



# Fragilidad: Aproximación terapéutica

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# Objetivos

- ❖ Comparacion de casos
- ❖ Aproximacion fisiopatologica
- ❖ Aproximacion molecular
- ❖ Perspectivas futuras

## **Patofisiología**

**Arteriosclerosis**  
**Acumulación lipídica**  
**Degeneración endotelial**

## **Consecuencia Clínica**

**Angina**  
**Infarto**  
**Muerte**

## **Secuela**

**Insuficiencia cardiaca**  
**Deterioro funcional y de**  
**Calidad de vida**

**Patofisiología**

**Consecuencia  
Clínica**

**Secuela**

## **Cambios en células Mesenquimatosas**

- Neurona
- Osteoblastos
- Miocitos

**Sarcopenia**

**Osteopenia**

**Caídas**

**Velocidad de la marcha**

**Muerte**

**Deterioro emocional**

**Deterioro funcional y de**

**Calidad de vida**



# Aproximación terapéutica

## ❖ Enf. Coronaria

### ❖ Fisiopatológica

- ❖ Control de lípidos
- ❖ Control metabólico
- ❖ Control de agregación

### ❖ Eventos clínicos:

- ❖ Cateterismo
- ❖ UCI
- ❖ Control de deterioro funcional

## ❖ Fragilidad

### ❖ Fisiopatológica

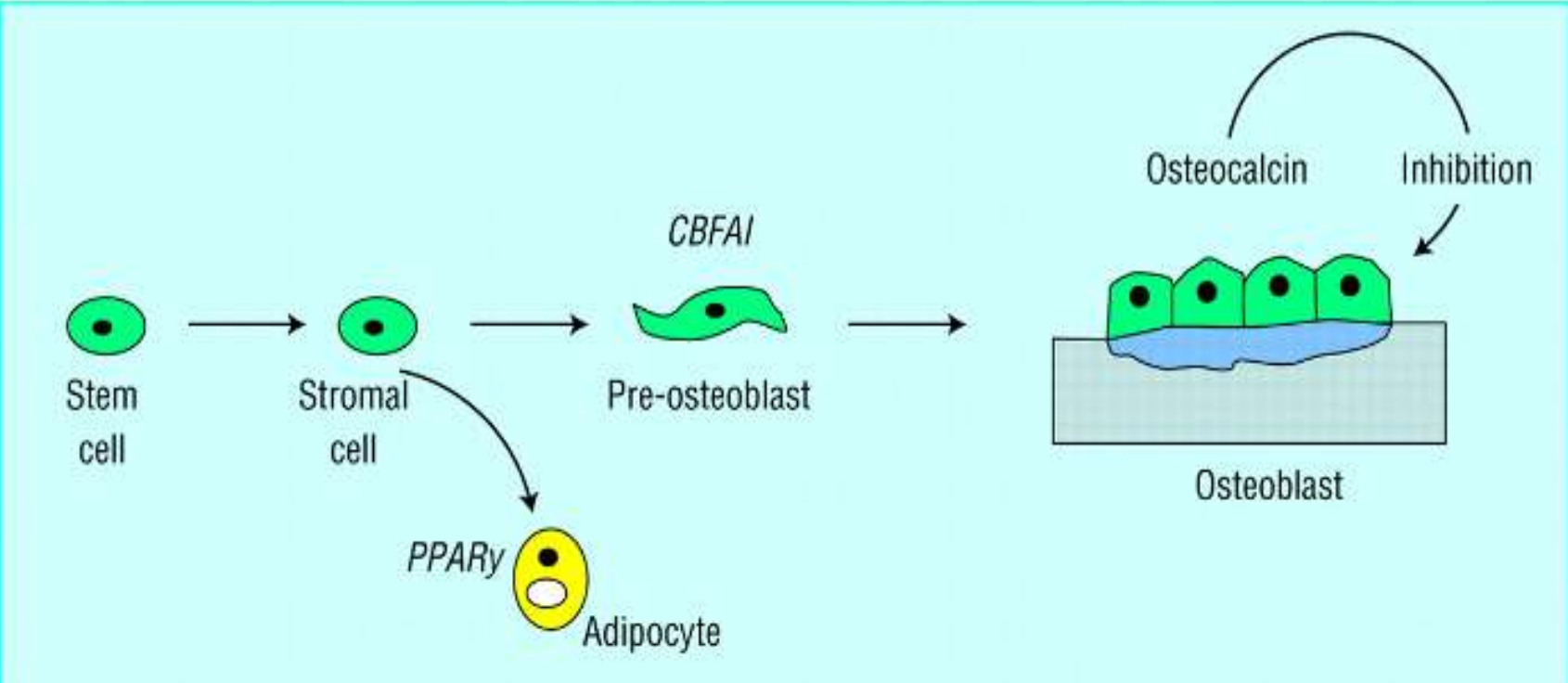
- ❖ Control de diferenciación celular
- ❖ Aporte hormonal?

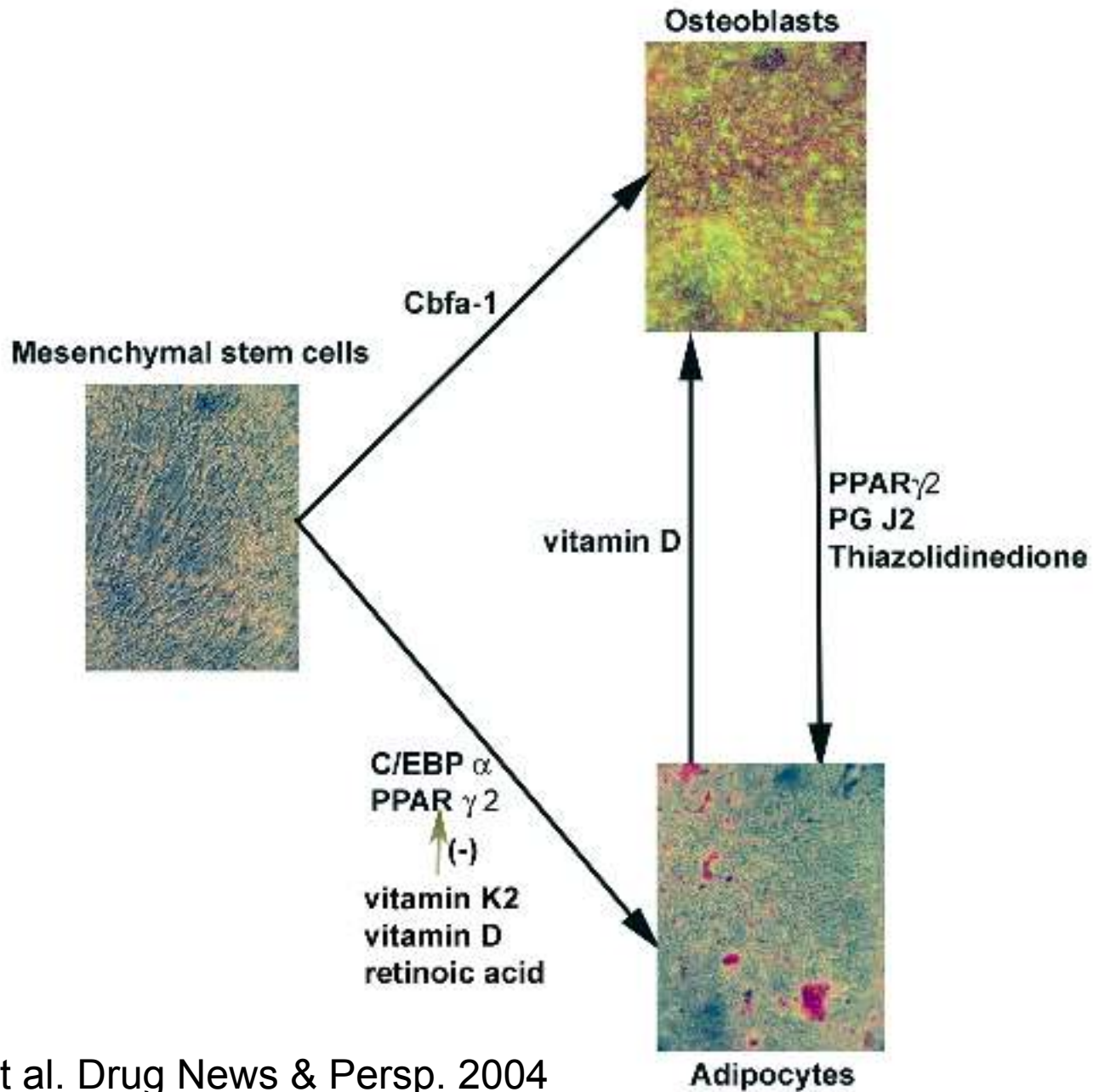
### ❖ Eventos clínicos:

- ❖ Prevención de caídas/Fx
- ❖ Control post-caída
- ❖ Prevención de co-morbilidad



# Control de diferenciación celular

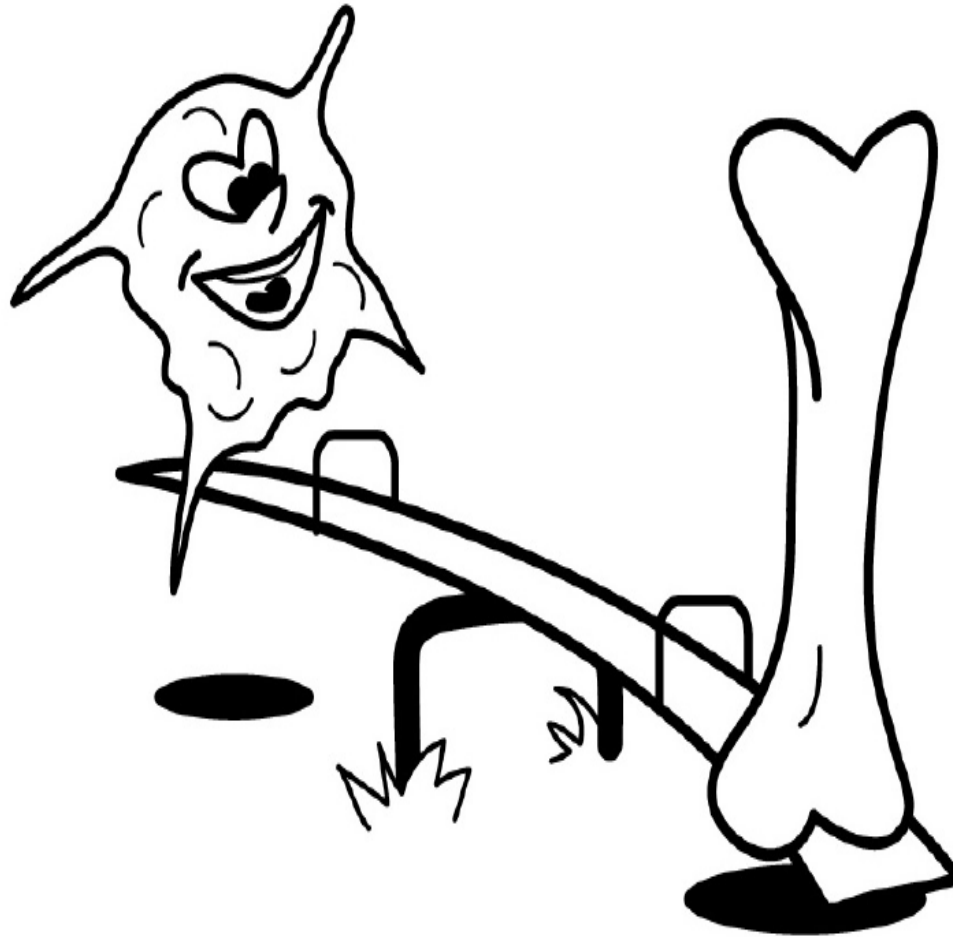




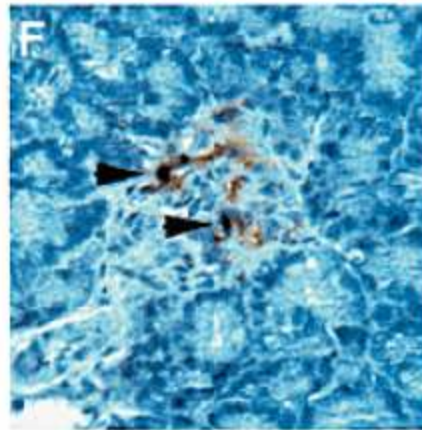
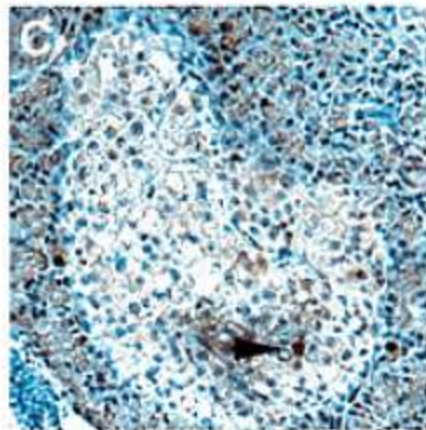
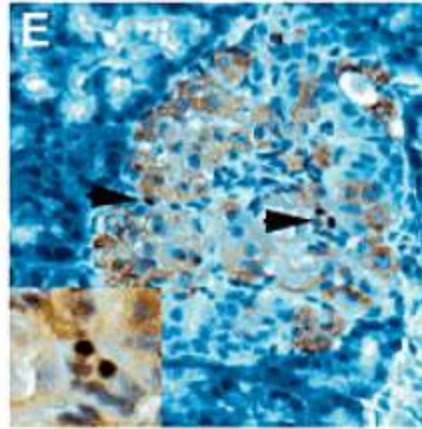
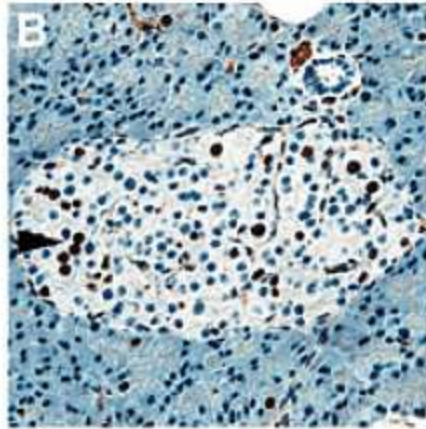
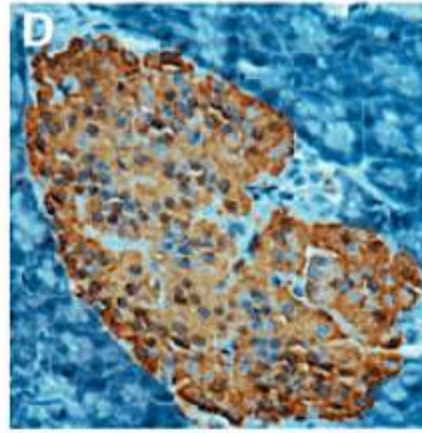
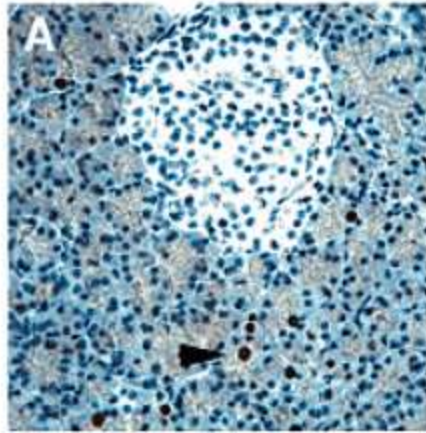
Duque et al. Drug News & Persp. 2004

