developed more than 10 years ago; it characterizes a technology that uses NMR to activate cellular metabolism and regenerative processes (4, 5). Clinical studies demonstrate effects of NMR-Therapy (NMRT) on pain relief in degenerative rheumatic diseases (6, 7).

The influence of therapeutic nuclear magnetic resonance therapy (NMRT) on osteocytes depicts an interesting, alternative active principle that is used since several years.

To verify the effect of the therapy of osteoporosis, two parameters can be determined: Bone density and markers for bone turnover.

Accurate determination of changes in bone density is possible by DEXA (Dual Energy X-ray Absorptiometry) measurement.

Bone GLA Protein – also called Osteocalcin, a major noncollagenous bone matrix protein – is only known to be synthesized by bone forming cells. Osteocalcin can be determined in serum by specific enzyme immunoassays and has proved itself as a marker for bone turnover / bone

formation (8). Crosslinked degradation products of collagen serve as degeneration markers. These fragments of collagen can be determined with ELISA (Enzyme Linked Immunosorbent Assay) as peptidbound crosslinks like CTx(BCTX//Cross Laps/Beta-CrossLaps. They describe the resorption activity in the bone. Increased BCTX values in blood indicate enhanced bone degeneration.

METHODS

103 patients (male n = 10, female n = 93) with a mean age of 68.4 years were included in this open trial. The study was performed in the K-Center (Polyclinic / Centre for Osteoporosis and other bone- and joint disorders, head: Prof.Dr.Sc. Dalibor Krpan, Prim.Dr.Med, Zagreb, Croatia).

All enrolled patients suffered from osteoporosis, secured by DEXA measurement (T-score less than -2.5), and were treated 10 days with therapeutic NMRT (one hour treatment per day on 10 consecutive days; using MBST Osteo-System 700, MedTec Inc., Wetzlar, Germany).

All patients have been taking VitD3 800 I.j, continuously, started more than year before they did NMR treatment. Patients never used other drugs for osteoporosis. Times of measurement was baseline and 12 months after NMRT.

Parameters of DEXA measurement: Changes of T-Score, Z-Score, Bone Mineral Density (BMD) of intertrochanteric area, greater trochanter, ward's triangle, femur neck and lumbar vertebra (L1 – L4).

All DXA measurements have been done on the same device by same technician on the DXA device, Discovery, QDR series (Hologic Inc., USA).

Laboratory measurement of Osteocalcin (Osteocalcin (OCN)-Elecys) and Beta cross laps (Elecys Bone Marker Assay CrossLaps have been done from serum by electro-chemoluminescence immunoassays (ECLIA) on a cobas(Elecys-analyzer (Roche Diagnostics International Ltd., Switzerland).

Statistical analysis of data was done by the Ludwig Boltzmann Institute for Rehabilitation of Internal Diseases Saalfelden using the program Sigma Plot 12.3 (SPSS Inc., USA)

RESULTS

A significance analysis with paired t-test resp. Wilcoxon Signed Rank Sum Test showed a significant improvement of T-scores of the lumbar vertebra (L1 – L4) in the patients with osteoporosis (male and female). T-scores at the femoral neck and the ward's triangle also showed significant enhancement from baseline to 12 months after NMRT (Table 1). Mean and median values demonstrate an increase of bone density. No change of T-score could be depicted in greater trochanter and intertrochanteric area.

The change of the T-score at the ward's triangle correlated with a shift of the T-score in the intertrochanteric area and femoral neck. Improved T-score values of the trochanter area are associated with T-score levels of the femoral neck and lumbar vertebra. The difference from baseline to 12 months after NMRT of the T-score in the intertrochanteric area correlated with the T-scores of the femoral neck and lumbar vertebra 3, but not with the residual lumbar vertebrae. An improvement of the T-score values at the femoral neck correlated with all other enhancement of parameters.

The serum levels of the bone turnover marker osteocalcin increased significantly within the 12 months, in average about 55% (Figure 2). Female patients (90%) outweighed males. In the group of male patients (n = 10) no significance for this marker could be detected due to the low number

of cases. The median, which is independent of the relatively broad distribution, also showed a clear enhancement of the osteocalcin concentrations from 14 to 18 ng/ml.

Interestingly, a decrease in BetaCrossLaps-Levels correlates with an increased T-score at the trochanter area.

