Vitamin D and Fracture Healing

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Vitamin D and Fracture Healing

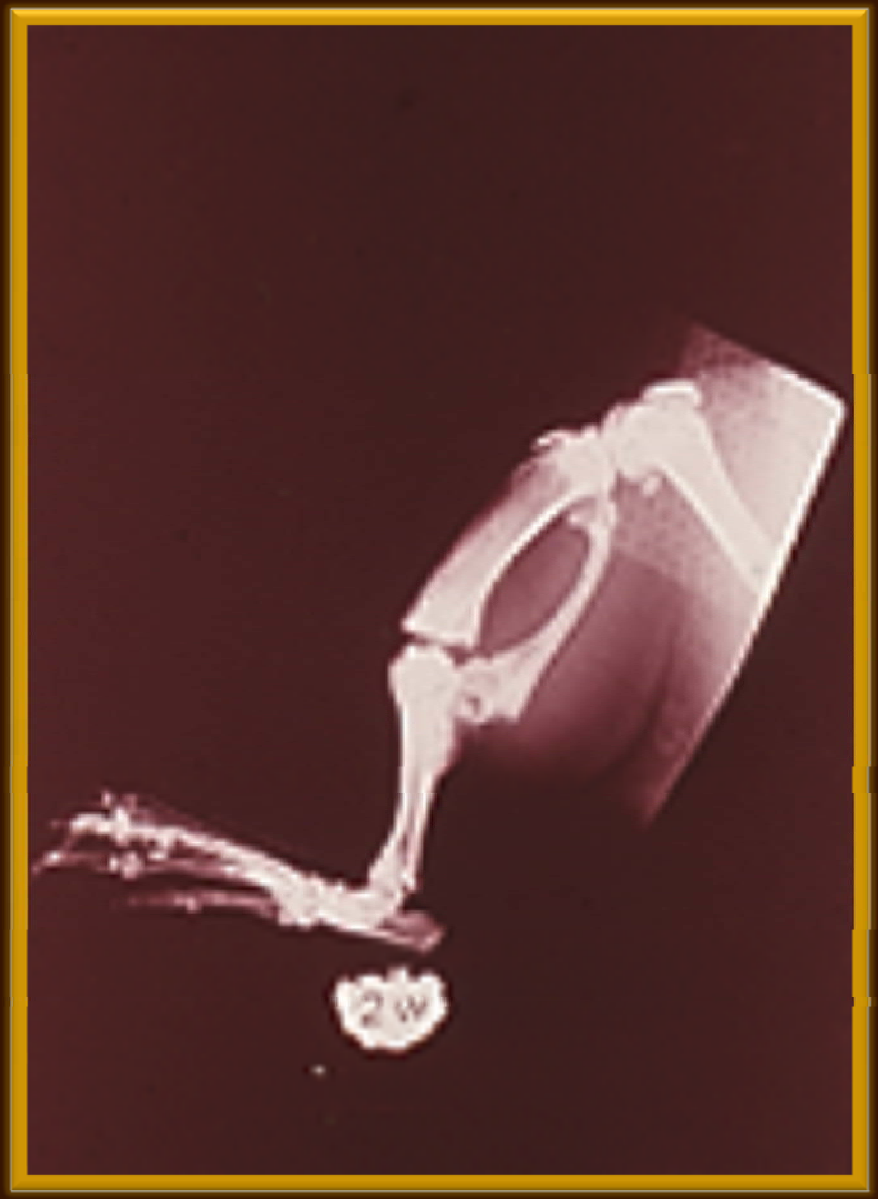
1. Physiology of Fx Healing
2. Clinical Studies of Vitamin D and Fx Prevention
3. Experimental Studies of Vitamin D and Fx Healing

