Vitamin D receptor signaling prevents long-term glucocorticoid induced bone fragility by preserving several components of bone quality

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Bone fracture incidence with excess of glucocorticoids (GC) surpasses the risk predicted by the loss of bone mineral density (BMD), implicating GC effects on other determinants of bone quality such as microarchitecture, remodeling rate, degree of collagen mineralization, and mechanical properties of collagen fibrils. We showed earlier that ligands of the vitamin D receptor (VDR) prevent GC-induced BMD loss. We investigated here their effect on bone fragility at the tissue, micro, and nanoscale levels. Skeletally mature 4mo C57Bl6 female mice (N=10) received for 8wks placebo or GC (2.1 mg/kg/d prednisolone pellets), and vehicle, $1,25D_3$ or eldecalcitol-71 (ED) (50ng/kg/d 5x/wk, gavage, starting 3d prior pellet implantation). GC decreased the structural (extrinsic) properties ultimate force, energy to ultimate load, and stiffness by ~20%, and the material (intrinsic) properties ultimate stress and toughness ~17%, tested by femoral 3-point bending. VDR ligands did not affect mechanical properties, but prevented all GC effects; although $1,25D_3$ increased ultimate force and GC decreased this index even with $1,25D_3$. We then investigated the mechanisms underlying bone strength preservation by the VDR ligands. GC-induced microarchitectural deterioration in cancellous bone (low BV/TV and Tb.N, and increased Tb.Sp) was fully prevented by the ligands. In contrast, ED fully protected from GC-induced cortical bone deterioration (low Ct.Ar/Tt.Ar, Ct.Th, and Ct.Ar, and increased Ma.Ar), but $1,25D_3$ did not. Regarding bone remodeling, both VDR ligands prevented GC-induced resorption, quantified by circulating CTX and osteoclast number/surface; and ED by itself markedly decreased resorption. In contrast, the VDR ligands did not prevent GC-induced reduction in bone formation, quantified by circulating P1NP, osteocalcin, and MS/BS and BFR. Consistent with the effects on resorption, GC decreased material density measured by micro-CT and the VDR ligands prevented this effect. Small-Angle X-ray Scattering (SAXS) with *in situ* tensile testing showed a GC-dependent increase in bone deformation (ultimate and yield strain), which was prevented by the VDR ligands. Further, VDR ligands alone decreased tissue ductility. Moreover, GC transferred strain away from collagen fibrils increasing collagen ductility, which was prevented by VDR ligands. These findings demonstrate that VDR signaling prevents GC-induced bone fragility by preserving bone mass and several key components of bone quality.

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