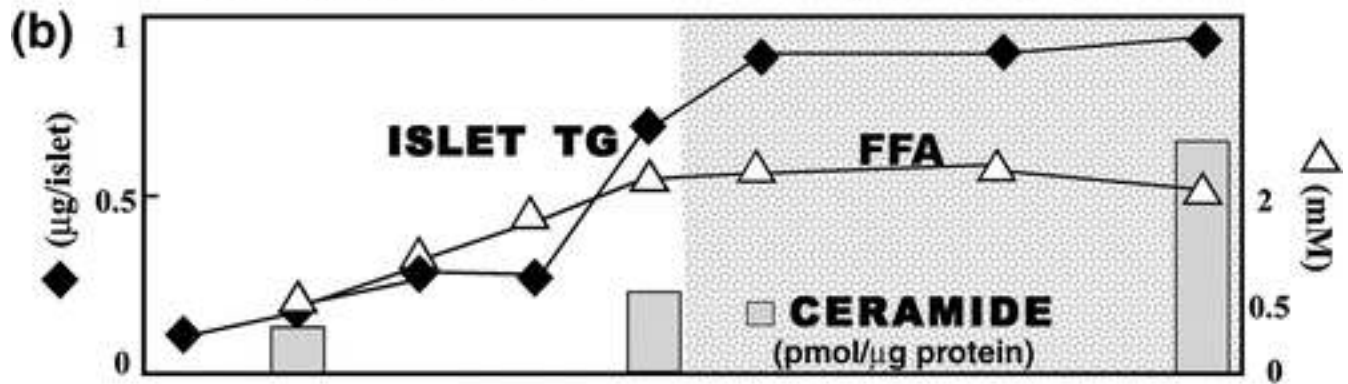
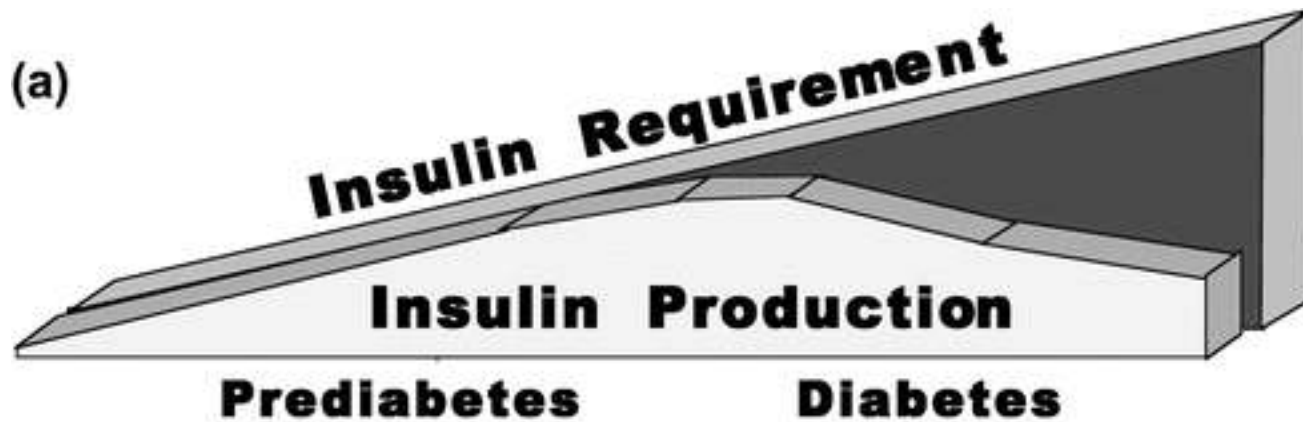


# Grasa vs. Hueso



Gimble et al, JLD, 2006





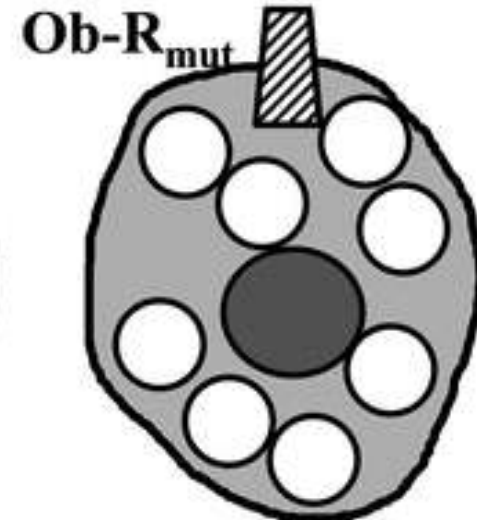
**(a) NORMAL**

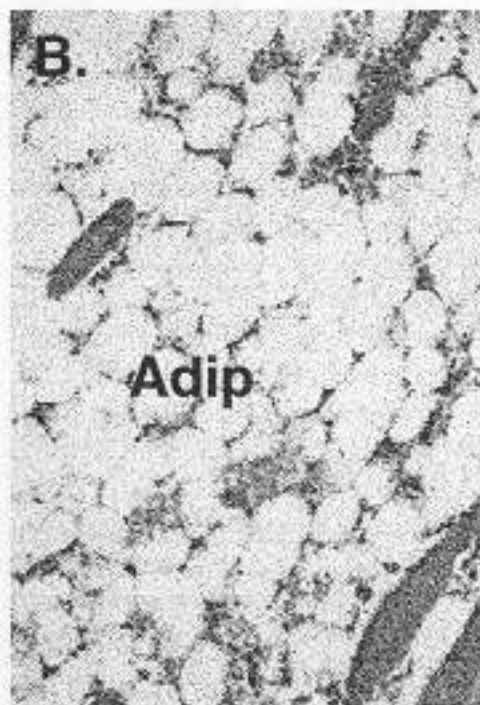
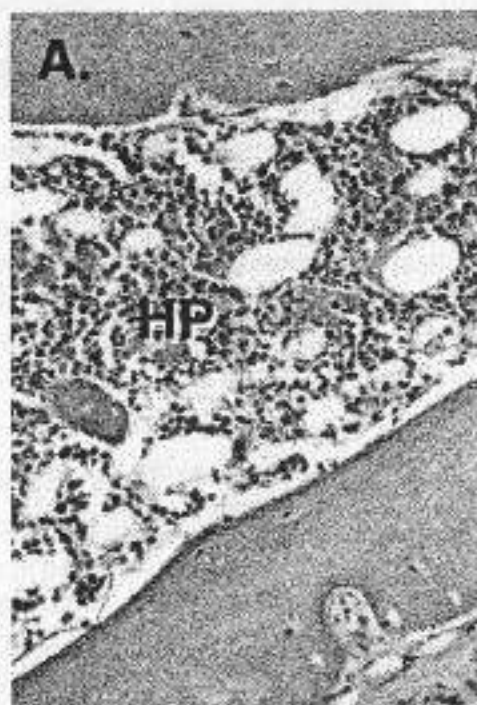


**(b) LIPOPENIA  
dysfunctional**



**(c) STEATOSIS  
dysfunctional**

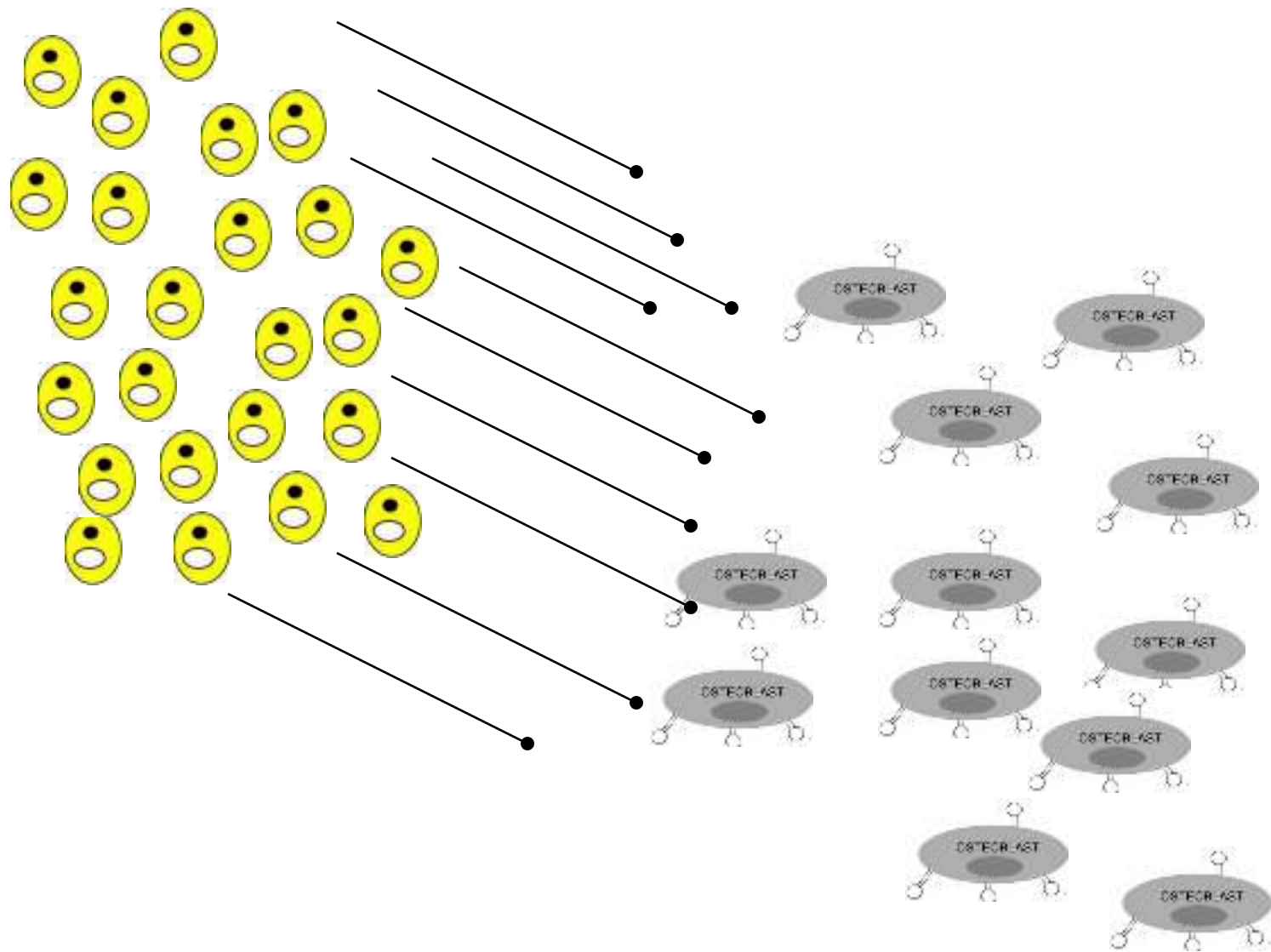




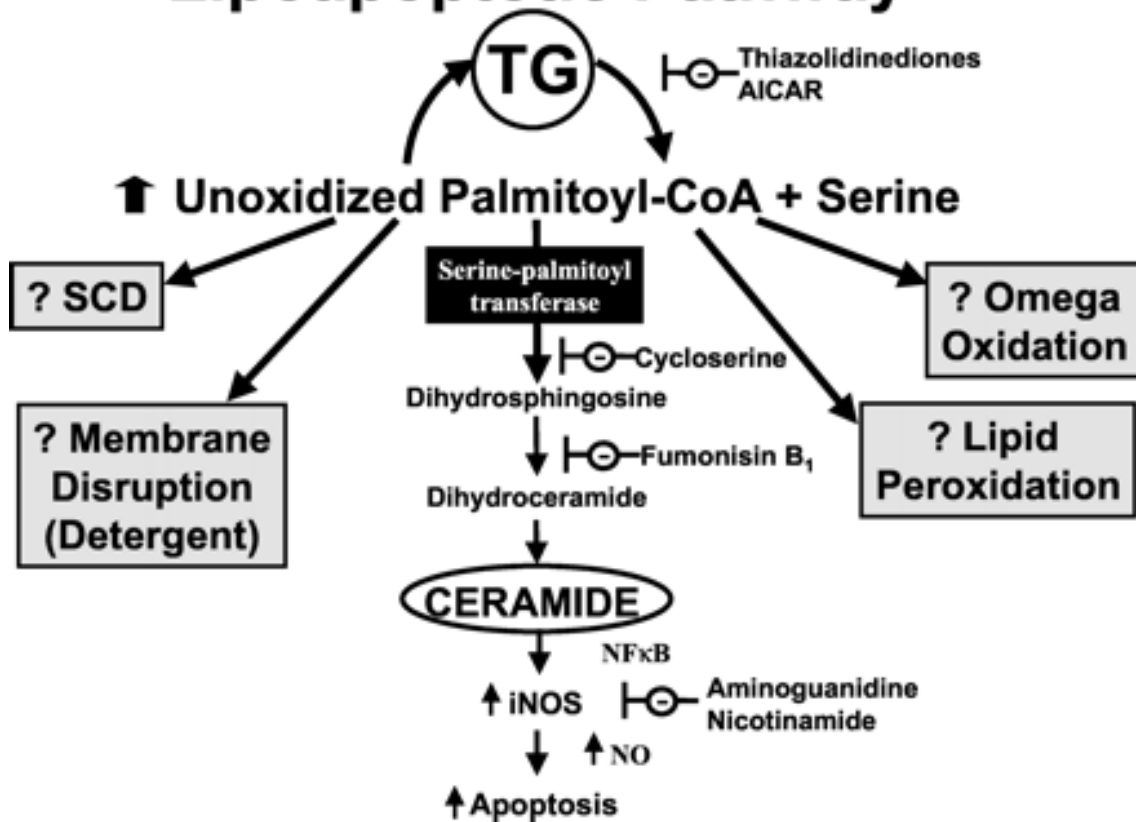
**FIGURE 3** Conversion of red marrow to yellow marrow during aging. (A) During postnatal growth, the bone marrow stroma supports hematopoiesis (HP). In addition, stroma supports osteoblastogenesis and osteoclastogenesis during bone turnover, which is essential for maintaining normal skeletal functions. (B) With aging, the stroma shifts its phenotype to one primarily of adipocytes, thereby causing a defect in osteoblastogenesis and possibly osteoclastogenesis.