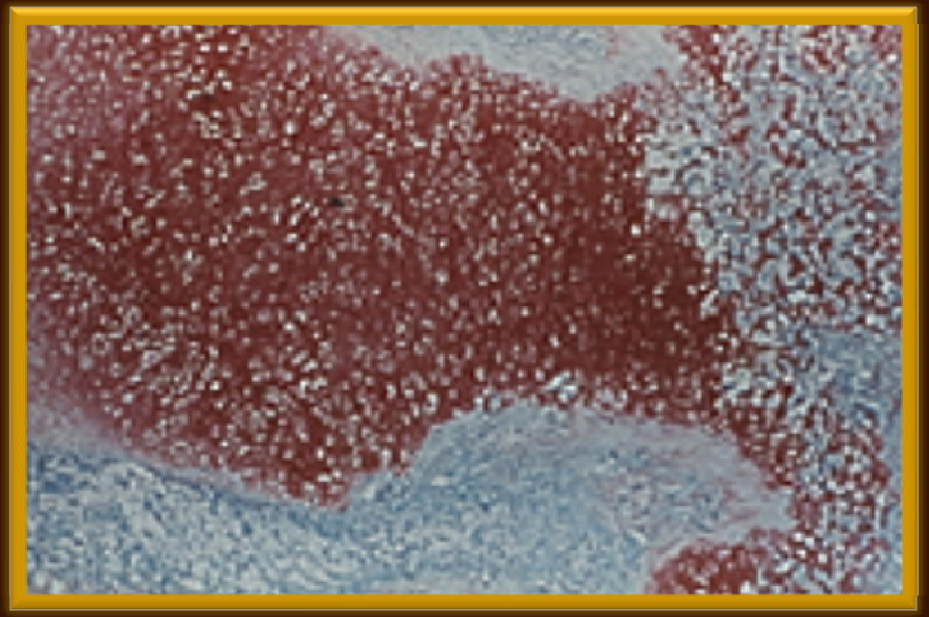
1. Inflammation/Hematoma
2. Chondrogenesis
3. Endochondral Ossification
   - Chondrocyte Hypertrophy
   - Angiogenesis
   - Mineralization