Crosslaps are fragments of collagen. During bone resorption in osteoporotic processes collagen is degraded and crosslaps (β -CTX) are released into circulation. Elevated levels indicate increased bone loss. We investigated the effects of NMRT on β -CTX in all study patients with osteoporosis. The serum concentrations of Beta-Crosslaps remained stable at 0.3 ± 0.2 (baseline as well as after 12 months) and did not increase during 1 year, indicating that there was no enhanced bone loss after NMRT.

DISCUSSION

A DEXA measurement, the „gold standard” in osteodensitometry (9), offers good precision and low radiation exposure. The measurement points at the lumbar spine and the hip (proximal femur/trochanter area) are the most prevalent used. Hence, these sites comprising femoral neck, intertrochanteric area, ward's triangle and trochanter were included in the presented determinations.

Currently the WHO recommends measuring the BMD of the spine and proximal femur by DEXA to diagnose Osteoporosis (10).

Osteoporosis is a disorder that often leads to significant morbidity when untreated.

Denosumab, a monoclonal antibody to RANKL, given twice a year, reduces the risk of vertebral, non-vertebral and hip fractures in osteoporosis parallel to a percent range in BMD of 6 % (lumbar spine) respectively 3 % (total hip) after 12 months therapy (11). The significant improvements of BMD by bisphosphonates amount to 2.4 – 3.7 % (risedronate or alendronate) at the hip resp. 4.2 – 6 % at the lumbar spine after 24 (not 12!) months

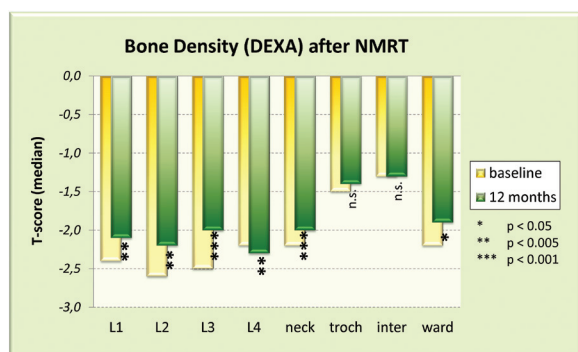


Figure 1. DEXA assessment of BMD (T-score) in 103 patients with osteoporosis before and 12 months after NMRT. * indicates significant changes

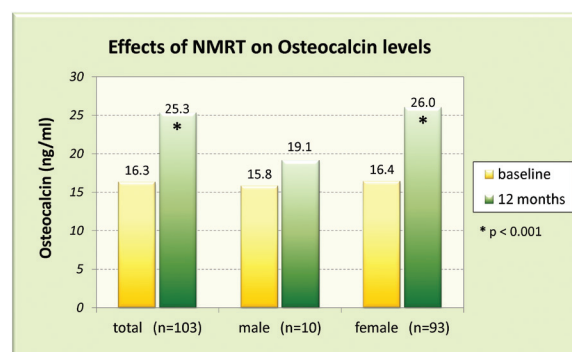


Figure 2. Osteocalcin levels in serum of patients with osteoporosis at baseline and 12 months after NMRT in the total group and divided in males and females;

(12). During one year surprisingly, the NMR therapy enhanced the BMD by the same percentage range or more (up to 10 %). *Ipsa facto*, in any case the physiological bone loss up to 4 % can be more than offset by NMRT!

12 months after NMRT, the bone density (DEXA) was significantly higher and the bone formation parameter Osteocalcin increased as well (Figure 1, 2). Osteocalcin levels are consistently related to the level of bone formation and therefore it is a sensitive marker in osteoporosis (13). In most cases of osteoporosis normal or slightly reduced values of Osteocalcin are found and the discrimination between different groups is rather poor, but a clear correlation exists with spontaneous bone loss (14, 15).

It is not routinely recommended to use bone turnover markers (BTMs) but baseline measurements of bone markers can be checked 3-6 months later to monitor response to treatment (8).

It is interesting that one year after NMR therapy there could be observed a significant increase of the Osteocalcin levels ($p < 0.001$) in the total population as well as in female patients who account for 90 % of the total collective.

The small changes of Cross-Laps indicate unaltered bone degeneration.

A large body of evidence indicates that pulsed electromagnetic fields, a safe and non-invasive method, could promote osteogenesis. The FDA, USA approved therapy with pulsed electromagnetic fields as an effective method for osteoporosis therapy (16). Therapy with PEMF is frequently confused with nuclear magnetic resonance therapy which varies physically significant from PEMF by another magnetic field structure and the additional radio frequency. PEMF could also prevent bone loss through regulating the cytokine expression of RANKL and OPG in bone cells (17).

