



# **PATOLOGÍA CARDIOVASCULAR Y OSTEOPOROSIS**

## **MECANISMOS ETIOPATOGÉNICOS**

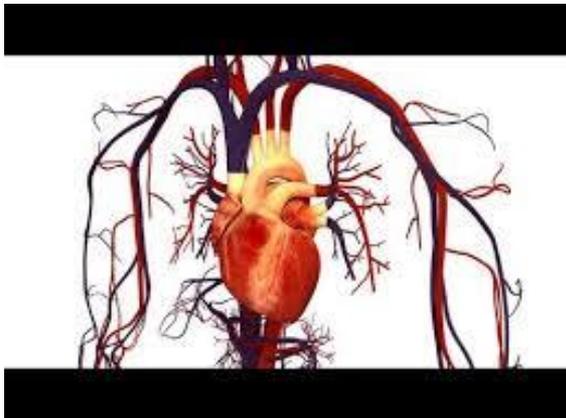
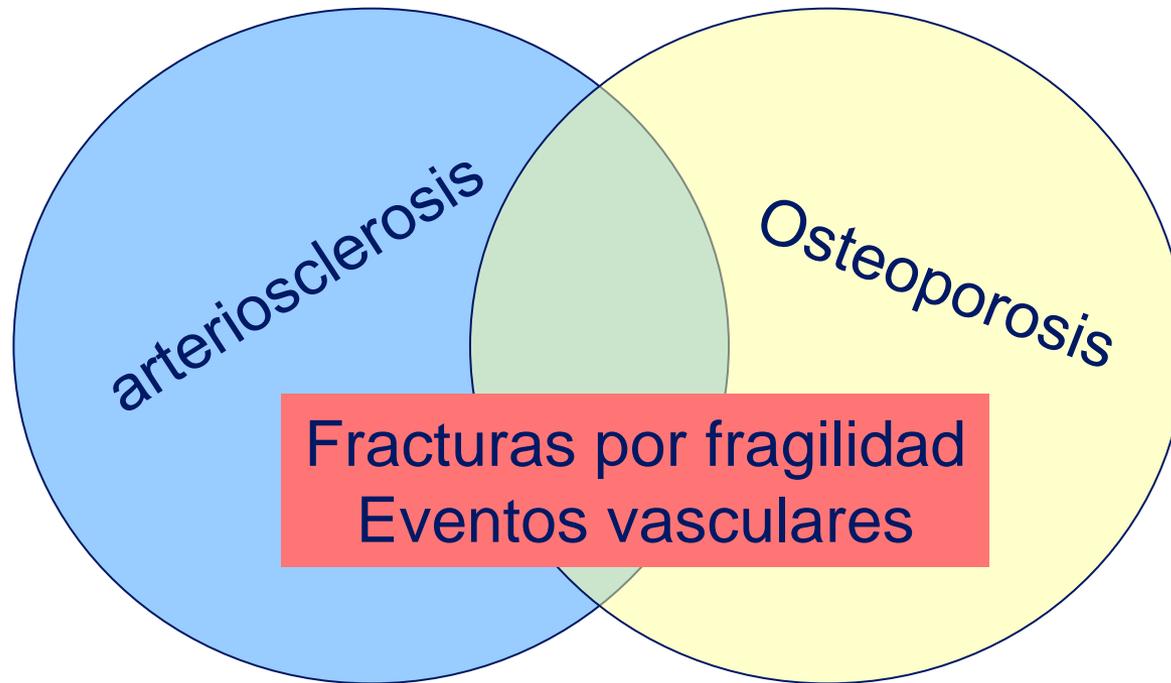
Pedro Rozas Moreno  
Hospital General Universitario de Ciudad Real

# Agenda

1. Datos epidemiológicos.
2. Mecanismos etiopatogénicos.
3. Conclusiones y Aplicabilidad Clínica.



# Arteriosclerosis y fragilidad ósea



# **Estudios epidemiológicos que relacionan fragilidad ósea y enfermedad cardiovascular**

- 1.** Asociación entre osteoporosis y calcificación vascular.
- 2.** Asociación entre calcificación vascular y riesgo de fractura.
- 3.** Asociación entre osteoporosis y eventos cardiovasculares

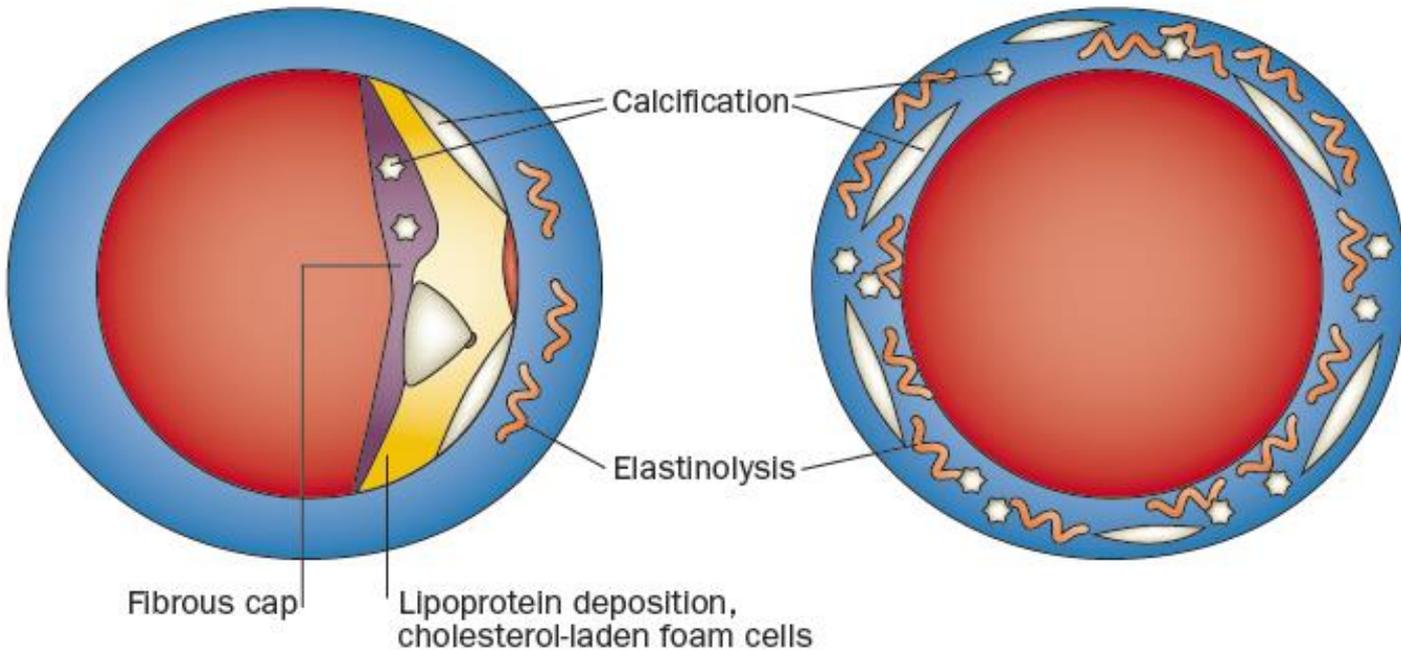
# Tipos de calcificación vascular

## Atherosclerotic calcification

- Eccentric
- Lumen deforming
- Fibrous intimal cap
- Focal elastinolysis
- Vessel stiffening

## Medial calcification

- Concentric
- Vessel stiffening
- Medial fibrosis and elastinolysis
- Adventitial inflammation



La calcificación arterial es el presagio de la enfermedad cardiovascular

# Hallazgo clínico común: el síndrome osteoporosis-calcificación vascular



TC mostrando calcificación severa en varón de 71 años con fracturas vertebrales y de cadera (DXA con T-score lumbar -3.1 SD y femoral -2.6 SD)

# Association of Coronary Artery and Aortic Calcium With Lumbar Bone Density

## The MESA Abdominal Aortic Calcium Study

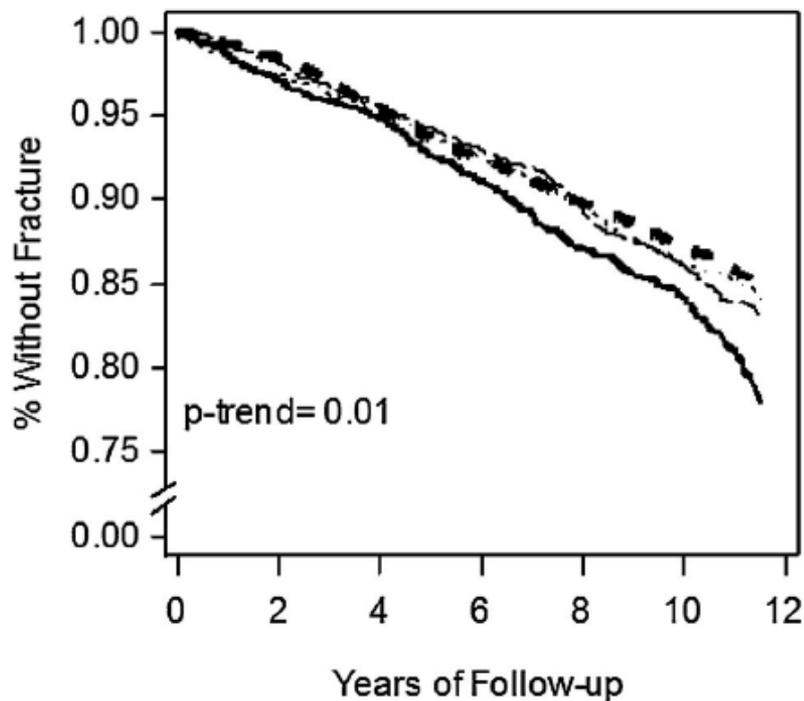
**Table 2.** Distribution of Coronary Artery Calcium and Abdominal Aortic Calcium Scores by Sex-Specific Quartile of Volumetric Trabecular Bone Mineral Density of the Lumbar Spine, MESA Abdominal Aortic Calcium Study, 2000–2005