Coagulation

PDGF

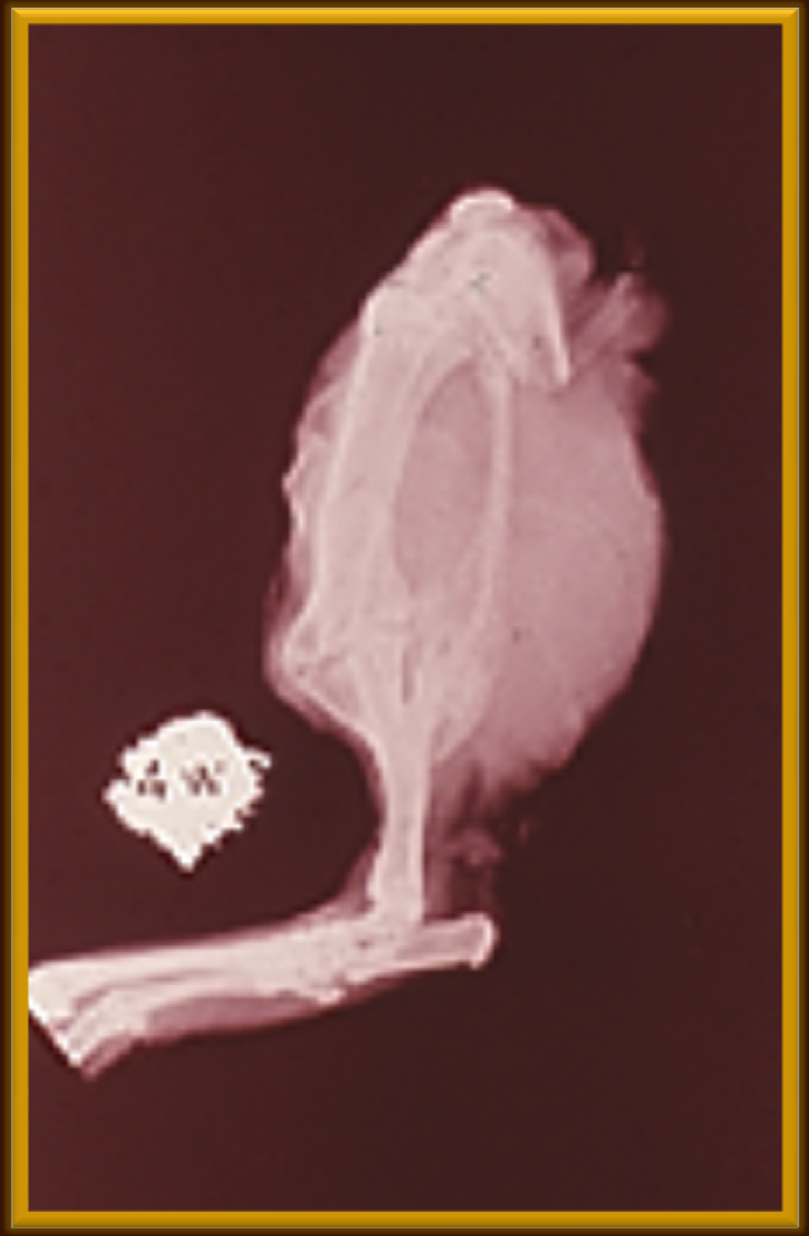
TGF-β

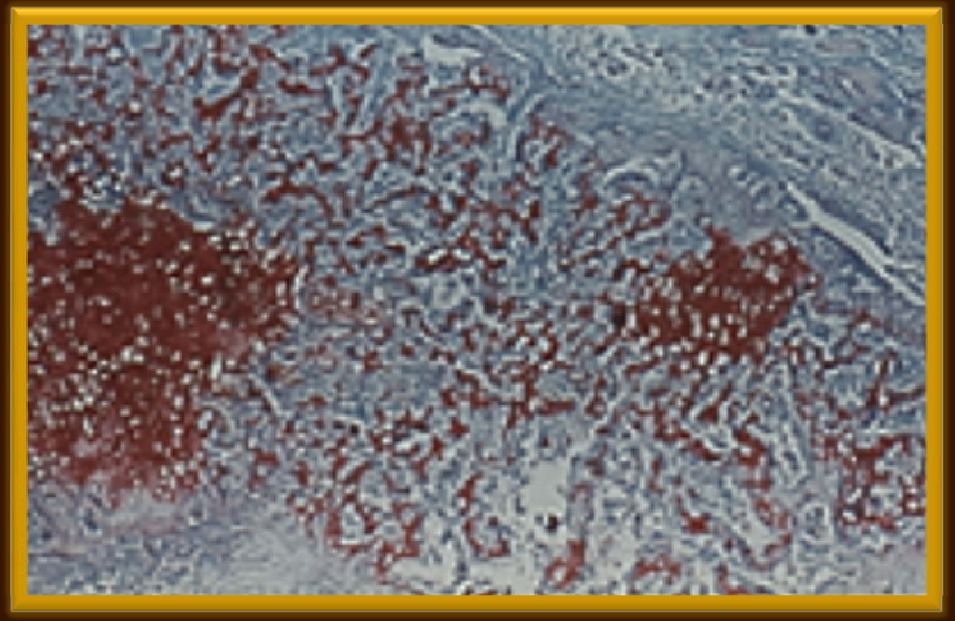




BMP 2,4,7

TGF-β



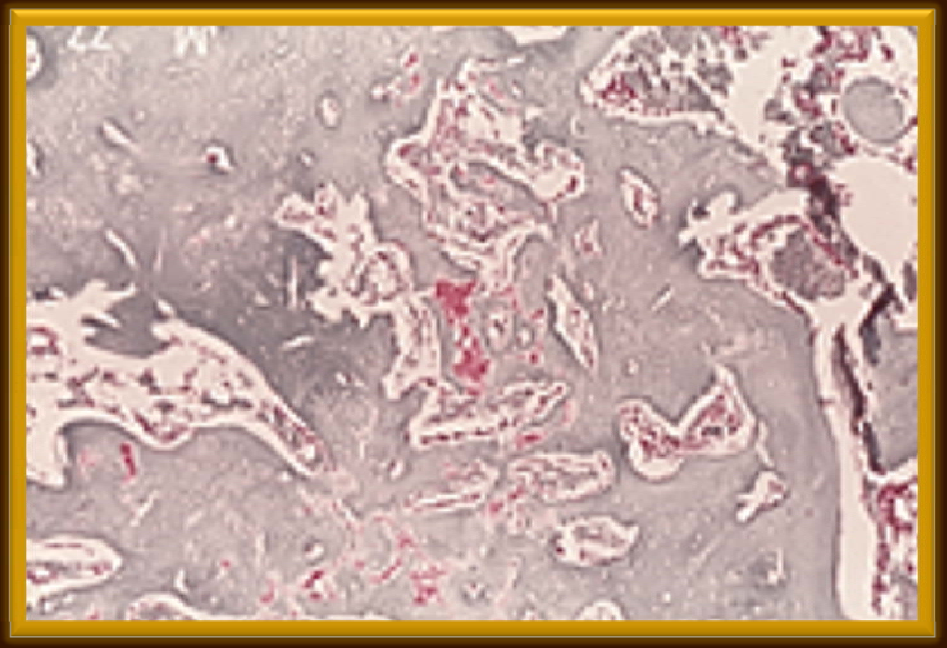


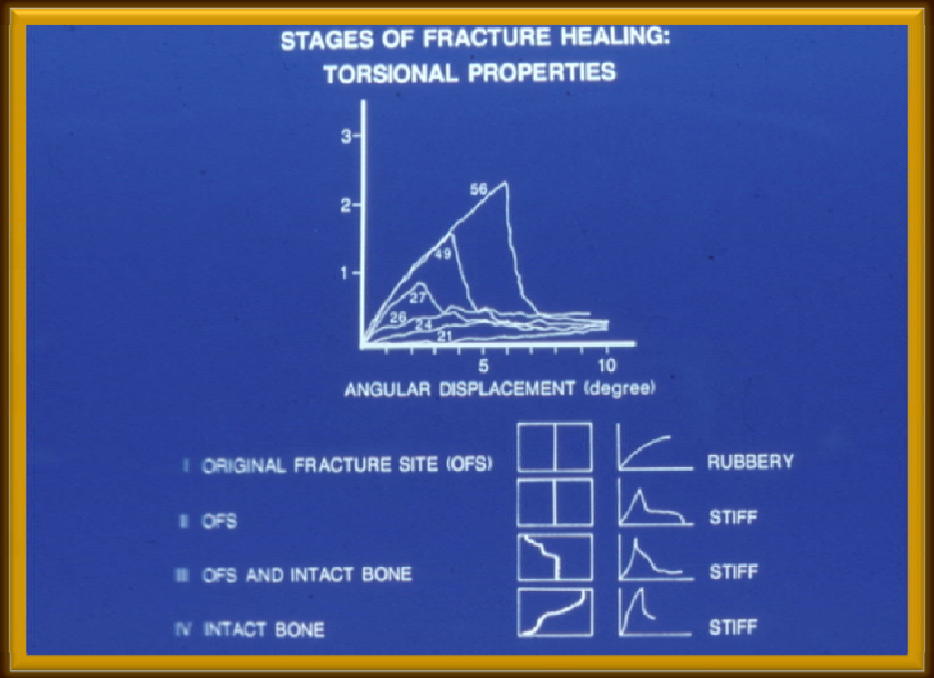
FGF-2

VEGF

PGE-2


7w




STAGES OF FRACTURE HEALING:
TORSIONAL PROPERTIES
3
2
1
56
49
27
26
24
21
5
10
ANGULAR DISPLACEMENT (degree)
I ORIGINAL FRACTURE SITE (OFS)
II OFS
III OFS AND INTACT BONE
IV INTACT BONE
RUBBERY
STIFF
STIFF
STIFF