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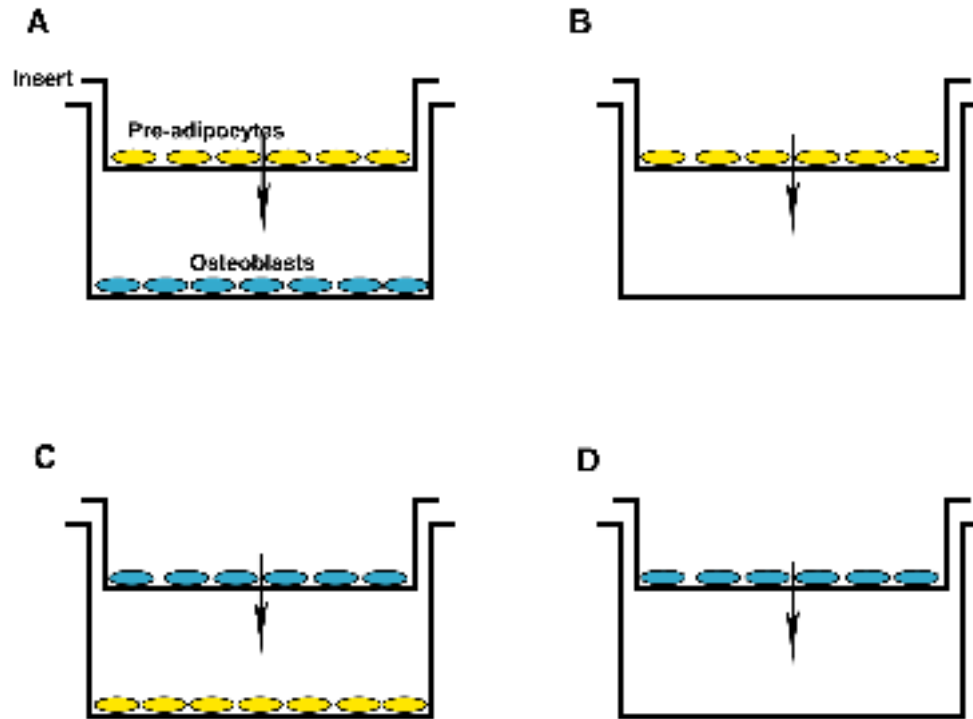


# Lipoapoptotic Pathway





# Zona de guerra

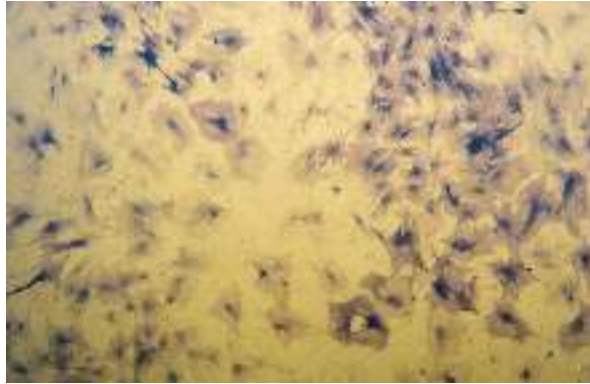


Duque et al, Submitted data

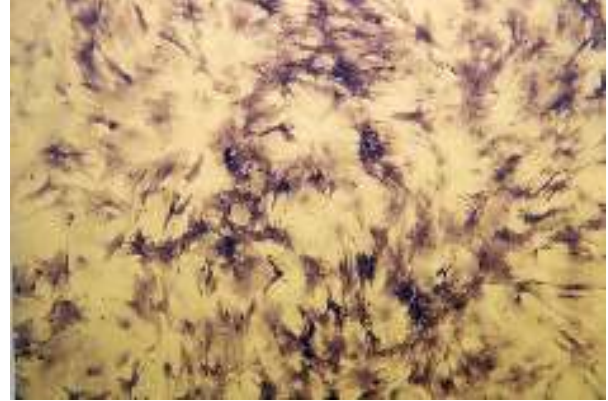
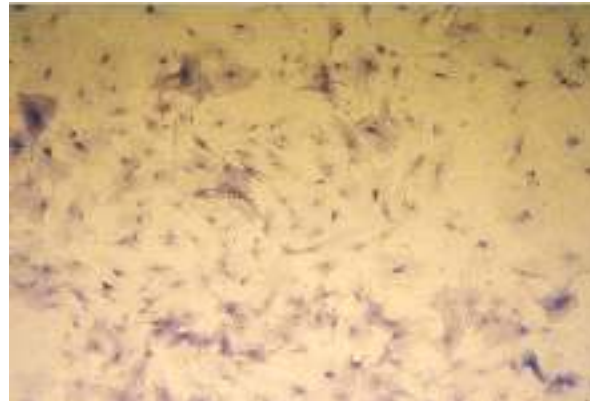
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**OB/AD**

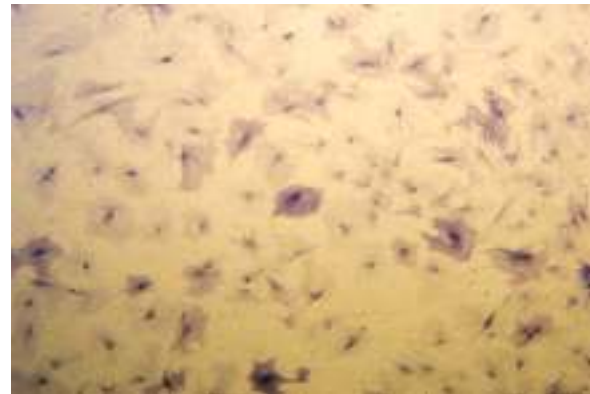
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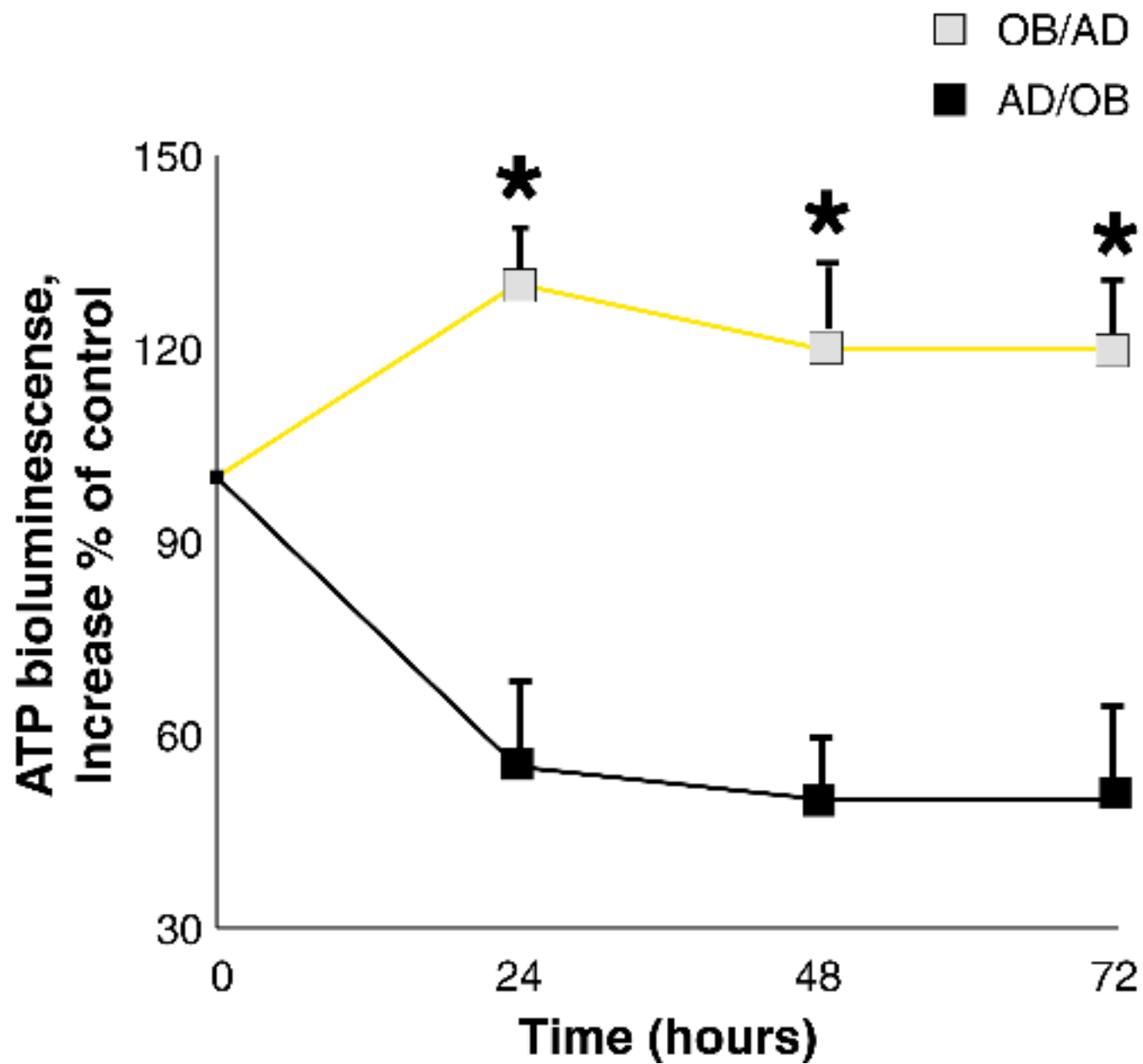