	Quartile of vBMD							
	Women				Men			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
No. of subjects	242	235	235	234	244	236	241	242
vBMD cutpoint, mg/cm <sup>3</sup>	<83	<108	<137	≥137	<94	<118	<145	≥145
Mean vBMD (SD)	63 (15)	96 (8)	122 (8)	164 (26)	75 (17)	107 (7)	131 (8)	172 (25)
Age, years								
Range	51–86	46–85	48–86	46–84	47–88	47–85	47–83	46–85
Mean (SD)	73 (7)	66 (8)	62 (8)	59 (8)	72 (9)	66 (9)	60 (9)	59 (9)
Median (IQR <sup>a</sup> )	73 (9)	66 (12)	62 (12)	57 (12)	71 (12)	67 (15)	59 (14)	57 (13)
In(CAC + 1)								
Median (IQR)	3.5 (5.4)	1.1 (4.3)	0 (3.2)	0 (2.1)	4.8 (3.4)	4.0 (5.7)	2.1 (4.9)	1.5 (4.7)
Mean (SD)	3.1 (2.5)	2.1 (2.4)	1.4 (2.1)	1.1 (1.9)	4.2 (2.4)	3.5 (2.7)	2.6 (2.6)	2.4 (2.5)
Prevalence, % (no.)	67 (163)	51 (120)	37 (88)	30 (71)	83 (202)	72 (170)	59 (141)	59 (142)
Adjusted prevalence <sup>b</sup> (95% CI)	50 (40, 61)	46 (37, 57)	41 (33, 52)	42	67 (59, 75)	64 (57, 72)	62 (55, 71)	66
In(AAC + 1)								
Median (IQR)	7.1 (3.1)	5.4 (7.4)	4.0 (6.3)	3.4 (5.9)	6.9 (2.7)	6.3 (4.2)	4.7 (6.8)	3.4 (6.3)
Mean (SD)	6.0 (2.7)	4.6 (3.1)	3.4 (3.1)	3.2 (3.1)	6.3 (2.5)	5.3 (3.0)	4.0 (3.2)	3.3 (3.3)
Prevalence, % (no.)	88 (212)	74 (175)	60 (140)	58 (135)	91 (222)	81 (190)	66 (159)	55 (132)
Adjusted prevalence <sup>b</sup> (95% CI)	71 (64, 79)	70 (63, 79)	62 (55, 71)	69	76 (68, 84)	72 (64, 81)	71 (62, 80)	63

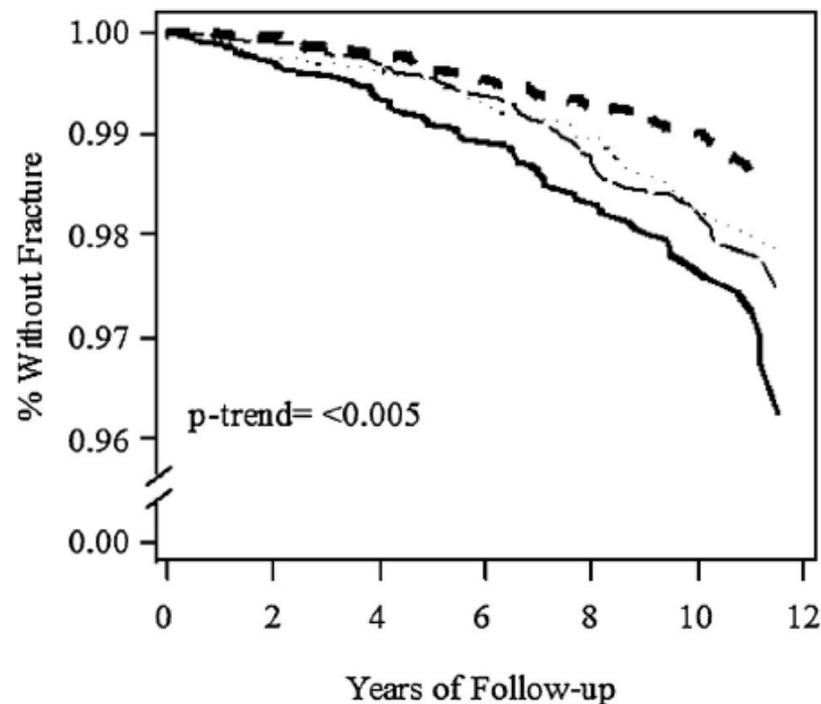
946 mujeres (65.5 años) y 963 varones (64.1 años)

# High Hip Fracture Risk in Men With Severe Aortic Calcification: MrOS Study

Fxs no vertebrales

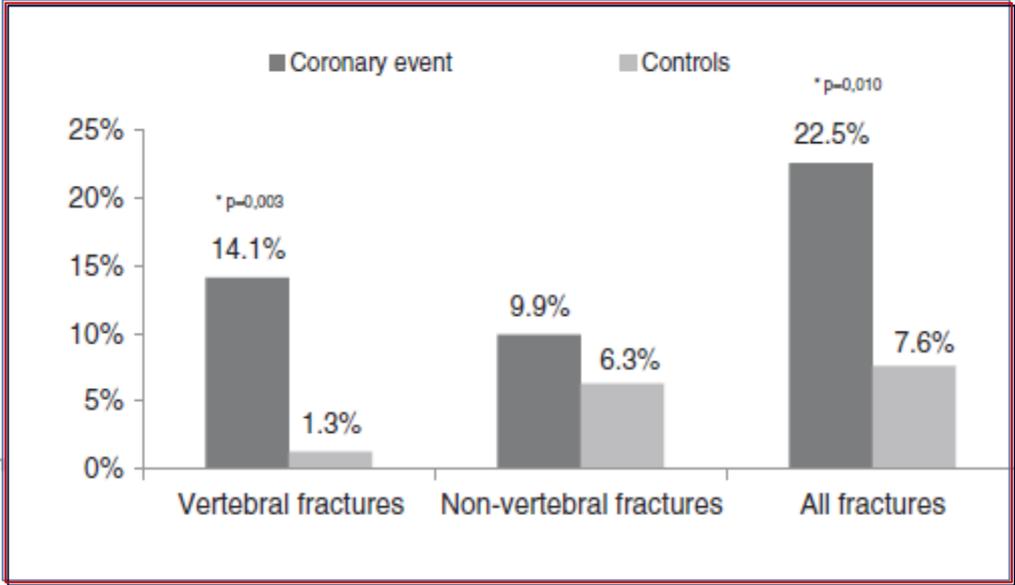
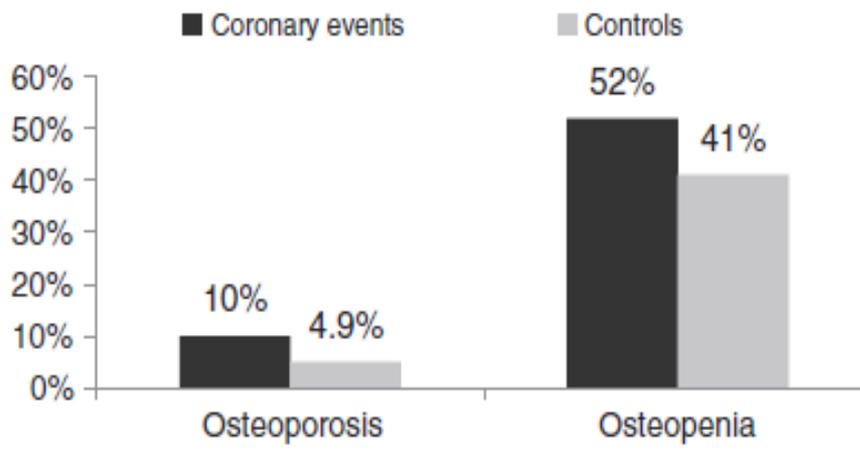


Fxs de cadera



5994 varones > de 65 años con un seguimiento de 10.5 años

# Higher prevalence of morphometric vertebral fractures in patients with recent coronary events independently of BMD measurements ☆



Estudio caso-control con 150 pacientes (30-80 años) con síndrome metabólico y evento coronario agudo

# Ischemic heart disease is associated with vertebral fractures in patients with type 2 diabetes mellitus

Manuel Muñoz-Torres<sup>1</sup>, Rebeca Reyes-García<sup>1</sup>, Antonia García-Martin<sup>1\*</sup>, José Juan Jiménez-Moleón<sup>2</sup>, Amanda Rocío Gonzalez-Ramírez<sup>3</sup>, María Jesús Lara-Villoslada<sup>4</sup>, Pedro Rozas Moreno<sup>1,5</sup>

**Table 3** | Associations between retinopathy, coronary heart disease, waist circumference and vertebral fractures

	OR	95% CI	P-value
<b>Retinopathy</b>			
Crude	4.09	(1.01–12.5)	0.043
Adjusted for age and sex	2.97	(1.01–8.7)	0.047
Full model	2.27	(0.71–7.27)	<i>P</i> = 0.16
<b><u>Ischemic heart disease</u></b>			
Crude	5.02	(1.1–9.7)	0.025
Adjusted for age and sex	3.31	(1.13–9.7)	0.029
Full model	3.33	(1.02–10.91)	0.047
<b>Waist circumference</b>			
Crude	1.058	1.006–1.114	0.029
Adjusted for age and sex	1.052	0.997–1.11	0.66
Full model	1.063	0.967–1.169	0.20

Full model: adjusted for age, sex, retinopathy, ischemic heart disease and body mass index.