Fracture Healing as a Developmental System

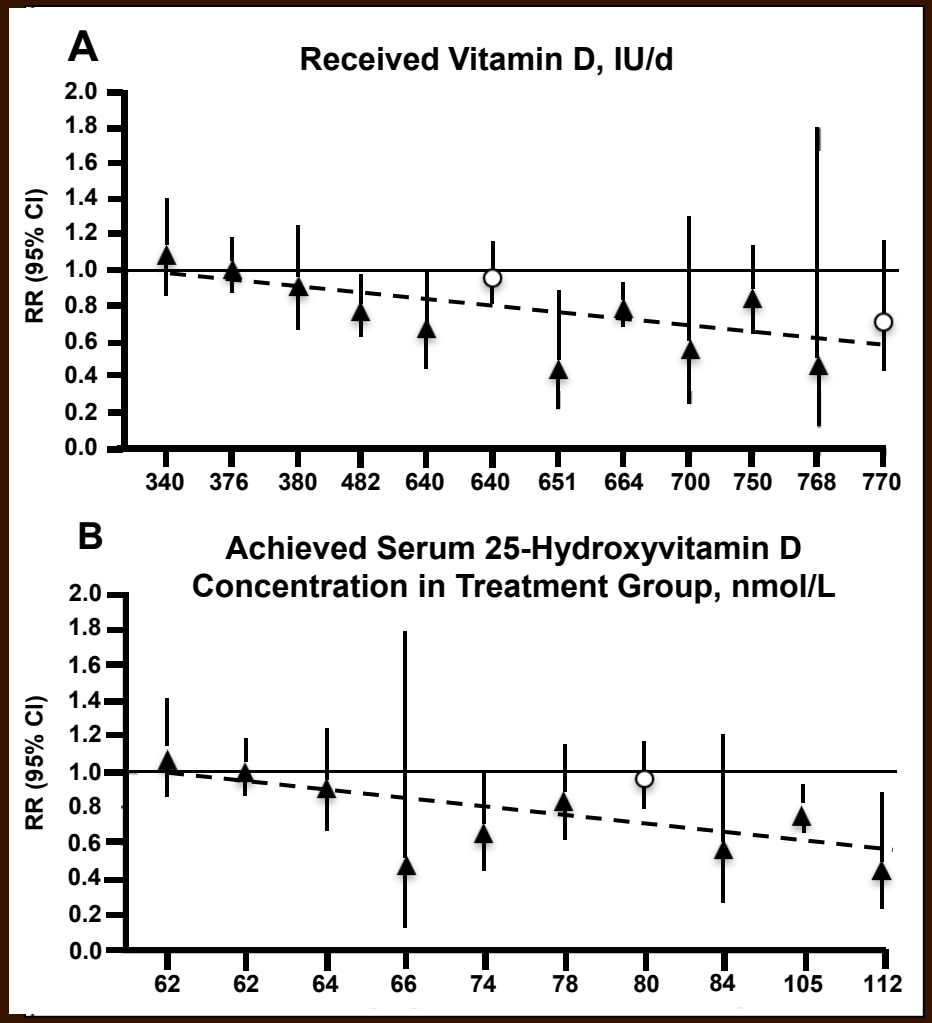
1. Post Natal Fx Repair Recapitulates Embryonic Bone Development
2. Re-Expression of Genes which Regulate Skeletal Development