In a recent study the inhibitory effects of PEMF on osteopenia in rats with disuse-induced bone loss could be demonstrated by increased mineral apposition and bone formation rates over promotion of the genes of Wnt1, OPG, Osteocalcin, LRP5 and others (18). In contrast other research groups found no support for the use of PEMF in the treatment of osteoporosis (19).

Investigations of our working group detected influences of the NMR-Therapy on the NFAT metabolism of osteo- and chondrosarcoma cells (20). PEMF might also modulate the process of osteoclastogenesis and subsequent bone resorption, at least through NFAT Carbonic Anhydrase II (CAII) and RANK (21).

Therapeutic nuclear magnetic resonance in medicine characterizes a novel technology that makes use of NMR to activate metabolic processes and to indicate regenerative processes in specifically selectable cellular tissue. The technology of these therapeutic nuclear magnetic devices

differs to those using only static or pulsed magnetic fields. The easy-to-use therapeutic method for regenerative stimulation of disturbed and irreparable cell processes is directly based on the technology behind NMR imaging (=MRI). The biological effect of this technology is based on the knowledge that cell functions are only possible if energy supply is assured. Deficient energy flow in endogenous regeneration processes unavoidably leads to cell death. To prevent such conditions, the incurred energy deficit has to be compensated by suitable measures (e.g. nuclear magnetic resonance).

The application of 1 hour NMR-Therapy a day on 10 consecutive days has been found to be efficient.

Although in Germany NMR-Therapy is successfully adapted for the treatment of osteoporosis already more than 10 years, only a few clinical studies exist.

A comparable study to our investigations with DEXA measurements is a trial of a German group who explored the bone density with QCT (quantitative computer tomography) 6 months after whole-body-NMRT (10 x 1h). After 6 months, a significant growth of the bone mineral content ($p < 0.05$) was manifested in the NMR group but not with bisphosphonates in the comparison group. Parallel, the scores Osteoporosis Quality of Life Questionnaire, Fairbank Score and Roland & Morris Disability Questionnaire were reduced significantly under NMR-therapy (22).

To access NMRT on cellular processes, investigations of our own research group could demonstrate in microarray experiments modulating NMR effects on the regulation of NFAT (Nuclear Factor of Activated T-cells) metabolism and the Ca²⁺ release in osteosarcoma cell lines (20, 23).

As the annual bone loss amounts physiologically to 0.5 – 1 % and can rise up to 4 % postmenopausally (24), a non-drug therapy like NMRT which has shown (by DEXA measurement) to improve significantly decreased bone density can be a useful alternative or supplement to medical therapy in osteoporosis.

However, a randomized double blinded controlled trial is warranted to confirm the effects of NMR-Therapy on osteoporosis.

REFERENCES

1. DUQUE N 2014 Ostéoporose: traitement et soins pharmaceutiques [Osteoporosis: treatment and pharmaceutical care] (French Article). *J Pharm Belg* 2: 14-24
2. KAMEL H K 2007 Update on Osteoporosis Management in Long-term Care: Focus on Bisphosphonates. *J Am Med Dir Assoc* 8: 434-440
3. National Osteoporosis Foundation. Fast Facts. <http://nof.org/osteoporosis/diseasefacts.htm>. Accessed July 28, 2006.
4. TEMIZ-ARTMANN A, LINDER P, KAYSER P, DIGEL I, ARTMANN G M, LÜCKER P 2005 NMR in vitro