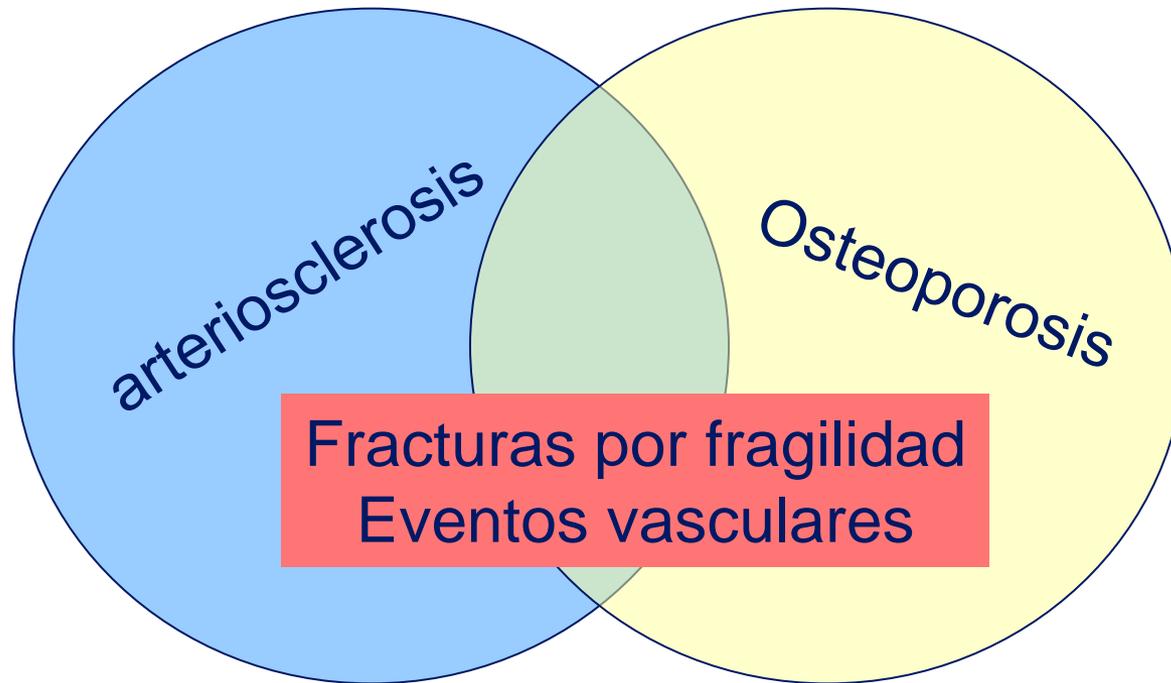
# Bone Mineral Density and Incidence of Stroke

## European Prospective Investigation Into Cancer-Norfolk Population-Based Study, Systematic Review, and Meta-Analysis

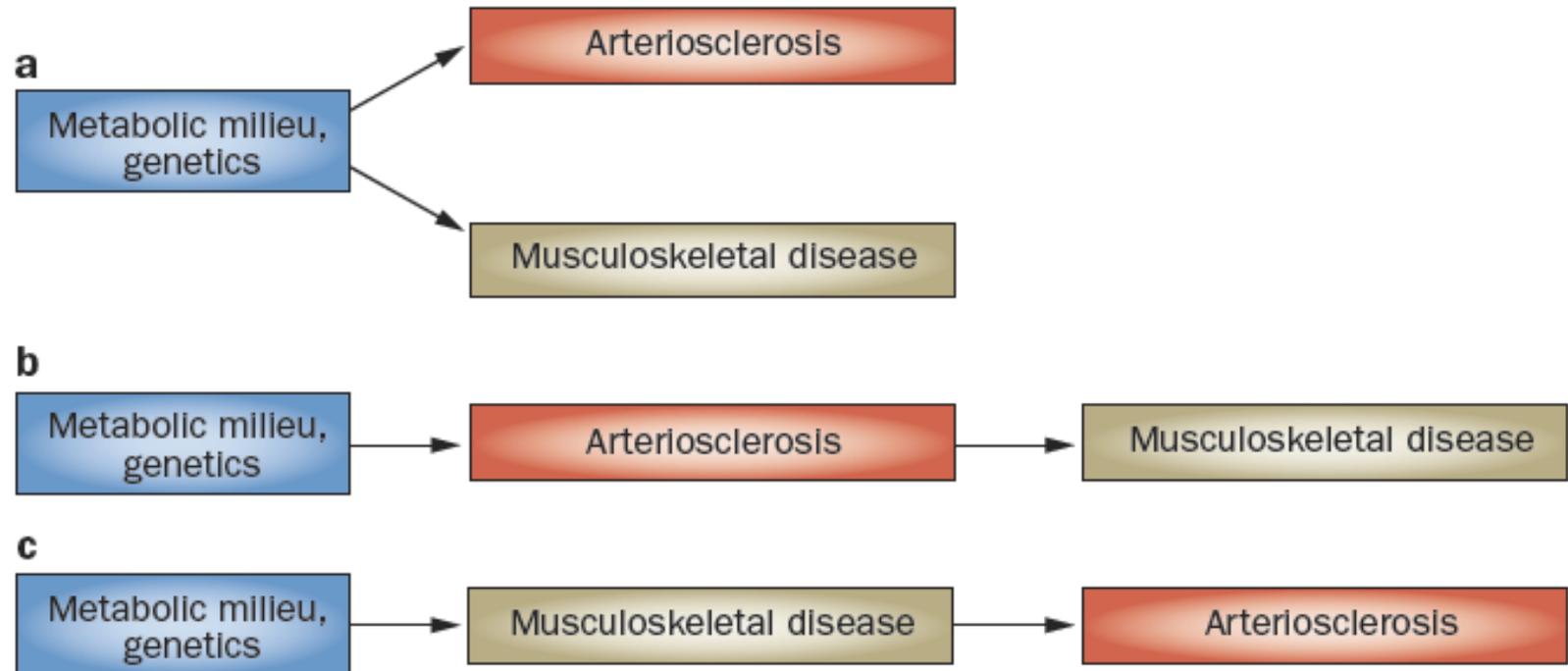
**Table 3. Cox Multivariate Regression Model of Risk Factors for Incidence Stroke According to BUA and VOS in 12 795 individuals, 42 to 82 Years Old of EPIC-Norfolk (1997–2000 and 2009–2011)**

	BUA Model		VOS Model	
	Relative Risk (95% CI)	<i>P</i> Value	Relative Risk (95% CI)	<i>P</i> Value
Age per 1-y increase	1.12 (1.10–1.13)	<0.001	1.12 (1.10–1.13)	<0.001
Sex	0.63 (0.50–0.79)	<0.001	0.69 (0.56–0.85)	<0.001
Systolic BP per 5 mm Hg increase	1.04 (1.02–1.07)	0.001	1.04 (1.02–1.07)	0.001
Cholesterol by 1 mmol/L increase	0.97 (0.90–1.05)	0.48	0.97 (0.90–1.05)	0.45
Current smoking	1.79 (1.33–2.41)	<0.001	1.80 (1.34–2.42)	<0.001
Being physically active	0.72 (0.58–0.89)	0.002	0.72 (0.58–0.89)	0.003
BMI >25 kg/m <sup>2</sup>	1.02 (0.81–1.29)	0.88	0.98 (0.77–1.23)	0.83
No or lower than A-level education	1.16 (0.96–1.39)	0.12	1.16 (0.96–1.39)	0.12
Lower occupational social class	0.92 (0.76–1.11)	0.39	0.92 (0.76–1.12)	0.42
Prevalent diabetes mellitus	1.50 (1.05–2.16)	0.028	1.53 (1.07–2.20)	0.021
Prevalent MI	1.92 (1.39–2.65)	<0.001	1.93 (1.40–2.67)	<0.001
BUA per 20 dB/MHz decrease	1.17 (1.05–1.30)	0.005		
VOS per 40 m/s decrease			1.12 (1.02–1.22)	0.019

# Arteriosclerosis y fragilidad ósea

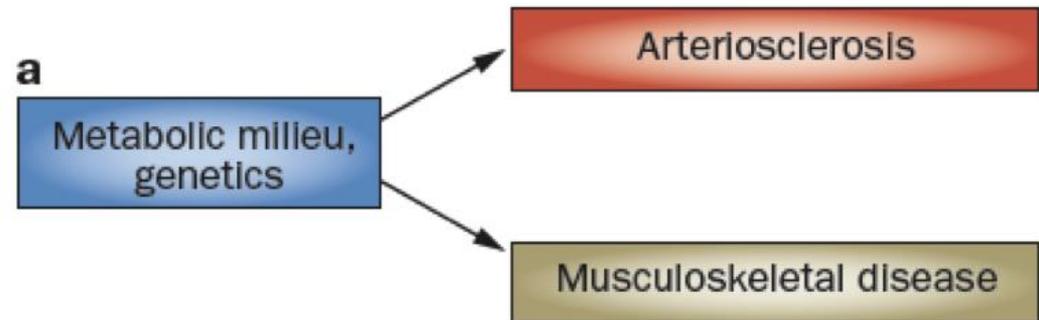


# Relaciones patogénicas entre fragilidad ósea y arteriosclerosis



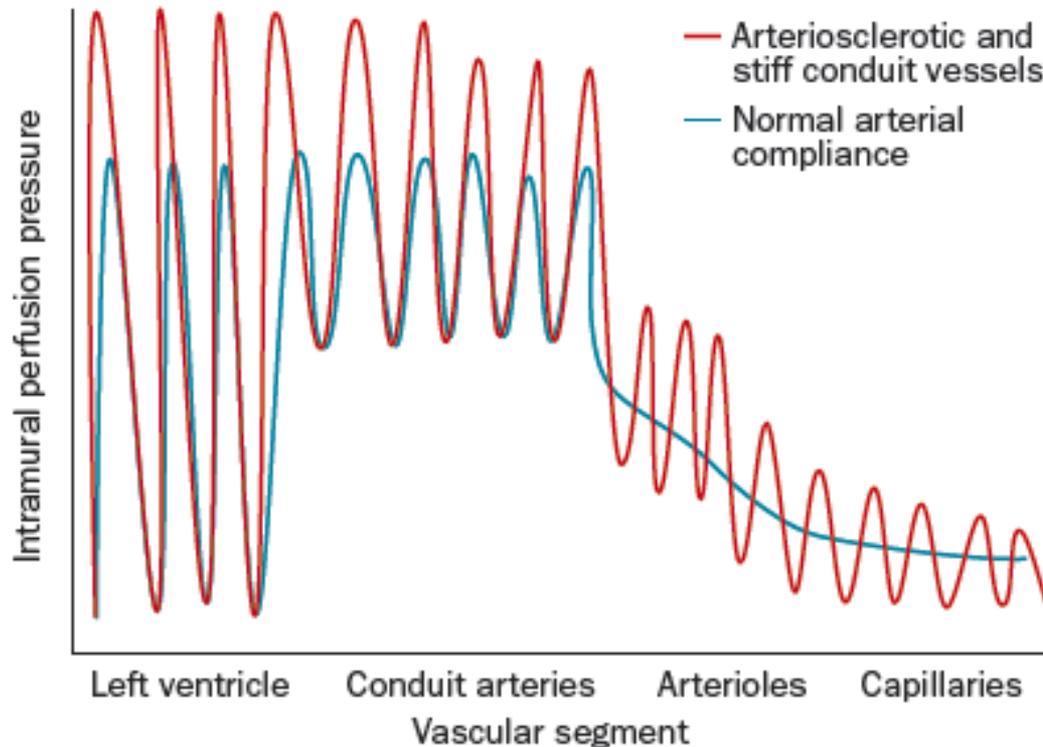
# Factores de riesgo comunes para fragilidad ósea y enfermedad vascular