Prevention of Nonvertebral Fractures with Oral Vitamin D and Dose Dependency

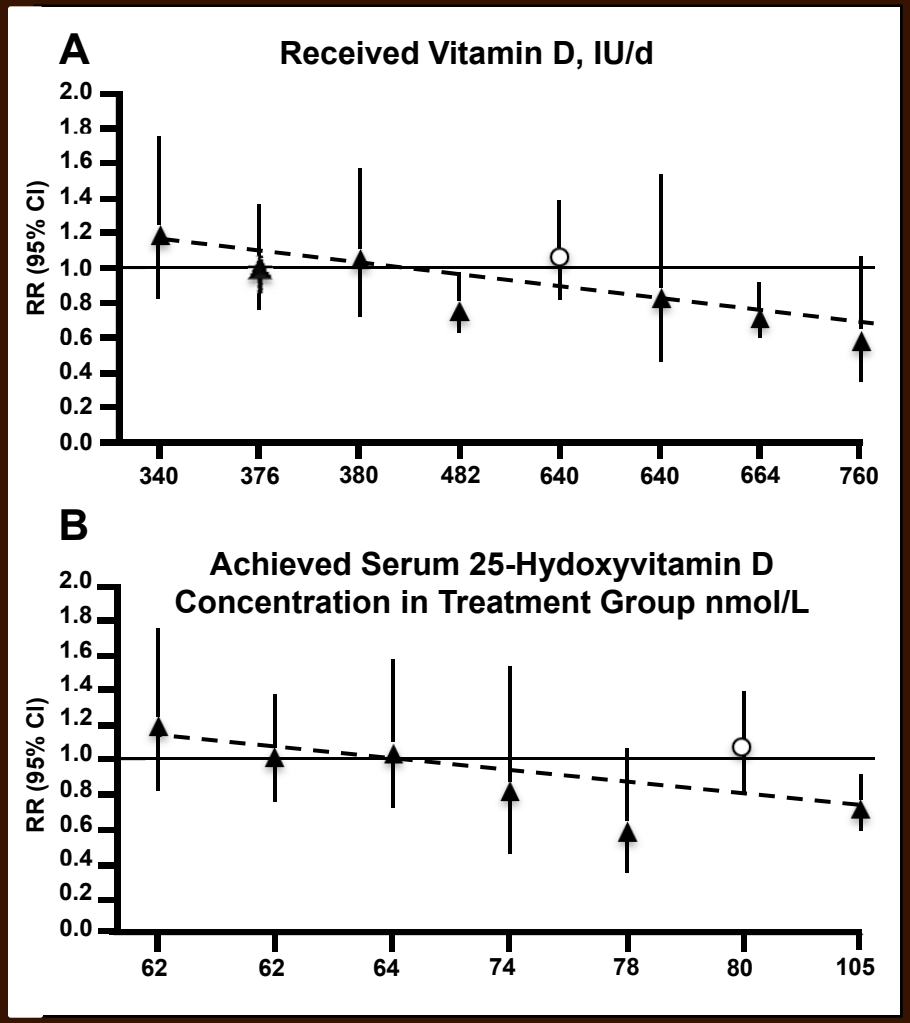
H. Bischoff-Ferrari, et. al. Arch Intern Med. 169(6): 551-561; 2009

- Meta-analysis of 12 RCTs for Nonvertebral Fx (N=42,279) and 8 RCTs for Hip Fx (N= 40,886)
- Anti-fx Efficacy: > 400 IU/d Received Vitamin D and > 28 ng / mL Achieved Vitamin D
- Pooled RR for Prevention of Nonvertebral Fx = 0.86 and for Hip Fx = 0.91
- Higher Serum 25(OH)D Reduced Fx Risk by 20%

Nonvertebral Fracture Prevention



Hip Fracture Prevention



Vitamin D and Fracture Reduction

S. Brown Altern Med Rev 13(1):21-33; 2008

1. Serum 25(OH)D ≥ 32 ng/mL Normalizes PTH and Ca Absorption and Reduces Fx Incidence
2. 800 IU/d Vitamin D Reduces Falls by 49%

Vitamin D Deficiency as a Risk Factor for Osteoporotic Fracture

N.M van Schoor, et. al. Bone : 260-266; 2008

- 1311 Men and Women > age 55
  - 115 (8.5%) Had at Least 1 Osteoporotic Fx
- 25(OH)D:
  - 11.3% < 10 ng/mL
  - 48.4% < 20 ng/mL
  - 82.4% < 30 ng/mL
    - Serum 25(OH)D of 12 ng/mL = Discriminator of Fx Risk
    - Lowest Fx Rate (5.6%) with 25(OH)D > 30 ng/mL