**48 h**

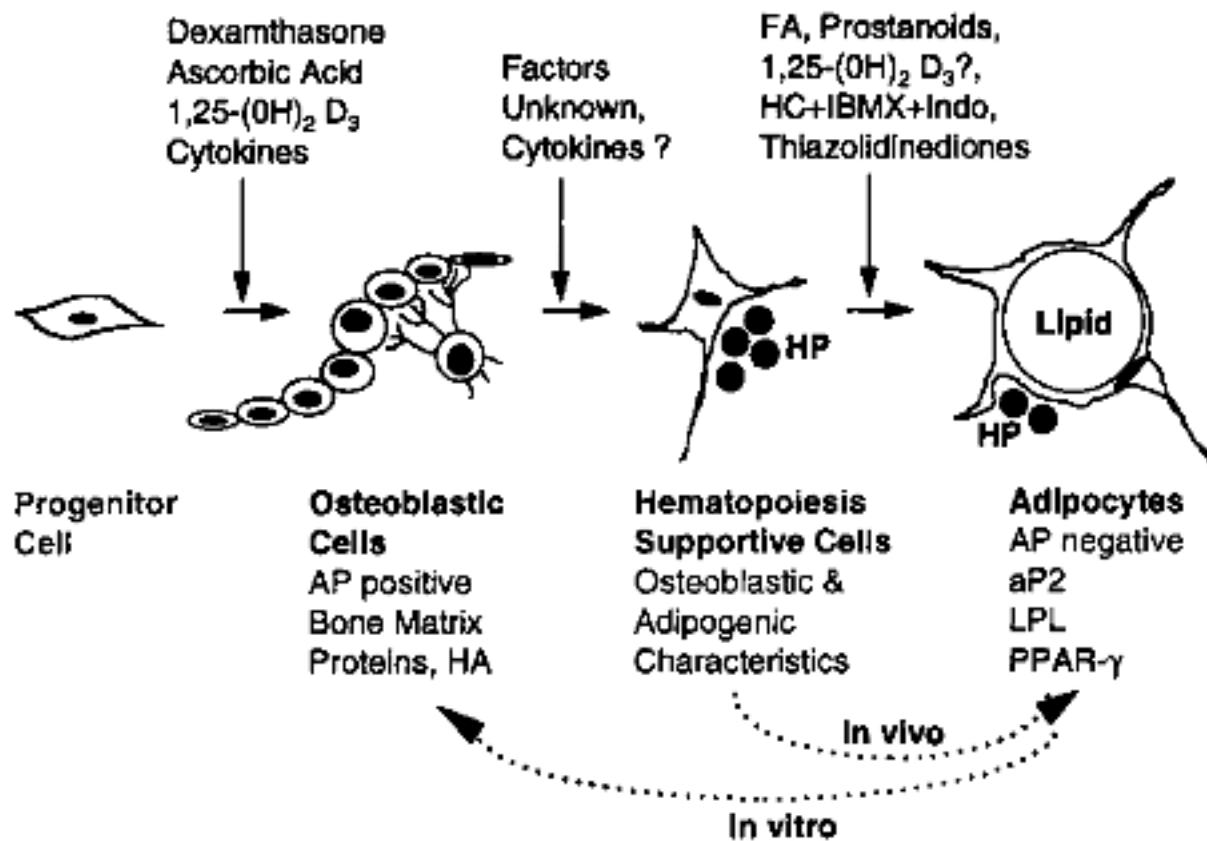


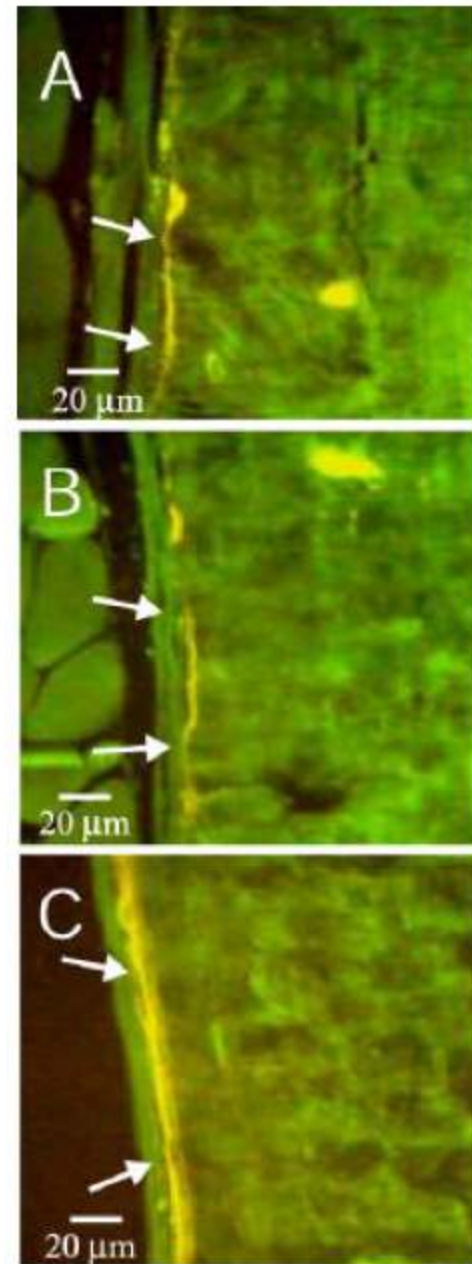
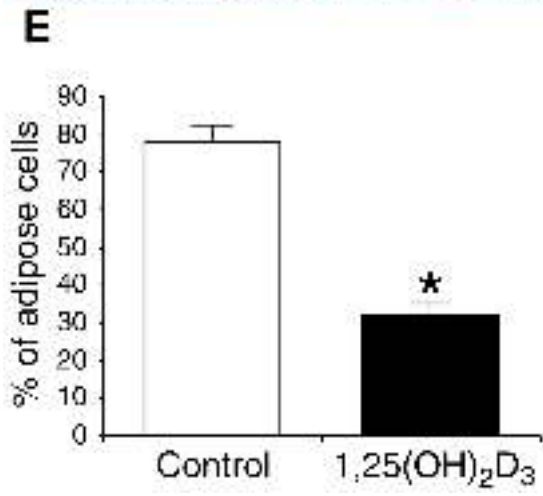
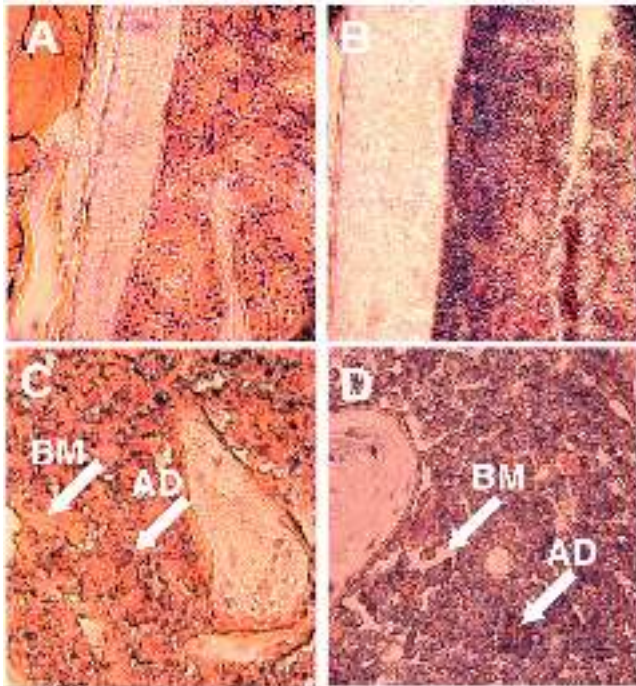
**72 h**



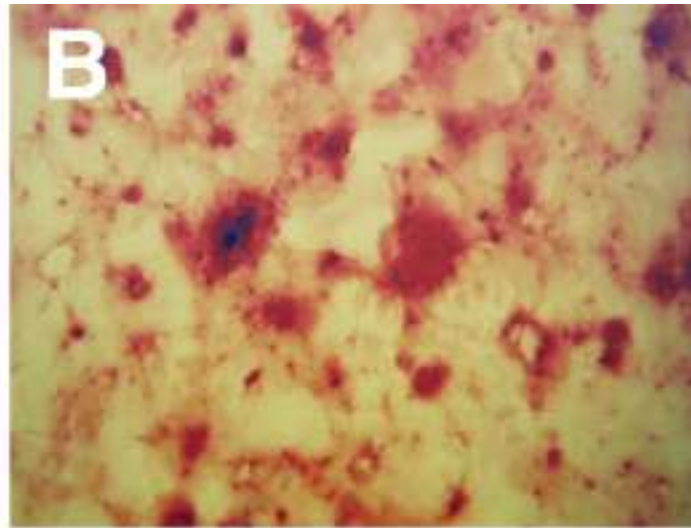
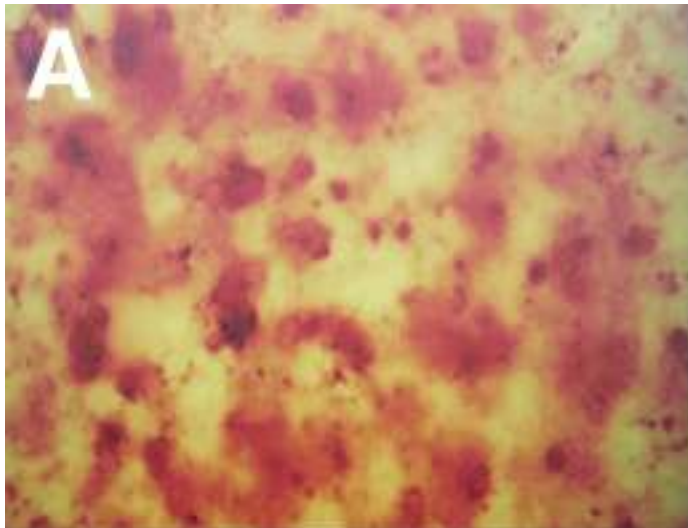


**Progression of phenotypic expression with bone formation**









# Adipocytic proportion of bone marrow is inversely related to bone formation in osteoporosis

S Verma, J H Rajaratnam, J Denton, J A Hoyland, R J Byers

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*J Clin Pathol* 2002;55:693-698

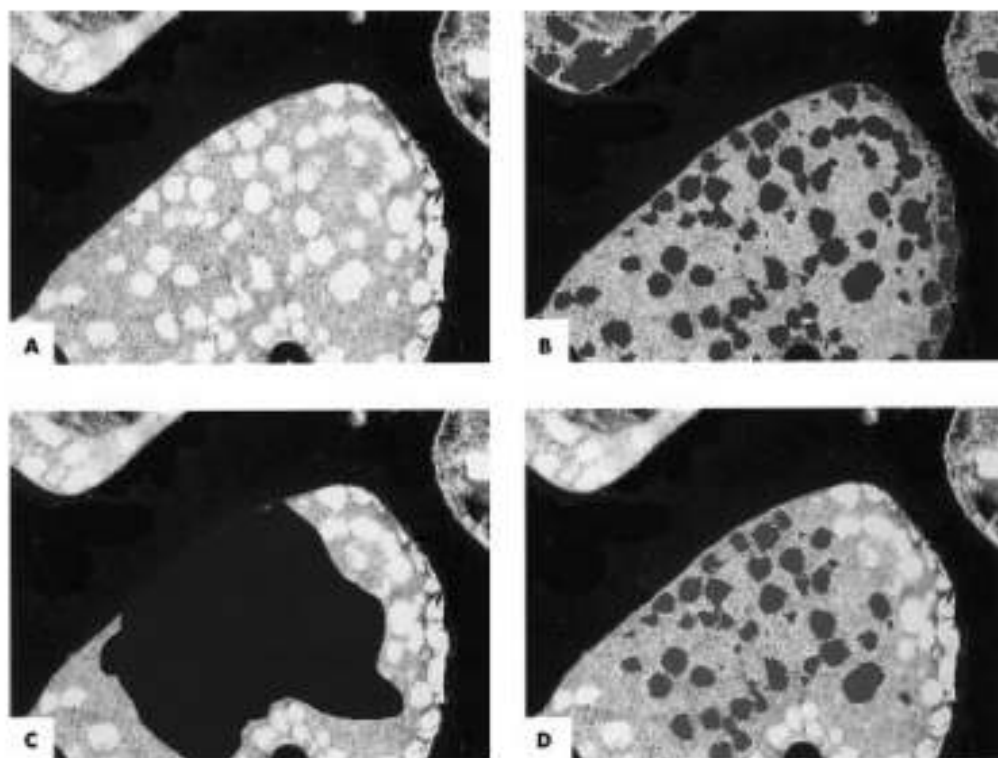
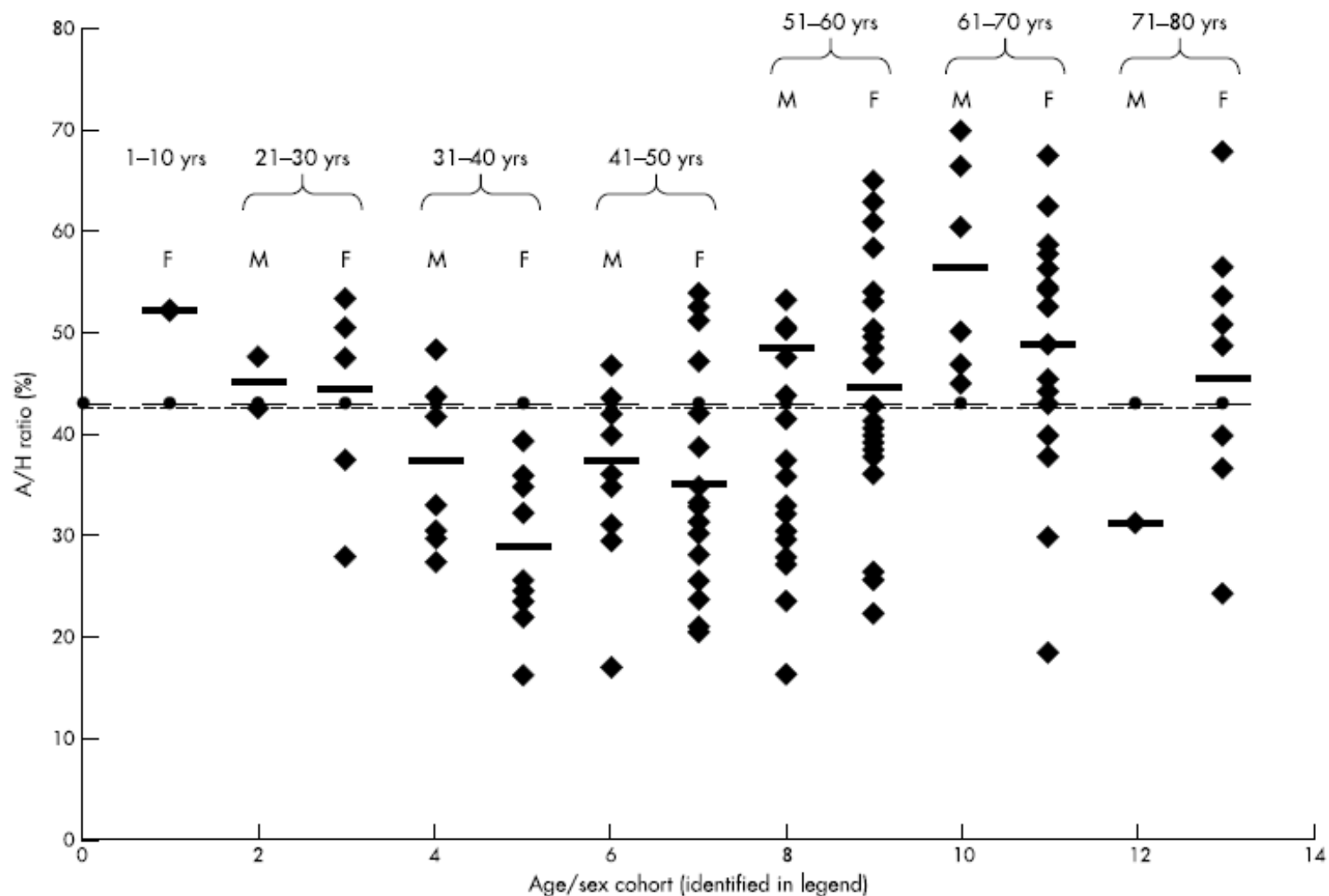