- Envejecimiento
- Inflamación crónica
- Tabaquismo
- Diabetes mellitus
- Deficiencia estrogénica
- Dislipemia y radicales libres
- Hipovitaminosis C, D y K
- Enfermedad renal crónica



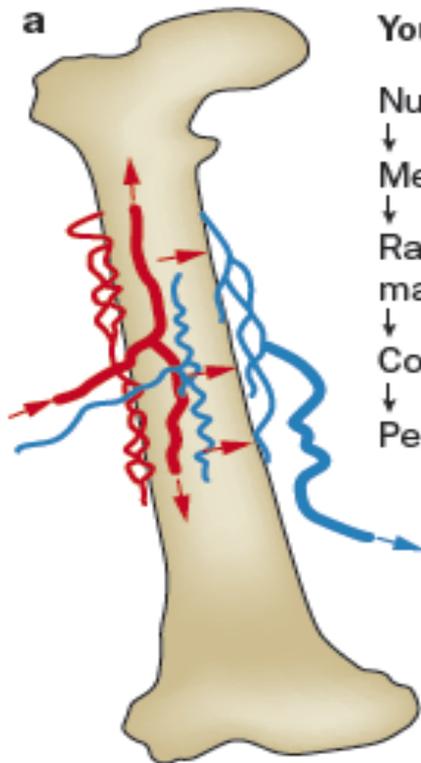
# Repercusión de la arteriosclerosis en la función vascular

b



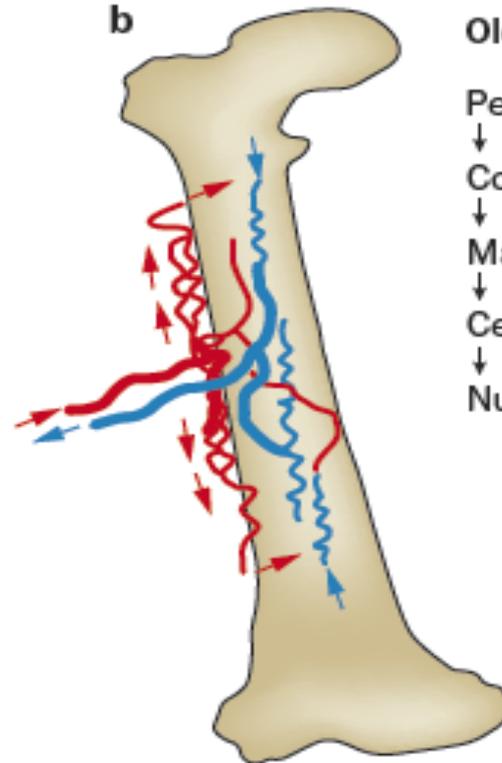
# Repercusiones de la enfermedad vascular sobre el hueso

**b**



**Younger centrifugal flow**

Nutrient artery  
↓  
Medullary arteries  
↓  
Radial branches and marrow sinusoids  
↓  
Cortical capillaries  
↓  
Periosteal venules



**Older centripetal flow**

Periosteal arteries  
↓  
Cortical capillaries  
↓  
Marrow sinusoids  
↓  
Central venous sinus  
↓  
Nutrient vein

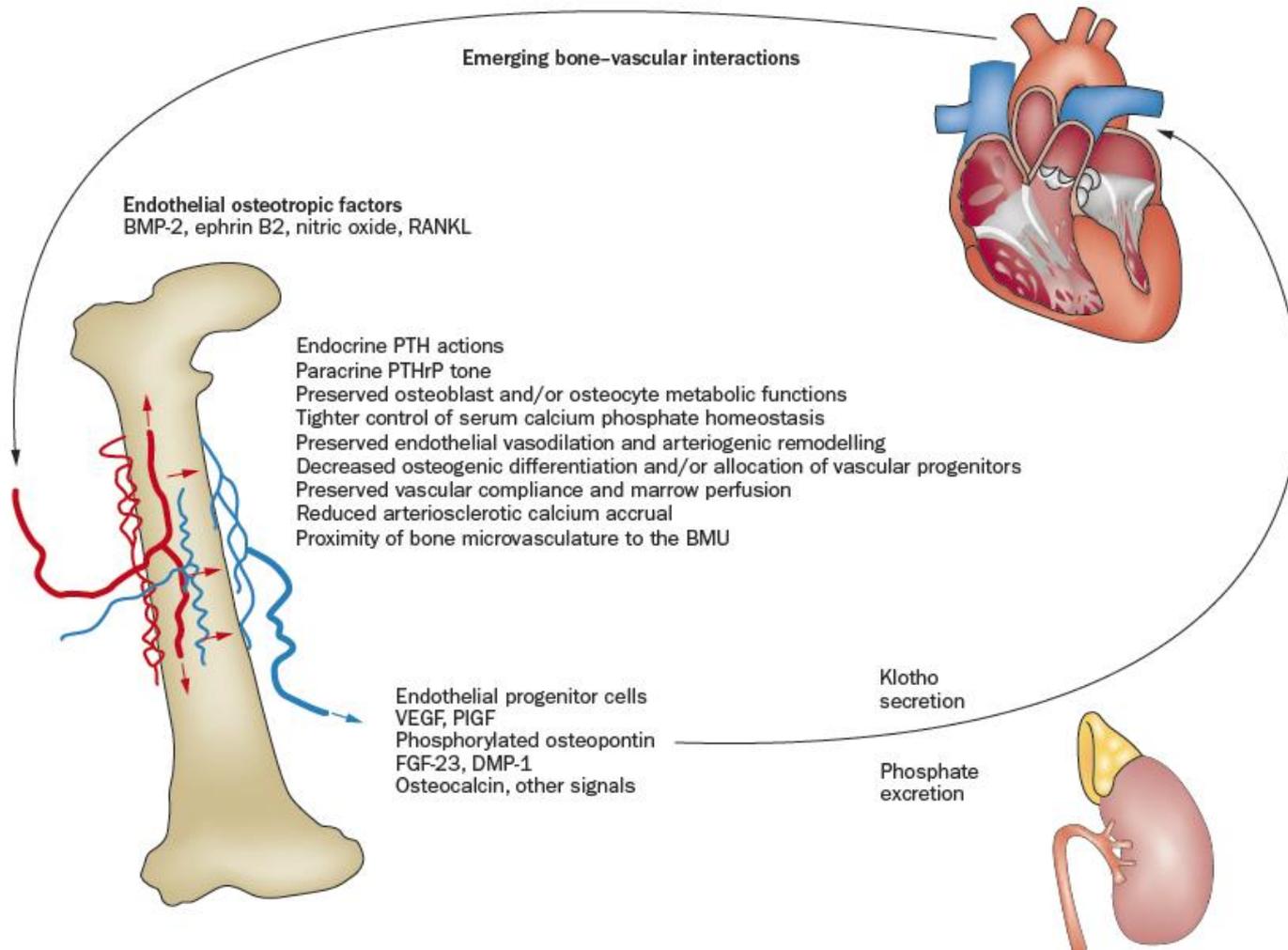
# Relación bidireccional hueso-sistema vascular