Vitamin D Insufficiency

C. Rosen N Engl J Med 364: 248-254; 2011

Vitamin D Supplementation

1. 800 IU + 1200 mg Ca Reduced Fx Rates
2. Cochrane Review = No Effect
3. 700 IU + 2000 mg Ca = No Effect
4. 400 - 800 IU = No Effect

Serum 25(OH)D Threshold

1. Fx↑Risk < 16 ng/mL
2. Bone Loss < 20 ng/mL
3. Fx↑Risk < 20 ng/mL
4. Fx↑Risk < 25 ng/mL

Vitamin D Deficiency and Supplementation

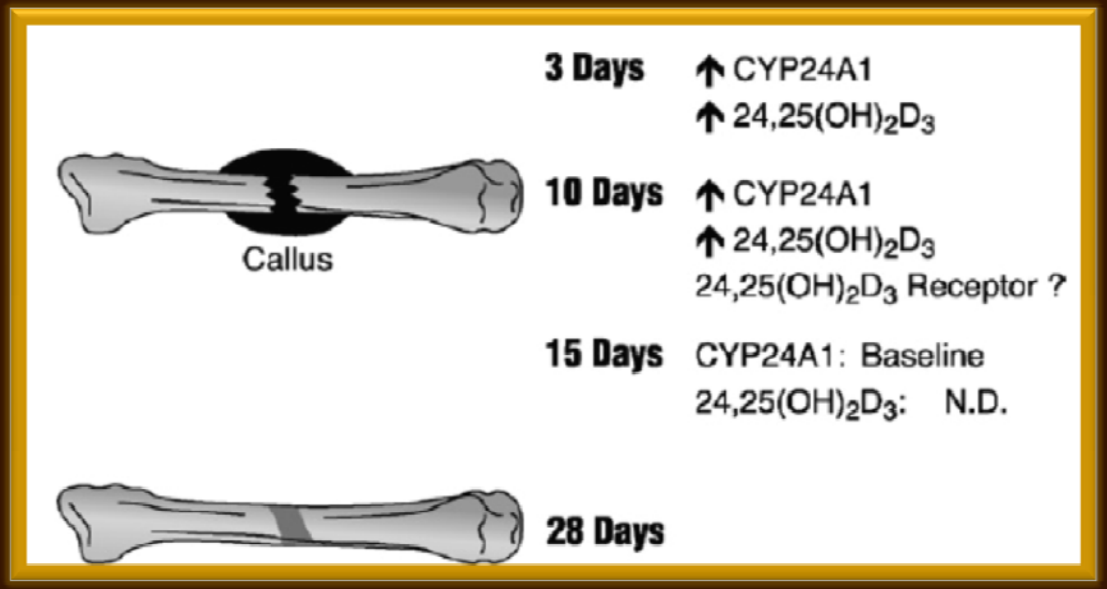
	Serum 25(OH)D	Supplement
IOM	20 ng/mL	600 IU/d
NOF	30 ng/mL	800-1000 IU/d
AGS	-	800 IU/d

Role for 24, 25$(OH)_2$ D in Fracture Healing

- Chick Tibial Fx Elevate 24, 25$(OH)_2$D and 25(OH)D – 24 Hydroxylase (CYP24A1)
- Binding Protein/ Receptor in Chick Tibial Callus for 24, 25$(OH)_2$D
- 24, 25$(OH)_2$D Optimizes Chick Fx Mechanical Strength

CYP24A1-Deficient Mice as a Tool to Uncover a Biological Activity for Vitamin D Metabolites Hydroxylated at Position 24

R. St-Arnaud jsbmb 212: 254-256; 2010



CYP24A1-Deficient Mice as a Tool to Uncover a Biological Activity for Vitamin D Metabolites Hydroxylated at Position 24

R. St-Arnaud jsbmb 212: 254-256; 2010

- Fx Healing in *cyp24a1-/-* Mice
- Delay in Endochondral Ossification and Mineralization Compared to Wild-type Controls
- Rescue of Fx Healing with 24, 25$(OH)_2$D