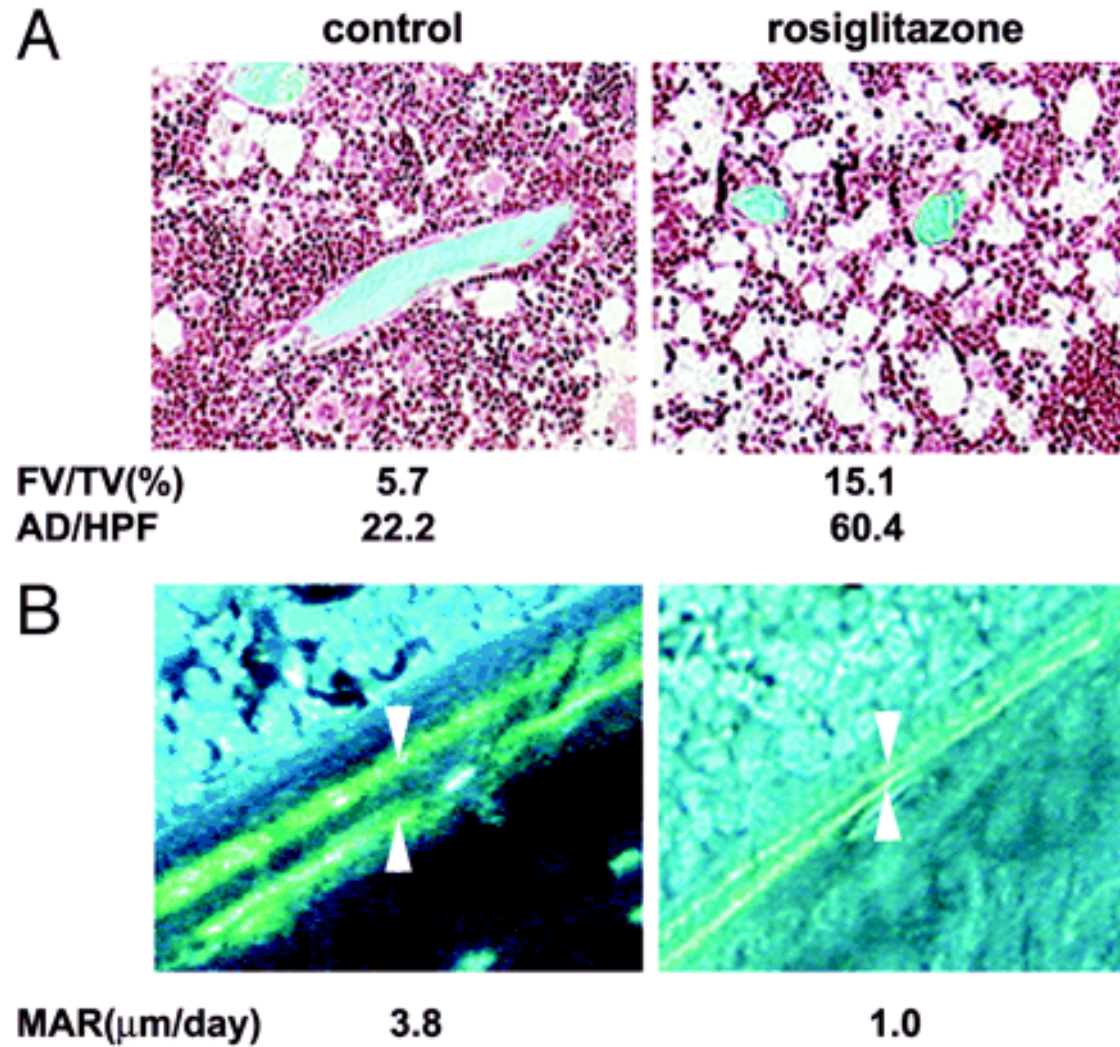
Figure 1 Image capture and calculation of the adipocytic ratio; all images von Kossa, original magnification,  $\times 40$ : (A) Live image of representative field of bone marrow captured digitally; (B) adipocytic tissue (darker areas) highlighted by semi-automated selection of area above gray scale cutoff; (C) area for calculation of adipocytic ratio (large dark area) selected with cursor, covering cancellous struts and artifact; (D) adipocytic tissue (darker areas) highlighted by subtraction from gray/haemopoietic tissue within the area selected and the ratio of clear/adipocytic to gray/haemopoietic stromal tissue calculated.



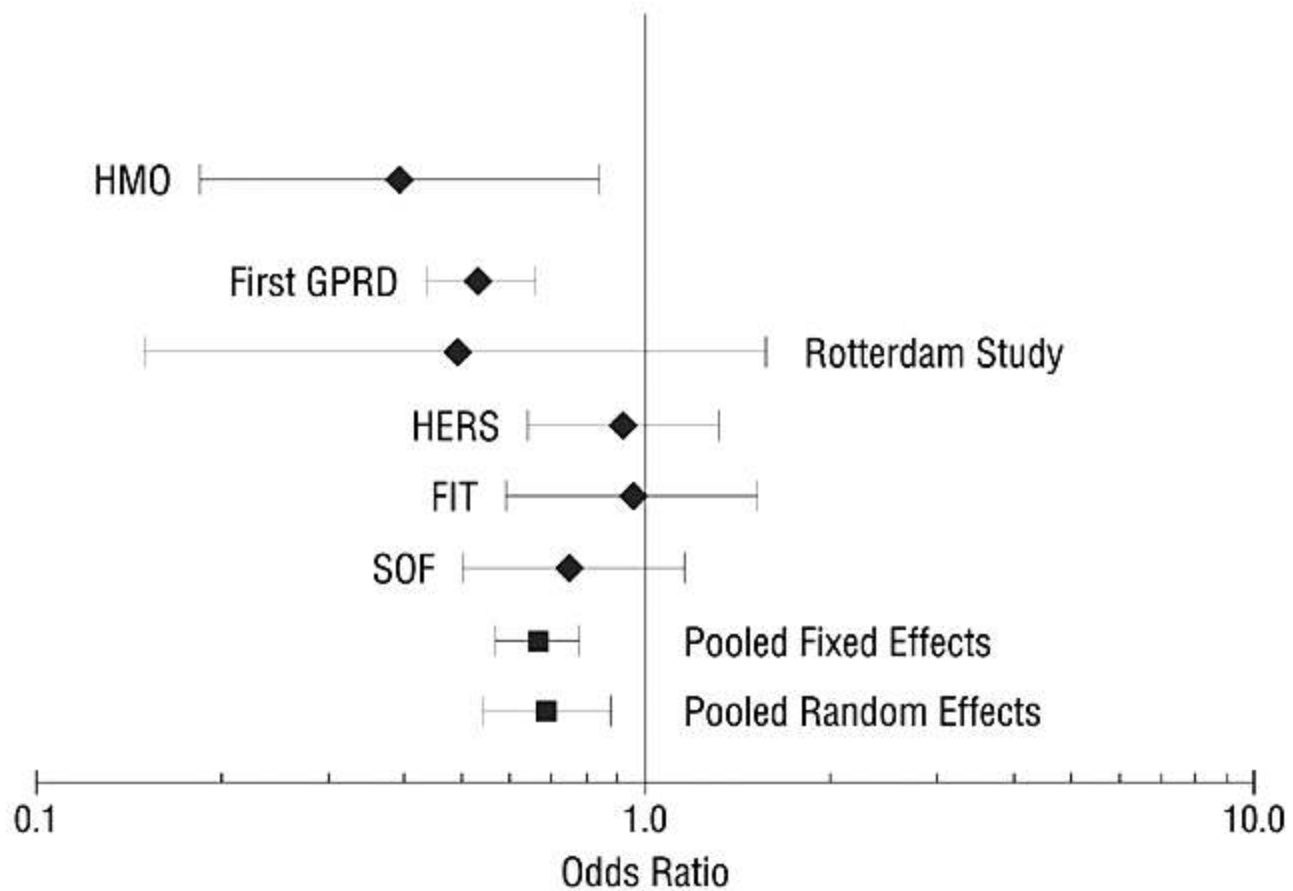


**Figure 4** Adipocytic/haemopoietic (A/H) ratios for patients in each of the age/sex cohorts, with mean of each cohort (thick horizontal bar), regression line for means of cohorts ( $y = 42.56 + 0.05x$ ) (dotted line), and mean of all cases (thin horizontal bar), demonstrating the lack of age bias of cohort means compared with the overall mean for all cases. Age/sex cohorts: 1, females 1–10 years; 2, men 21–30 years; 3, women 21–30 years; 4 men 31–40 years; 5, women 31–40 years; 6, men 41–50 years; 7, women 41–50 years; 8, men 51–60 years; 9, women 51–60 years; 10, men 61–70 years; 11, women 61–70 years; 12, men 71–80 years; 13, women 71–80 years.

# Bone Is a Target for the Antidiabetic Compound Rosiglitazone



Use of statins and fracture-Cumulative meta-analysis  
Bauer DC et al. Arch. Int. Med, 2004

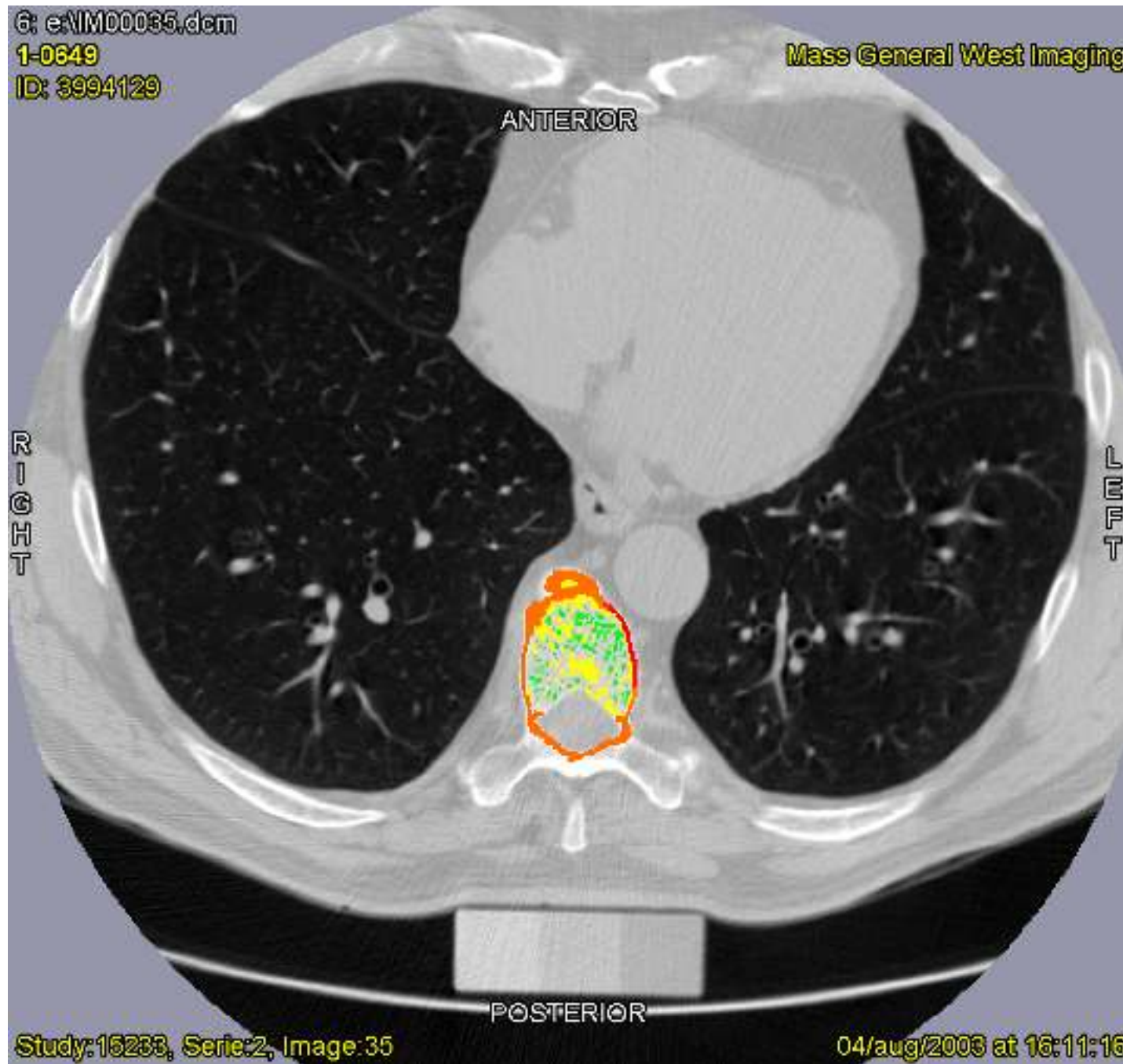


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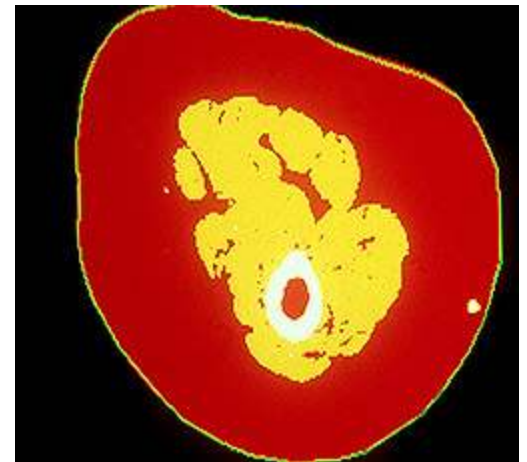
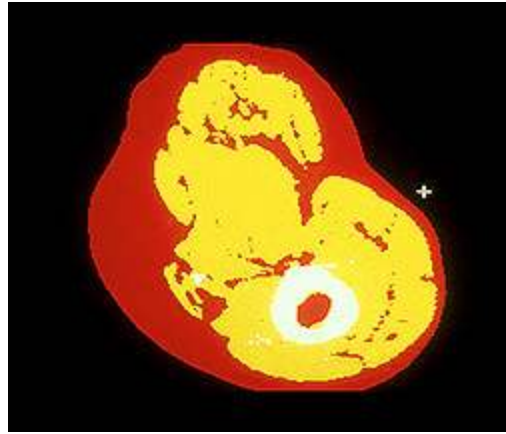
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Mass General West Imaging