c

Metabolic milieu,  
genetics

Musculoskeletal disease

Arteriosclerosis





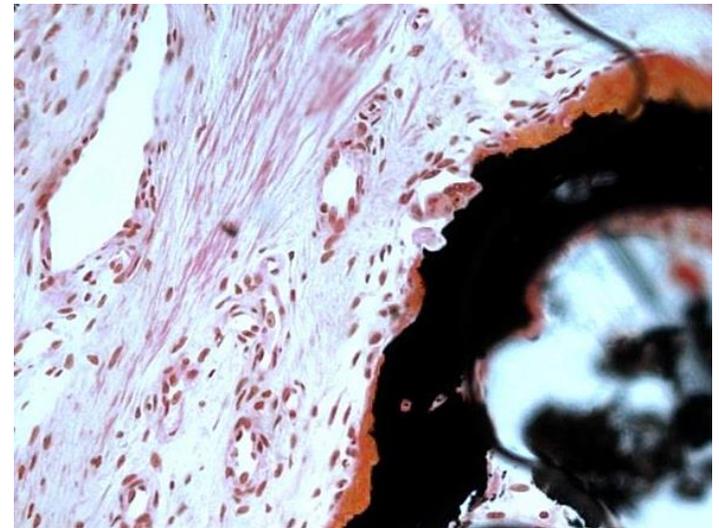
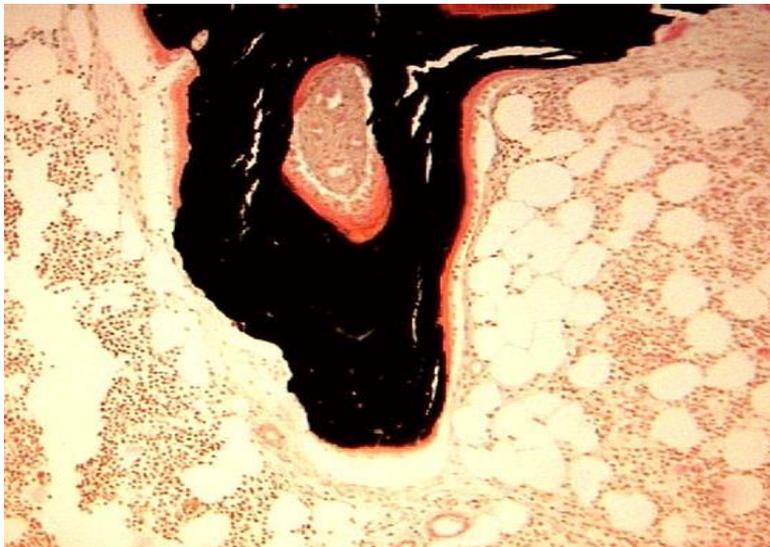
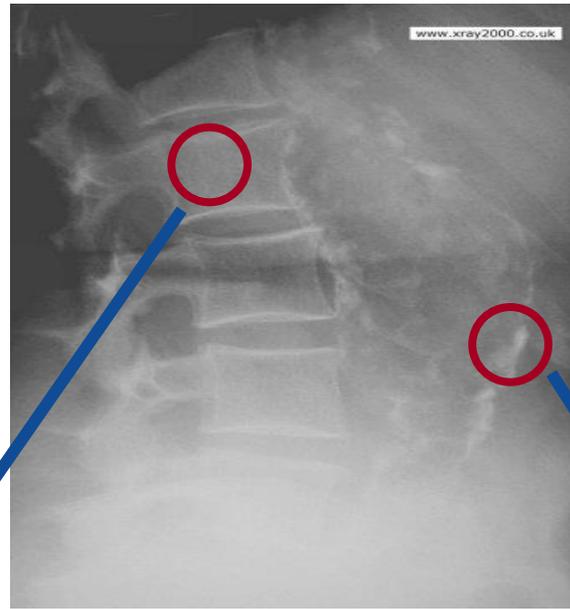
...lo que llamamos azar es nuestra ignorancia de la compleja maquinaria de la causalidad)...

(Jorge Luis Borges)

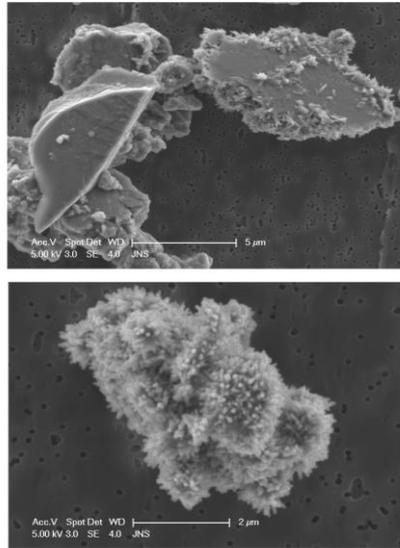
akifrases.com

**¿MECANISMOS BIOLÓGICOS COMPARTIDOS?**

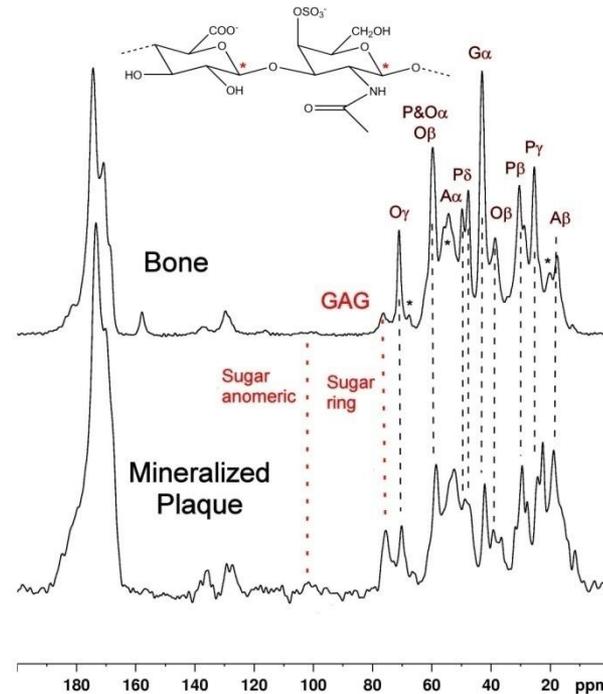
# Semejanzas entre tejido óseo y calcificación vascular



# Mineralized tissue from bone and plaques have physicochemical similarities



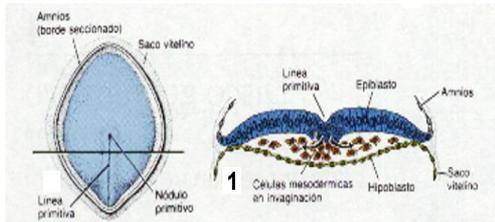
SEM



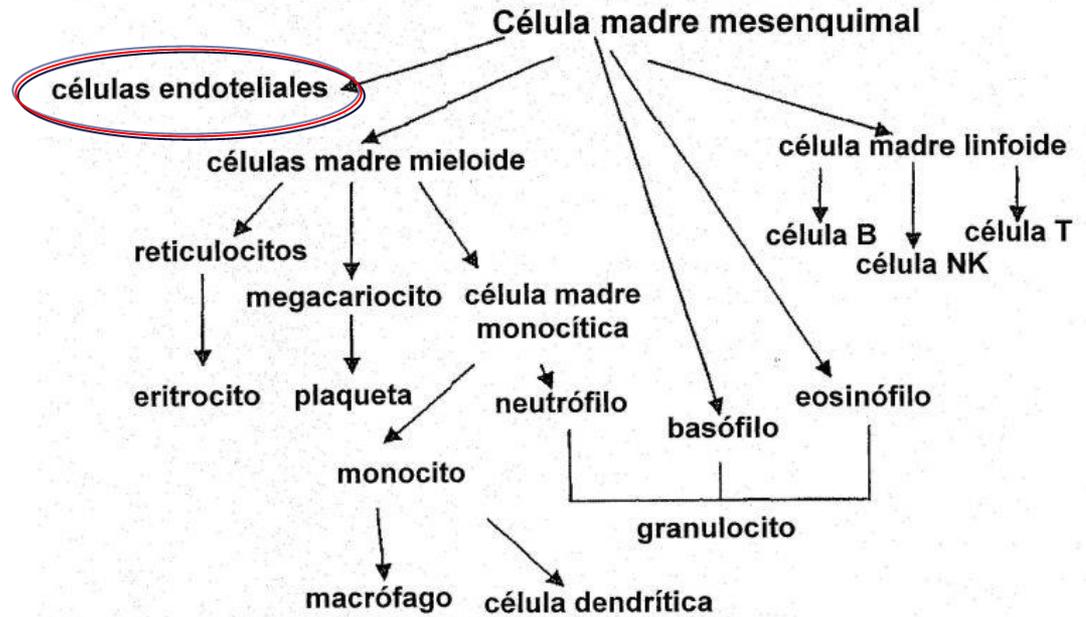
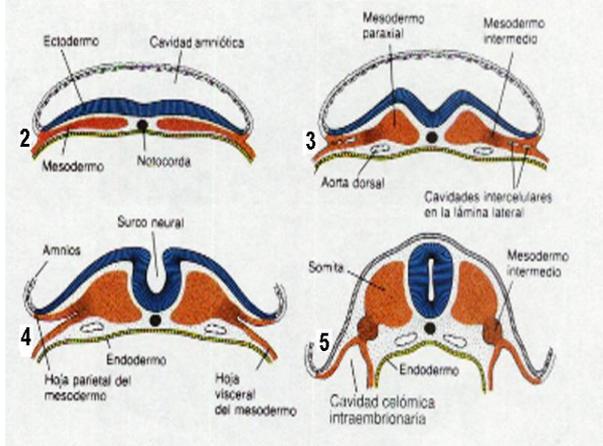
Comparison of typical  $^{13}\text{C}$  CPMAS spectra  
(Courtesy of Drs. M. Schoppet, Germany and C.M. Shanahan, UK)