- effects on proliferation, apoptosis, and viability of human chondrocytes and osteoblasts. *Methods Find Exp Clin Pharmacol* 27(6): 391-4
5. STEINECKER-FROHNWIESER B, WEIGL L, WEBERHOFER G, KULLICH W, KRESS HG 2014 The Influence of Nuclear Magnetic Resonance Therapy (NMRT) and Interleukin IL1- β Stimulation on Cal 78 Chondrosarcoma Cells and C28/I2 Chondrocytes. *J Orthopedics Rheumatol* 1(3): 9 <http://www.avensonline.org/wp-content/uploads/2014/05/JOR-2334-2846-01-0010.pdf>
 6. LEVERS A, STAAT M, van LAACK W 2011 Analyse der Langzeitwirkung der MBST® Kernspinresonanz Therapie bei Gonarthrose. *Orthopädische Praxis* 47(11), Sonderdruck.
 7. KULLICH W, OVERBECK J, SPIEGEL H U 2013 One-year-survey with multicenter data of more than 4.500 patients with degenerative rheumatic diseases treated with therapeutic nuclear magnetic resonance. *J Back Musculosk-elet Rehabil* 26(1): 93-104
 8. WHEATER G, ELSHAHALY M, TUCK SP, DATTA H K, van LAAR JM 2013 The clinical utility of bone marker measurements in osteoporosis. *J Transl Med* 11: 201
 9. RINGE J (ed.) 2003 Osteoporose Dialog. Thieme Verlag, Stuttgart, New York.
 10. KANIS J A, McCLOSKEY E V, JOHANSSON H, ODEN A, MELTON L J, KHALTAEV N 2008 A reference standard for the description of osteoporosis. *Bone* 42: 467-475
 11. CUMMINGS S R, San MARTIN J, McC LUNG M R, SIRIS E S, EASTELL R et al. 2009 Denosumab for Prevention of Fractures in Postmenopausal Women with Osteoporosis. *N Engl J Med* 361(8): 756-65
 12. REIS D M, HOSKING D, KENDLER D, BRANDI M L, WARK J D et al. 2008 A comparison of the effect of alendronate and resedronate on bone mineral density in postmenopausal women with osteoporosis: 24-month results from FACTS-International. *Int J Clin Pract* 62(4): 575-584
 13. DELMAS P D, CHRISTIANSEN C, MANN K G, PRICE P A 1990 Bone Gla Protein (Osteocalcin) Assay Standardization Report. *J Bone Min Res* 5(1): 5-11
 14. SEIBEL M J, RAUE F 1993 Biochemische Marker des Knochenstoffwechsels und ihre Bedeutung bei der Osteoporose-Diagnostik. Stellungnahme der Sektion „Calcium-regulierende Hormone und Knochenstoffwechsel“. *Endokrinol Invest* 17: 18-22
 15. SEIBEL M J 2003 Biochemical markers of bone metabolism in the assessment of osteoporosis: useful or not? *J Endocrinol Invest* 26(5): 464-471
 16. BASSETT C A 1989 Fundamental and practical aspects of therapeutic uses of pulsed electromagnetic fields (PEMFs). *Crit Rev Biomed Eng* 17: 451-529
 17. ZHOU J, CHEN S, GUO H, XIA L, LIU H, QIN Y, HE C 2013 Pulsed electromagnetic field stimulates osteoprotegerin and reduces RANKL expression in ovariectomized rats. *Rheumatol Int* 33(5): 1135-1141
 18. JING D, CAI J, WU Y, SHEN G, LI F, XU Q, XIE K, TANG C, LIU J, GUO W, WU X, JIANG M, LUO E 2014 Pulsed electromagnetic fields partially preserve bone mass, microarchitecture, and strength by promoting bone formation in hindlimb-suspended rats. *J Bone Miner Res* 29(10): 2250-2261
 19. van der JAGT O P, van der LINDEN J C, WAARSING J H, VERHAAR J A, WEINANS H 2012 Systemic treatment with pulsed electromagnetic fields do not affect bone microarchitecture in osteoporotic rats. *Int Orthop* 36(7): 1501-1506
 20. KULLICH W, WEIGL L, STEINECKER B, KRESS H G 2009 NFAT-Modulation in Knochen- und Knorpelzellen durch therapeutische Kernspinresonanz. <http://www.egms.de/static/en/meetings/dkou2009/09dkou591.shtml>
 21. HE J, ZHANG Y, CHEN J, ZHENG S, HUANG H, DONG X 2014 Effects of pulsed electromagnetic fields on the expression of NFATc1 and CAII in mouse osteoclast-like cells. *Aging Clin Exp Res* 29: PMID: 24869857
 22. HANDSCHUH T, MELZER C 2008 Behandlung der Osteoporose mit MBST® KernSpin. *ORTHODOC* 5 (Sonderdruck): 1-4
 23. STEINECKER-FROHNWIESER B, WEIGL L G, HÖLLER C, SIPOS E, KULLICH W, KRESS H G 2009 Influence of NMR therapy on metabolism of osteosarcoma- and chondrosarcoma cell lines. *Bone* 44(2): 295
 24. BARTL (ed.) 2004 Osteoporose: Prävention – Diagnostik – Therapie. Thieme Verlag, Stuttgart, New York