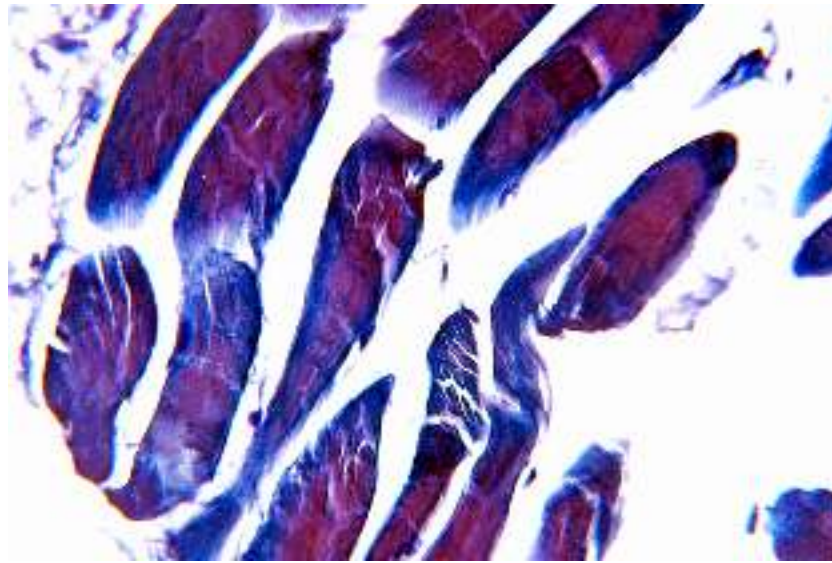


Study:16233, Serie:2, Image:35

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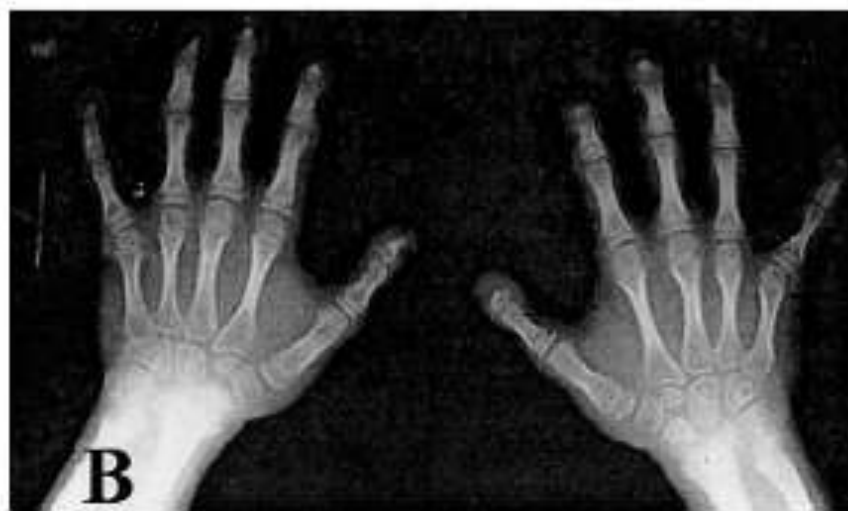
**Duque et al, submitted data**

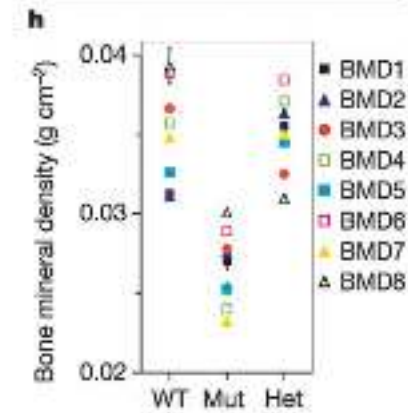
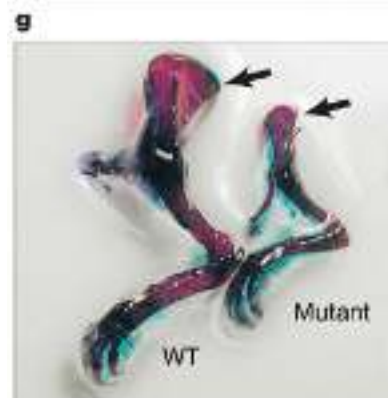
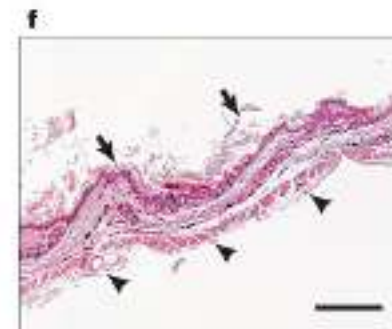
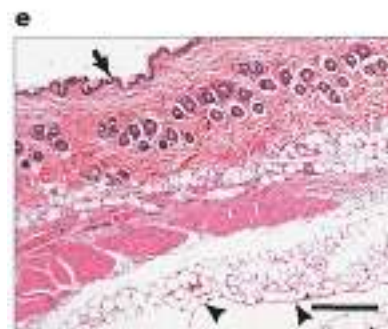
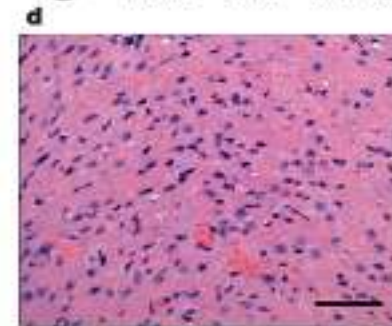
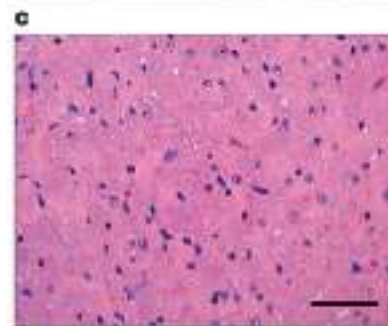
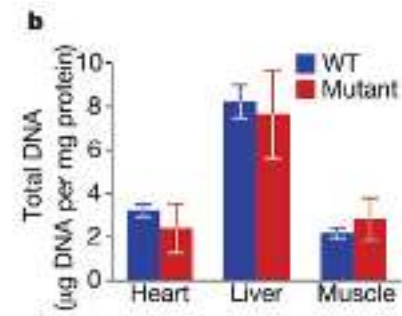


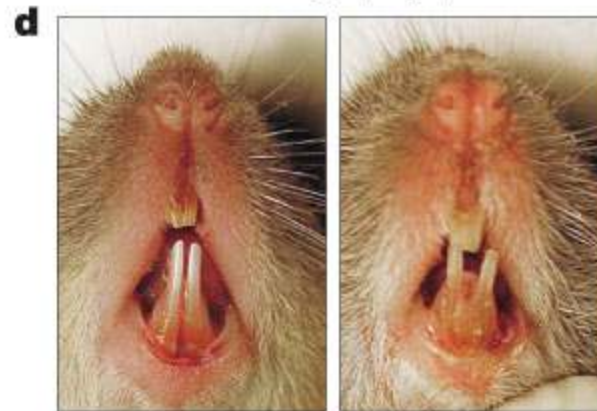
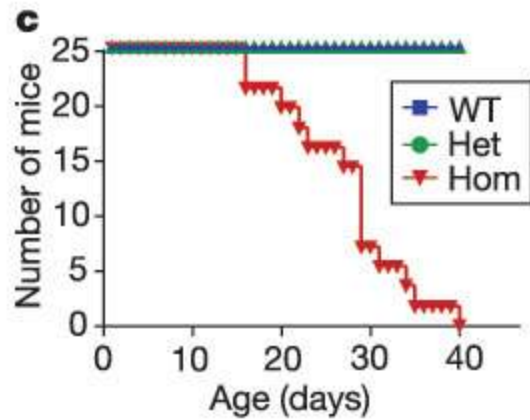
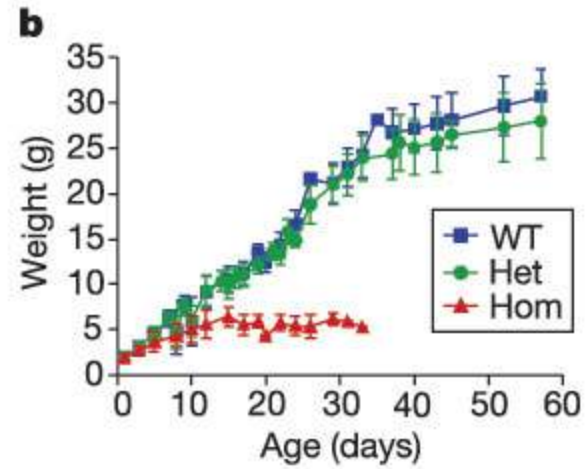




DePaula-Rodriguez et al, Annales de Genetique, 2003







## Age-related changes in lamin A/C expression in the osteoarticular system: Laminopathies as a potential new aging mechanism

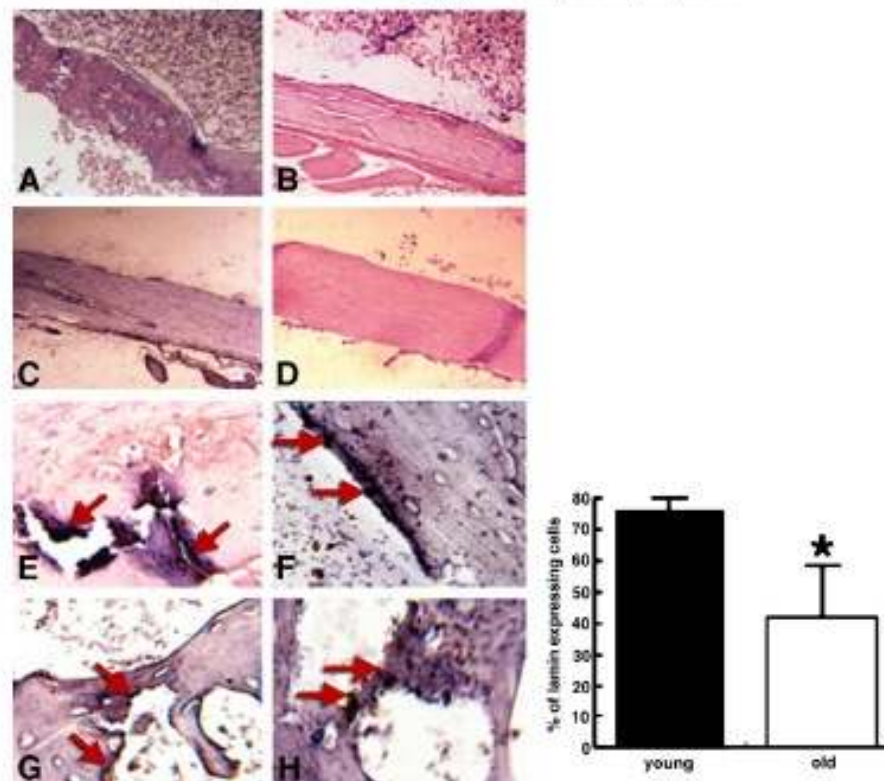
Gustavo Duque<sup>a,b,c,\*</sup>, Daniel Rivas<sup>b,c</sup>

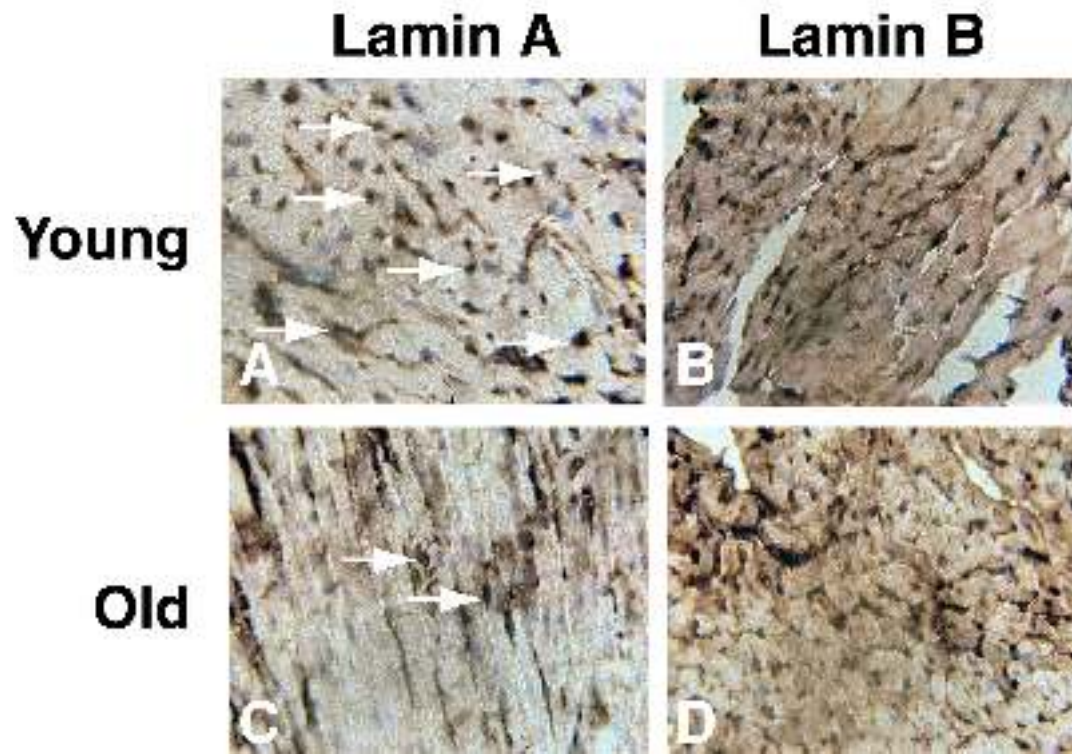
<sup>a</sup>Division of Geriatric Medicine, Jewish General Hospital 3755, McGill University Chemin de la Côte Sainte Catherine Montreal, Que., Canada H3T 1E2

<sup>b</sup>Lady Davis Institute for Medical Research

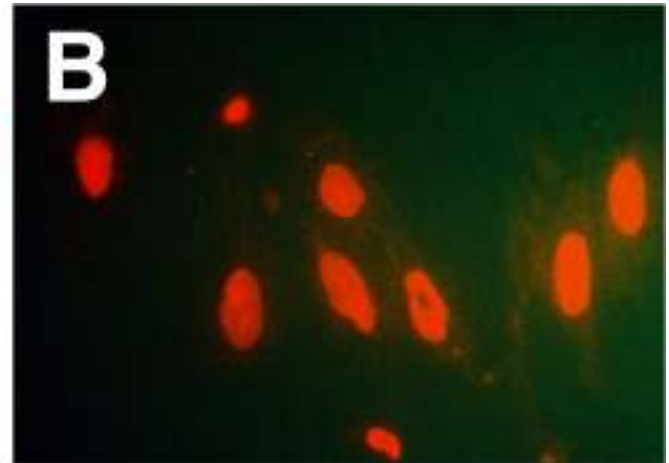
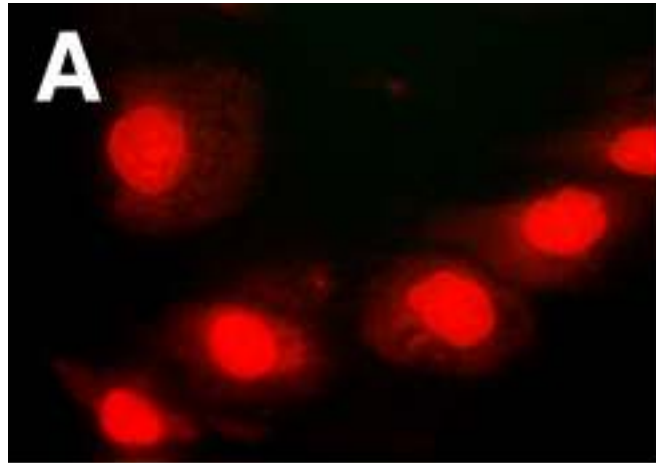
<sup>c</sup>Blossfield Centre for Research in Aging