# ORIGEN COMÚN: Sistema vascular y tejido óseo

## FORMACIÓN del MESODERMO



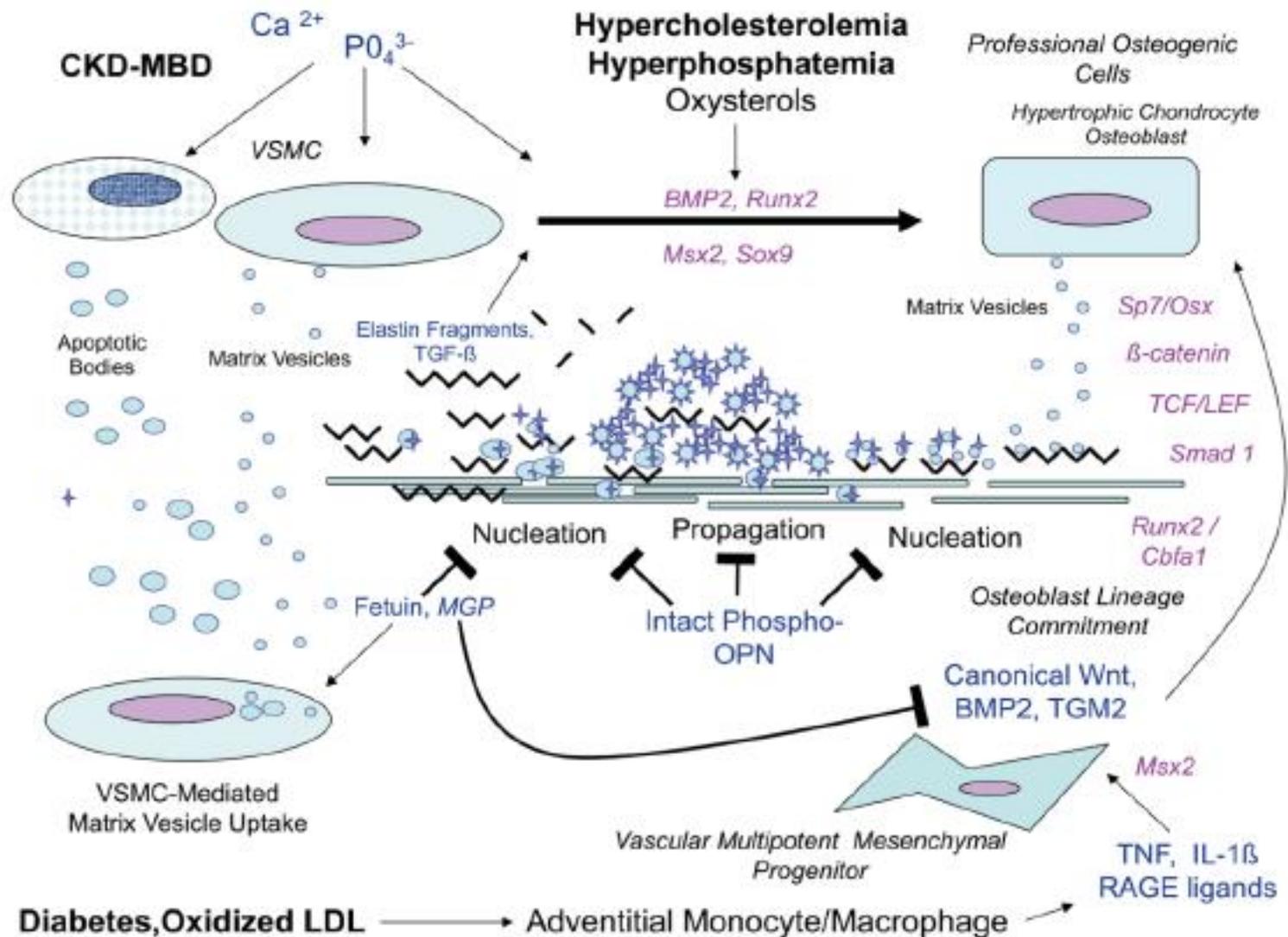
## DIFERENCIACIÓN del MESODERMO



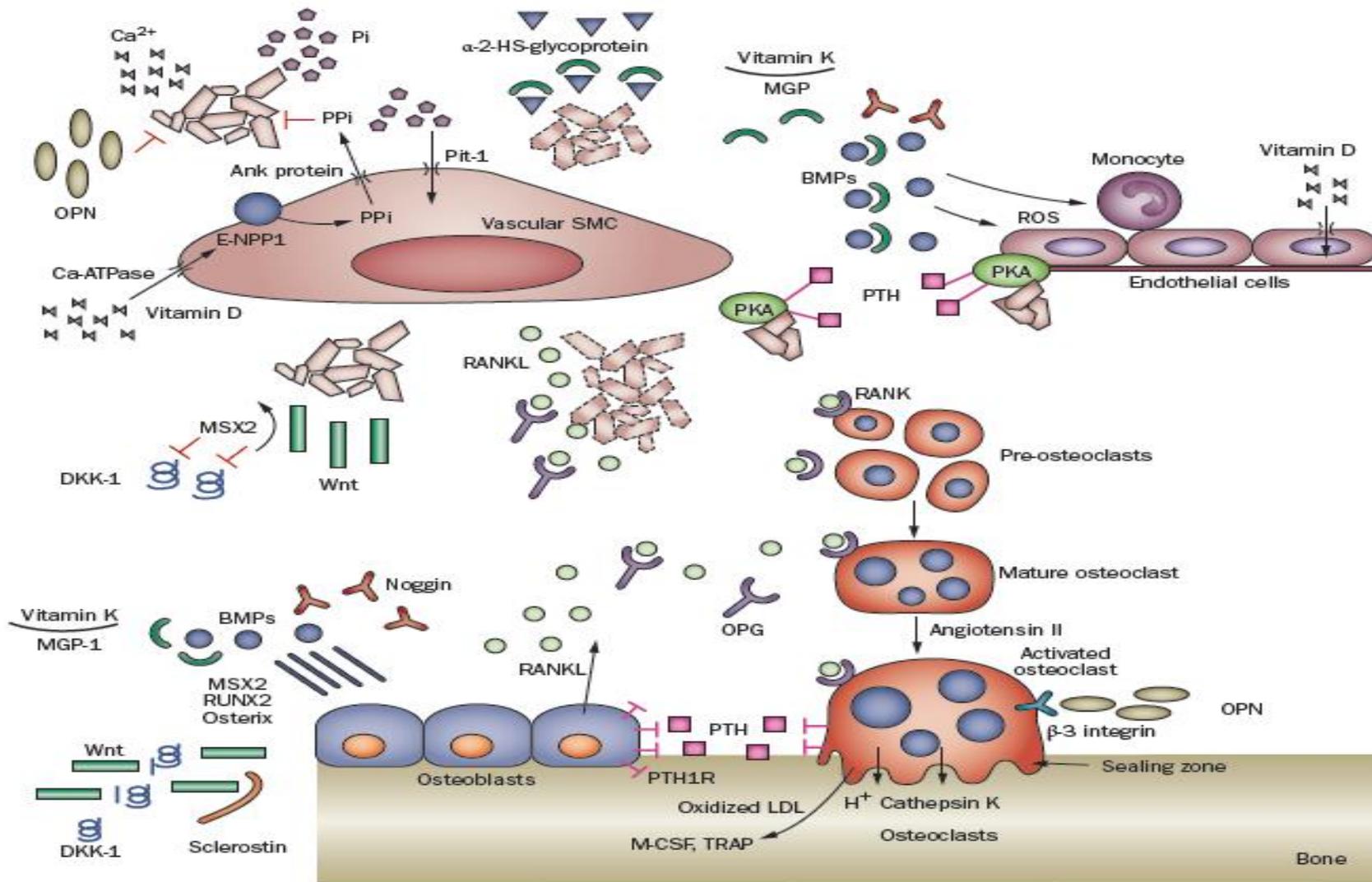
## MESENCHYMAL STEM CELL



# DIFERENCIACIÓN CELULAR OSTEOGÉNICA



# Remodelado óseo y calcificación vascular



# Factores compartidos en la asociación fragilidad ósea y enfermedad cardiovascular

- **Receptores**

- ER- $\alpha$ , ER- $\beta$ , CaSR, VDR

- **Citokinas y antagonistas de citokinas**

- RANKL, OPG, BMPs

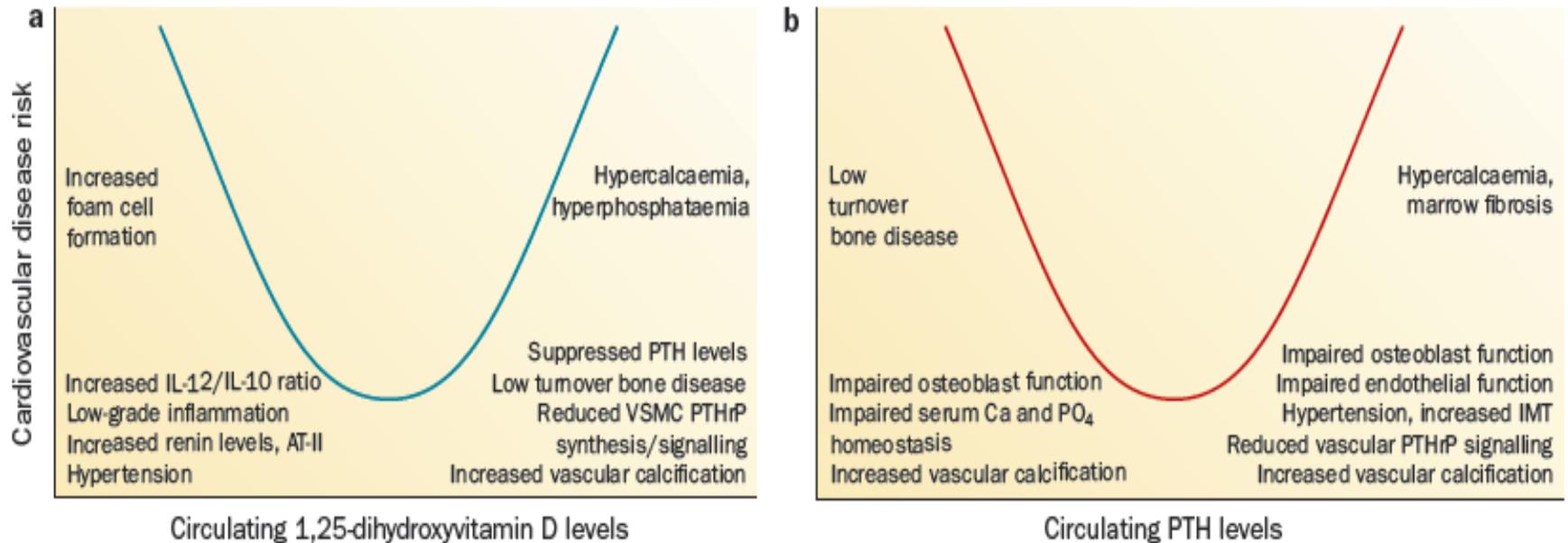
- **Proteínas óseas**

- MGP, Esclerostina, OPN, Fetuina-A

- **Otros**

- FGF-23, Proteínas Wnt, DKK1; vitamina K-D, PTH, Dislipemia

# Relaciones entre hormonas calciotropas y enfermedad cardiovascular



# Factores compartidos en la asociación fragilidad ósea y enfermedad cardiovascular

- **Receptores**

- ER- $\alpha$ , ER- $\beta$ , CaSR, VDR

- **Citokinas y antagonistas de citokinas**

- RANKL, OPG, BMPs

- **Proteínas óseas**

- MGP, Esclerostina, OPN, Fetuina-A

- **Otros**

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# Factores compartidos en la asociación fragilidad ósea y enfermedad cardiovascular

