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In Vivo Over-expression of Circulating Dlk1/Pref-1 Protein Using Hydrodynamic-based Gene Transfer Leads to Lower Bone mass With Marked Effects on Trabecular Bone Micro-architecture

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In Vivo Over-expression of Circulating Dlk1/Pref-1 Protein Using Hydrodynamic-based Gene Transfer Leads to Lower Bone mass With Marked Effects on Trabecular Bone Micro-architecture

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Dlk1/Pref-1 (delta like1/preadipocyte factor-1) is an imprinted gene encoding a transmembrane protein that belongs to EGF-like repeats protein family. We have recently identified Dlk1/Pref-1 as negative regulator for differentiation of human mesenchymal stem cells into osteoblasts and adipocytes (Abdallah BM, et. al., JBMR, May,19(5):841-852, 2004). To further investigate the in vivo effect of Dlk1/Pref-1 on bone, we generated mice expressing high serum levels of FA1 (biological soluble form of Dlk1) using the hydrodynamic-based gene transfer procedure. Full length of mouse Pref-1 cDNA was subcloned under human ubiquitin promoter and rapidly injected via tail vein into BALB/cA male mice (16 weeks old, n=15) every 2 weeks over a period of 2 months. DNA, mRNA analysis, immunohistology and ELISA for FA1 were assayed to identify the expression of the transgene. Bone mass and structure were determined by PIXImus (Lunar^R) and micro-CT (Scanco^R) respectively. We could only localize the plasmid in the liver and no complications were detected due to transgene expression. Serum levels of FA1 in Dlk1 injected mice (Dlk1⁺mice) was elevated by more than 15 folds compared to control saline injected mice (control) (198.0 ± 74.3 ng/ml vs 13.4 ± 1.1 ng/ml, $p < 0.001$, respectively). Dlk1⁺mice displayed lowered body weight and reduced total fat mass (13.5%, $p < 0.05$ and 17.8%, $p < 0.05$ respectively). Interestingly, Dlk1⁺mice displayed (16.6 %, $p < 0.005$) lowered total bone mineral density (BMD) compared to controls and BMD was negatively correlated with the circulating levels of FA1. Micro-CT analysis revealed significantly decreased micro-architectural parameters of trabecular bone in the distal femur and proximal tibia of the Dlk1⁺mice compared to controls (see table).

Naked DNA delivery by hydrodynamic injection is a simple and safe procedure for evaluating the effect of genes on bone phenotype in vivo. Our data suggest that Dlk1/Pref-1 is a novel regulator of bone mass.

Groups (n=8)/ Measurments	BV/TV	TbTh (μ m)	TbSp (μ m)	TbN (1/mm)	CD (1/mm ³)
Distal femur					
Control group	0.34 \pm 0.11	0.07 \pm 0.01	0.19 \pm 0.03	5.80 \pm 1.10	155.1 \pm 37.4
Dlk+ group	0.19 \pm 0.06	0.06 \pm 0.00	0.24 \pm 0.04	4.60 \pm 0.84	113.3 \pm 37.8
Proximal Tibia					
Control group	0.20 \pm 0.07	0.07 \pm 0.01	0.24 \pm 0.04	4.60 \pm 0.57	98.6 \pm 21.27
Dlk+ group	0.14 \pm 0.03	0.06 \pm 0.01	0.25 \pm 0.02	4.26 \pm 0.42	75.5 \pm 25.7

$P < 0.05$ for all tested parameters

TbTh, Sp, N=trabecular thickness, space, number, CD=connectivity

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