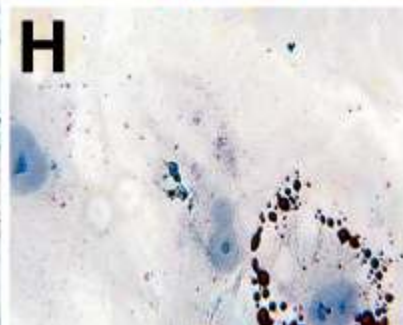
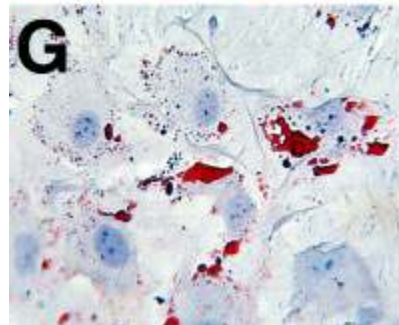
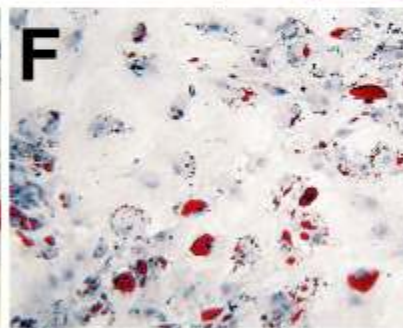
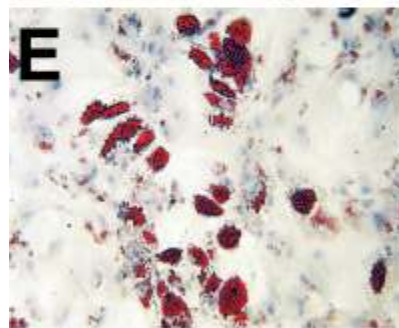
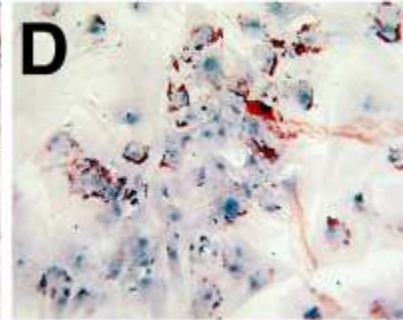
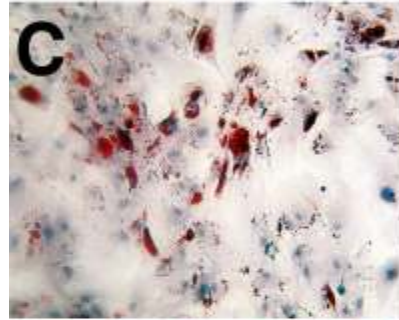
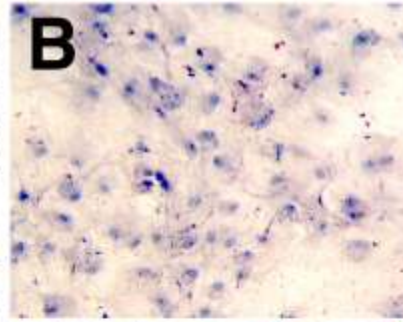
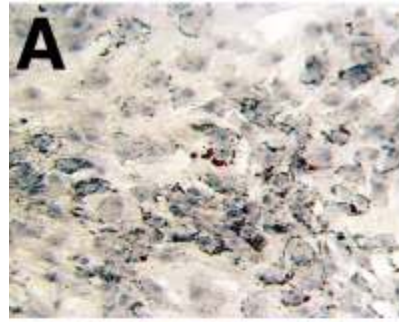
Accepted 9 December 2005





**Afilalo et al, submitted data**









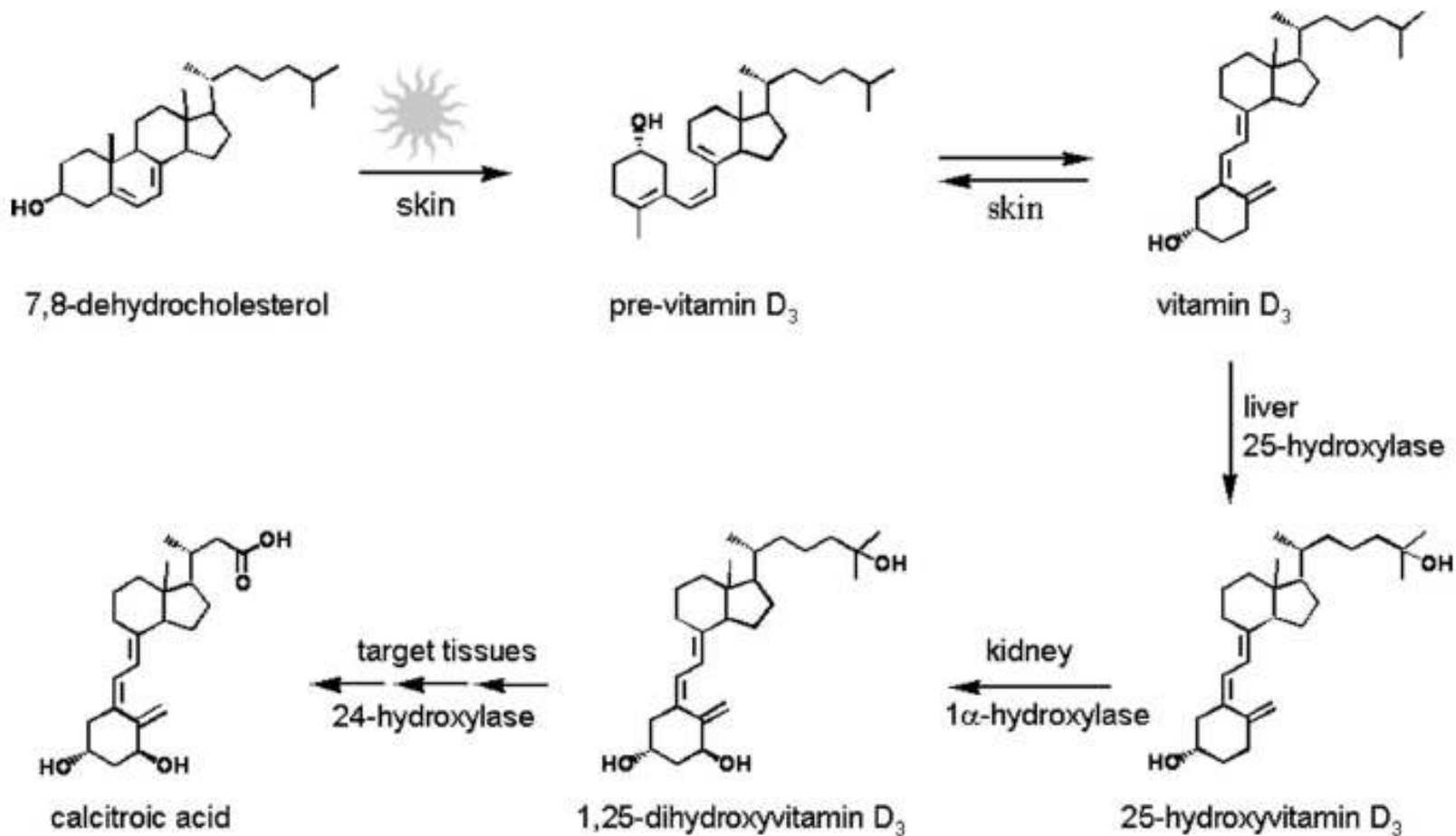
# Hormona vs. vitamina

## Vitamin

“One of a group of substances present in minute amounts in natural foodstuffs, that are essential to normal metabolism, insufficient amounts in the diet may cause deficiency diseases.”

## Hormone

“A chemical substance, formed in one organ or part of the body and carried in the blood to another organ or part; depending on their specificity, hormones can alter the function or the structure of just one organ or a group of them”

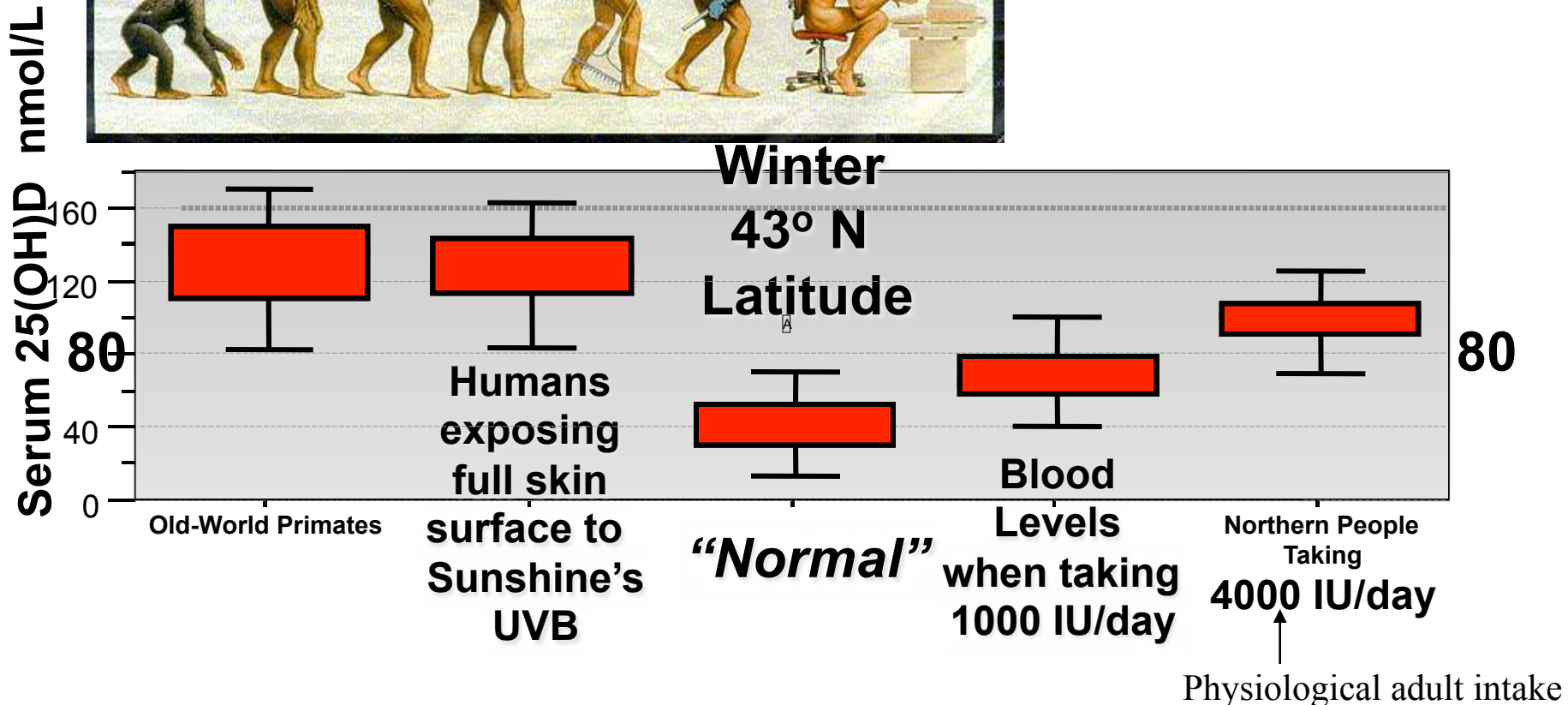
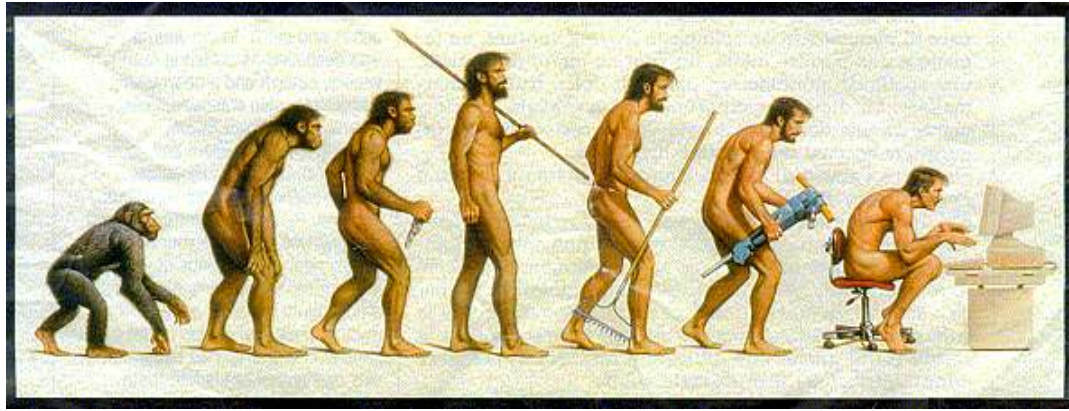