- **Receptores**

- ER- $\alpha$ , ER- $\beta$ , CaSR, VDR

- **Citokinas y antagonistas de citokinas**

- RANKL, OPG, BMPs

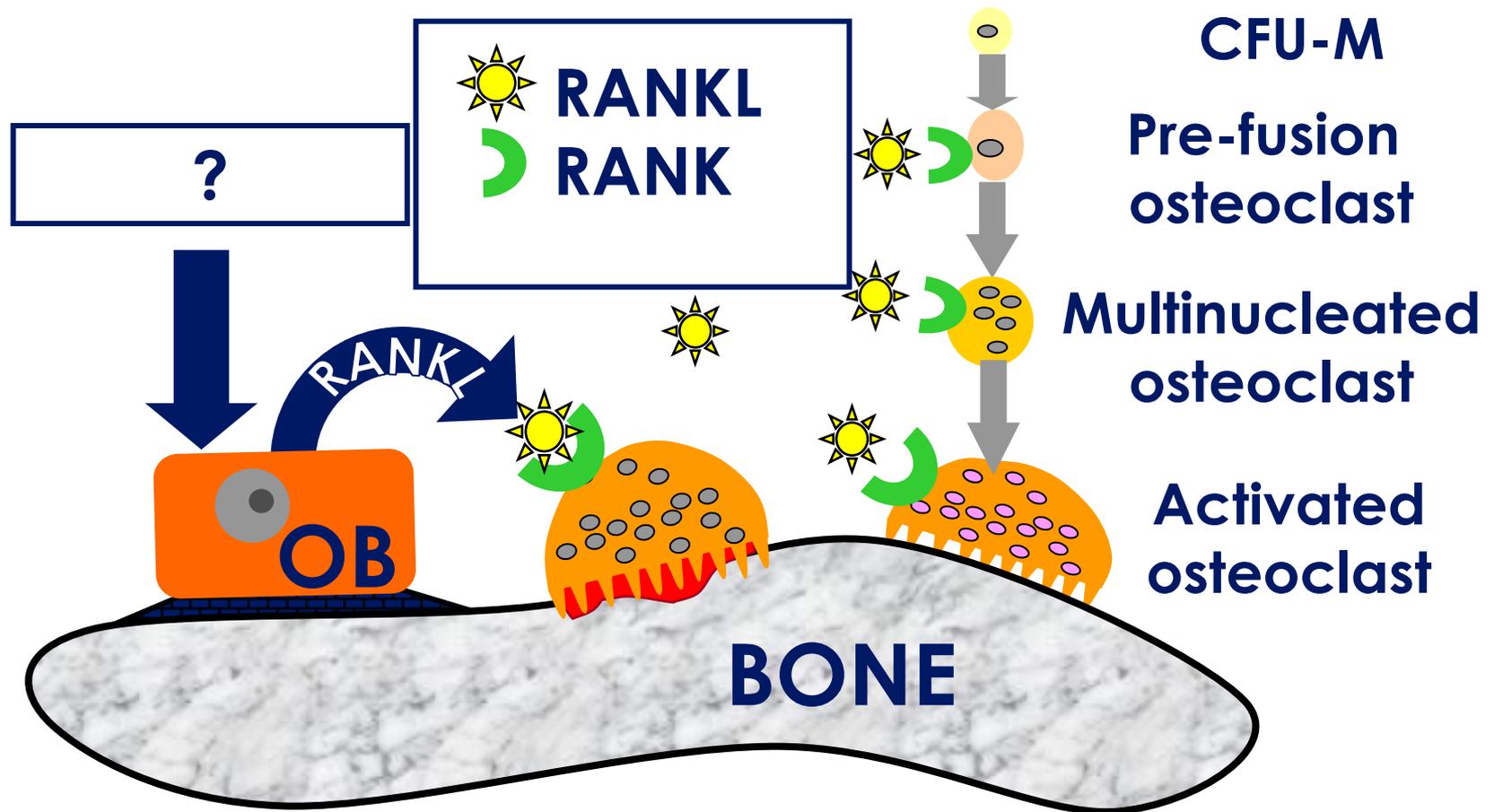
- **Proteínas óseas**

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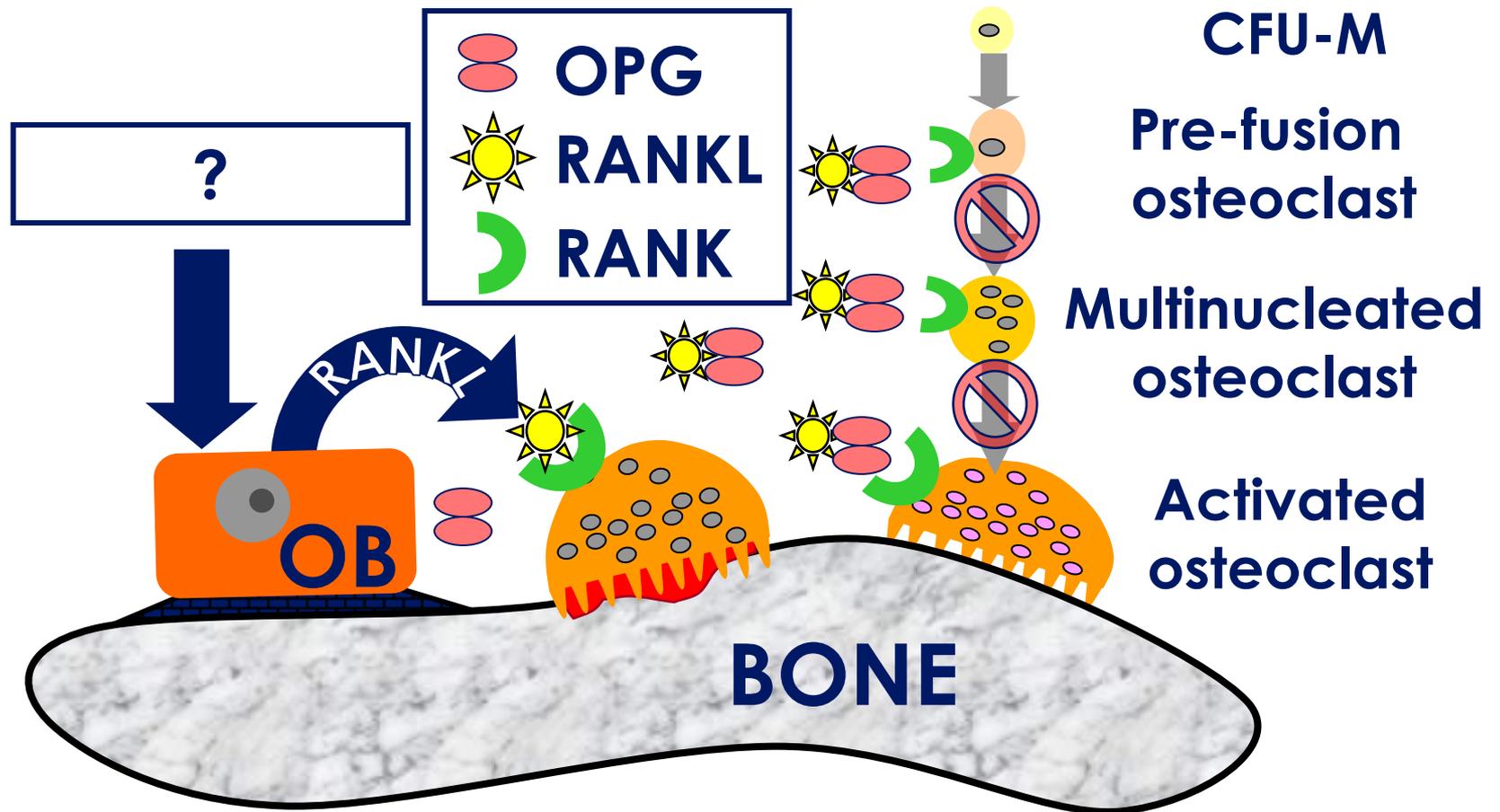
- **Otros**

- FGF-23, Proteínas Wnt, DKK1; vitamina K, PTH, Dislipemia

# RANK ligand is an essential cytokine for osteoclasts



# RANKL blockade by the soluble decoy receptor OPG

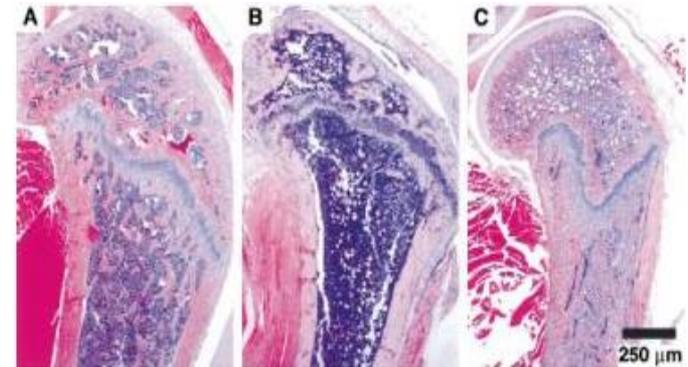


# OPG-deficient mice - Skeletal effects

2 months

1 month

OPG +/+ OPG -/- OPG -/-  
+ OPG  
transgene



6 months

5 months

**OPG deficiency causes osteoporosis, OPG transgene osteopetrosis**

Bucay N et al. *Genes Dev* 1998;12:1260-1268.

Min H et al. *J Exp Med* 2000;192:463-474.