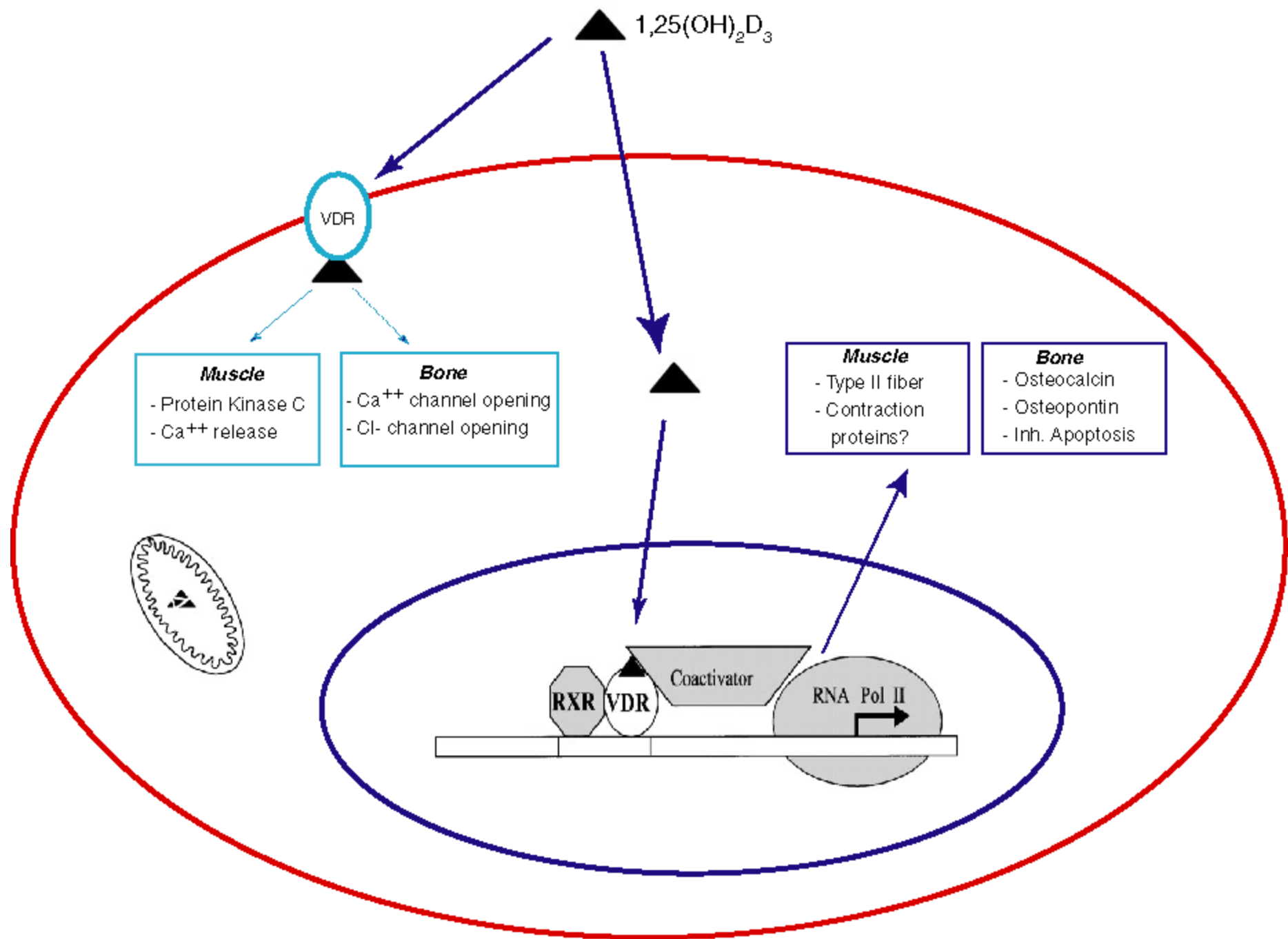
# Hormona vs. vitamina

 **Vitamina:** Vitamina D2 y D3

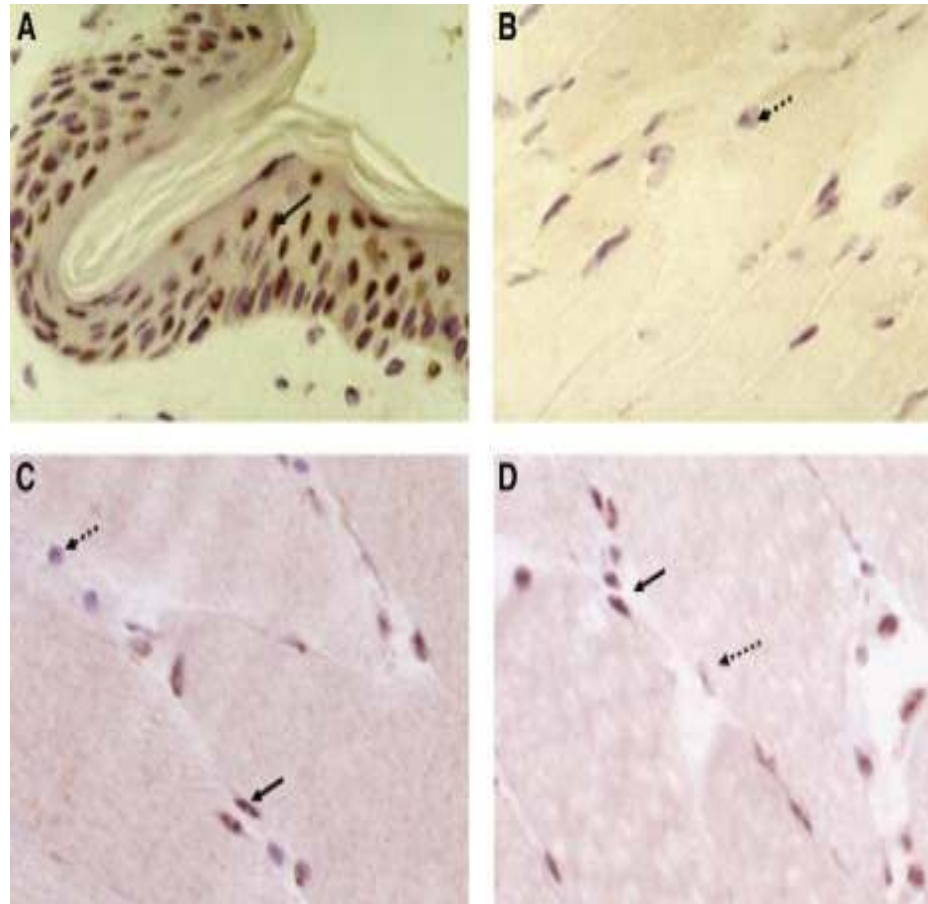
 **Hormona:**  $1,25(\text{OH})_2\text{D}_3$   
Deltanoids

# Vitamin D Status in Primates and Early Humans



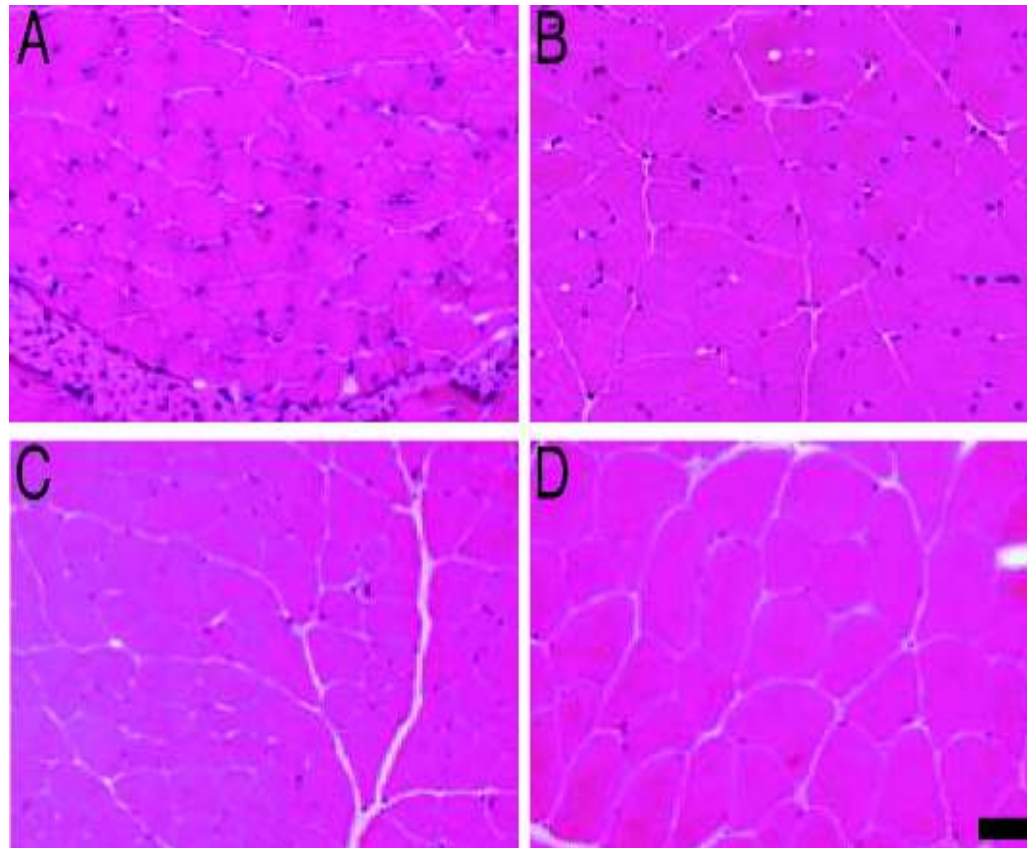


# Vitamina D y envejecimiento



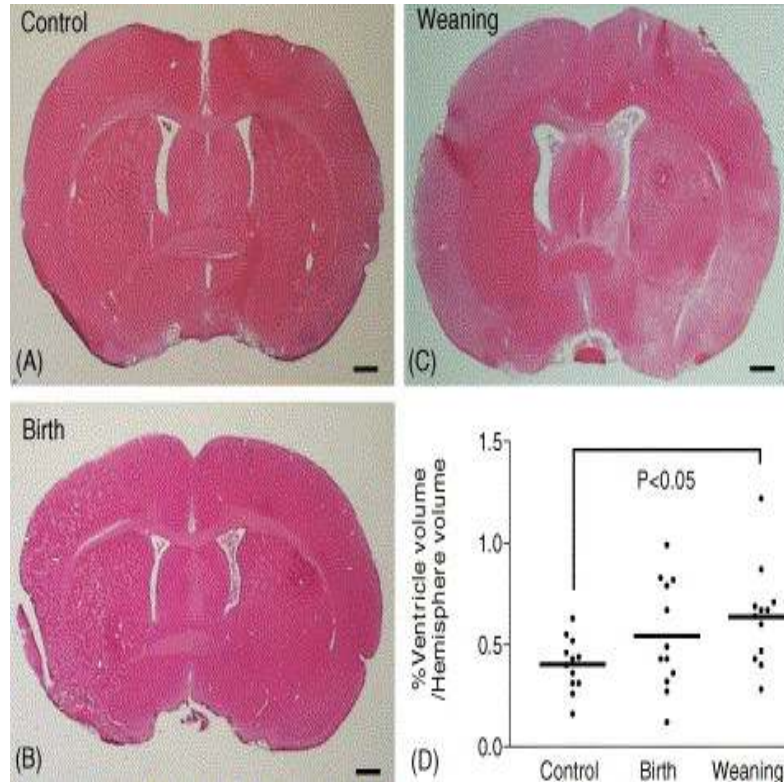
Bishoff-Ferrari H, et al. JBMR, 2004

# Efecto de la vitamina D en el sistema muscular



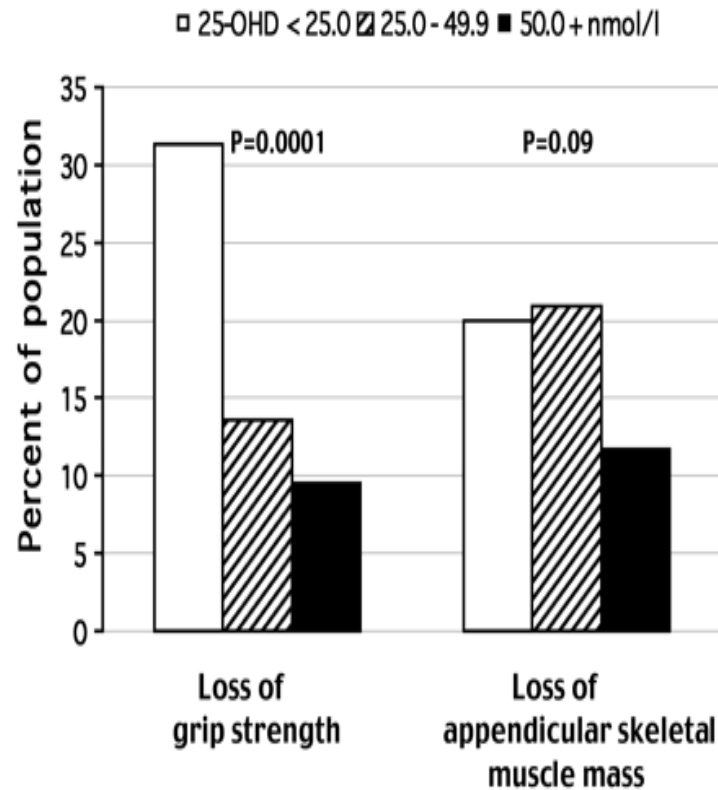


# Efecto de la vitamina D en el sistema neuromuscular



Feron F et al, Brain Res. Bull, 2004

# Efecto de la vitamina D en el sistema neuromuscular



Visser M, et al. JCEM, 2003

**Referencia**

**Evaluacion de Riesgo**

**Alto**

**Moderado**

**Bajo**

- **Intervencion**
- **Seguimiento cercano**

- **Intervencion**
- **Seguimiento**

- **Intervencion**
- **Referencia al Medico de familia**

**Investigación**



# Conclusion

- ❖ Unica intervencion efectiva:
  - ❖ Ejercicio
- ❖ No hay una aproximacion fisiopatologica
- ❖ Suplencia hormonal:
  - ❖ Testosterona
  - ❖ Estrogenos
  - ❖ Vitamina D: mas apropiada
- ❖ Prevencion de eventos clinicos
- ❖ Control de co-morbilidad



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