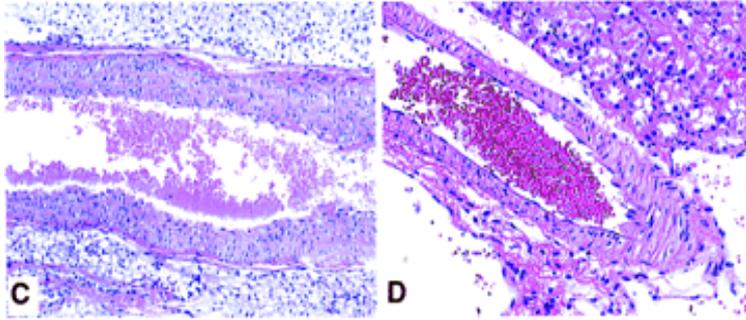
# OPG-deficient mice - Vascular phenotype

Aorta

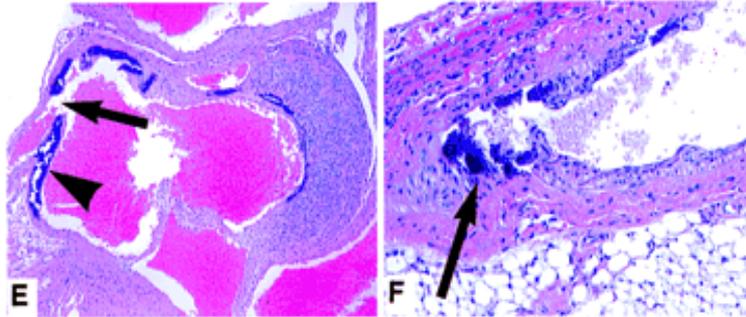
Renal arteries

Aorta

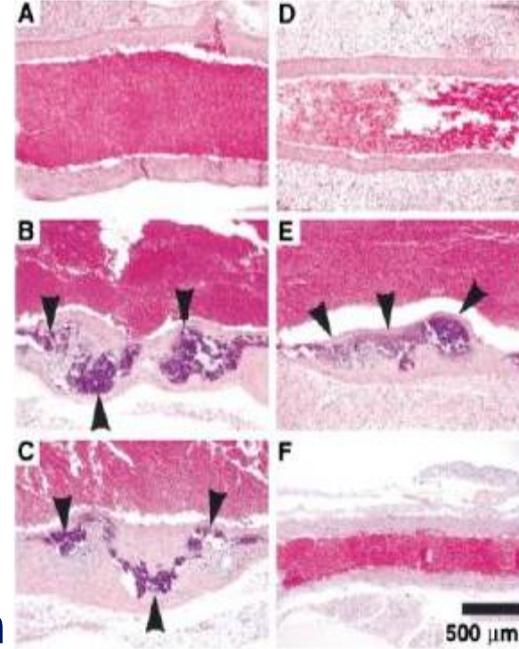
+/+



-/-



+/+



+/+

-/-

-/-

-/-

-/-

+ OPG  
protein

+ OPG  
transgene

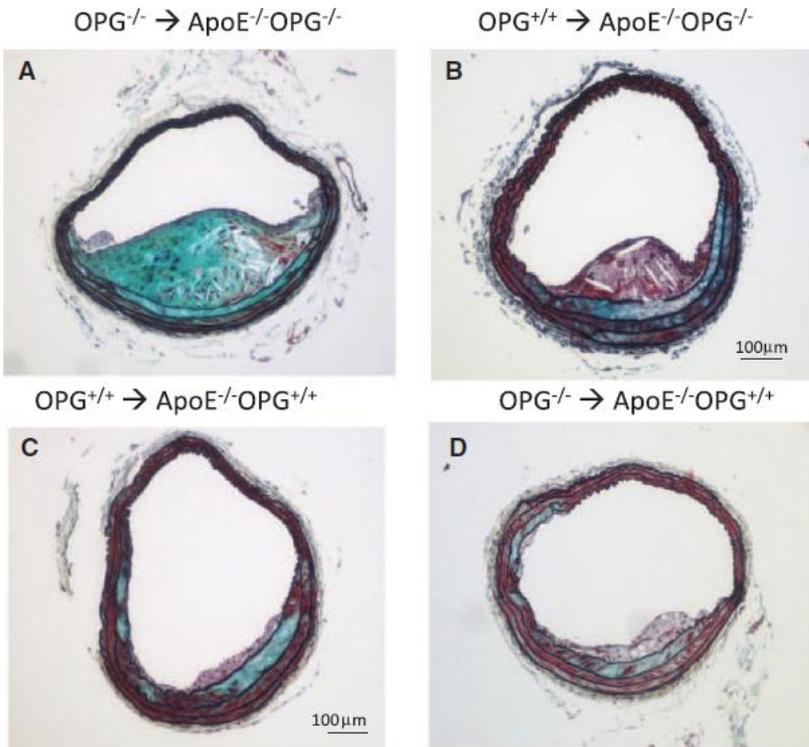
**Medial calcification reminiscent of Mönckeberg medial sclerosis**

*Bucay N et al. Genes Dev 1998;12:1260-1268.*

*Min H et al. J Exp Med 2000;192:463-474.*

# OPG: previene la calcificación y reduce la lesión arterioesclerótica

Bone Marrow- or Vessel Wall-Derived Osteoprotegerin Is Sufficient to Reduce Atherosclerotic Lesion Size and Vascular Calcification



Vitamin D intoxication of rats (alizarin red)



Vitamin D

Vitamin D  
+ OPG

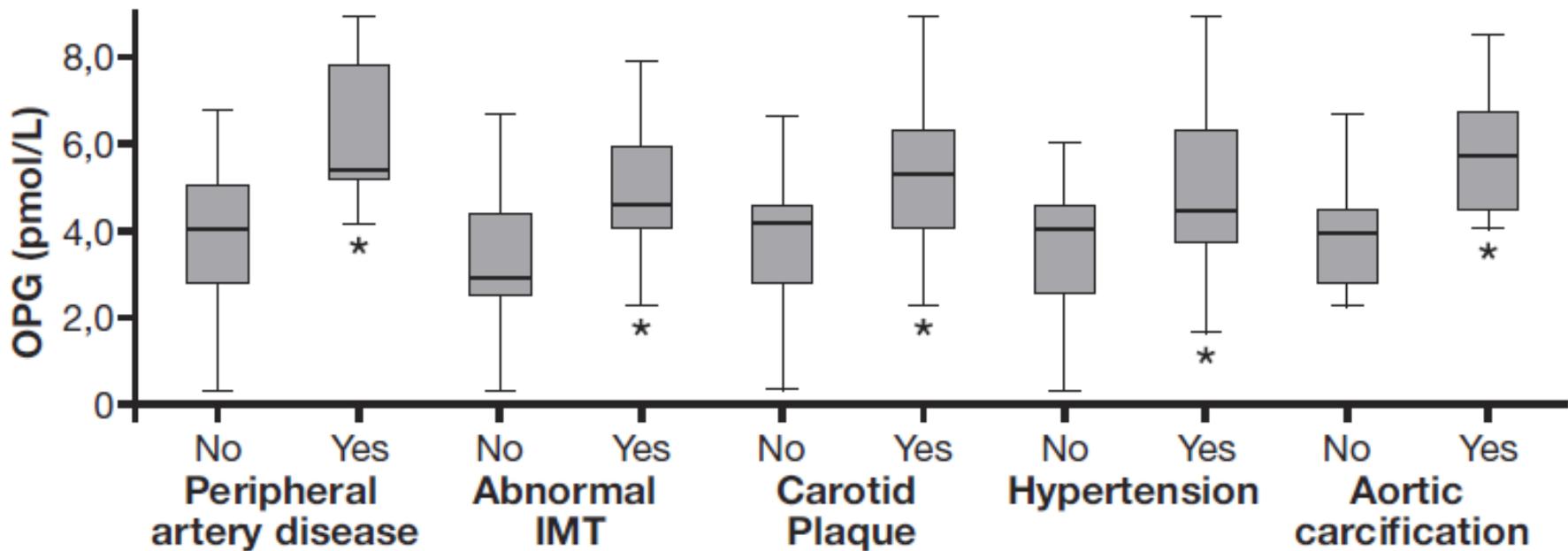
Control

Price PA et al. *Arterioscler Thromb Vasc Biol* 2001;21:1610-1616.

Callegari A et al, *Arterioscler Thromb Vasc Biol*. 2013

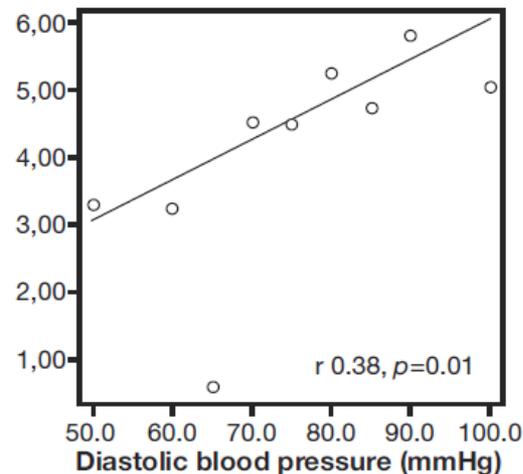
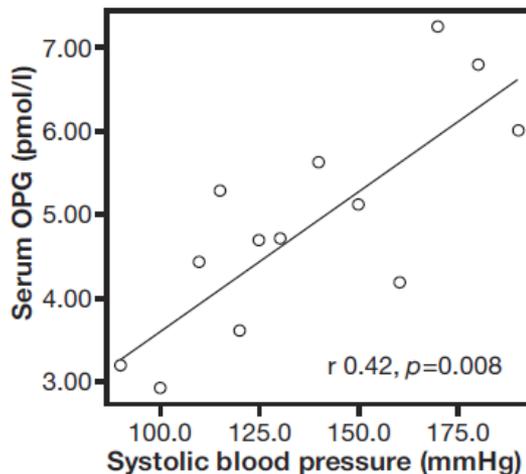
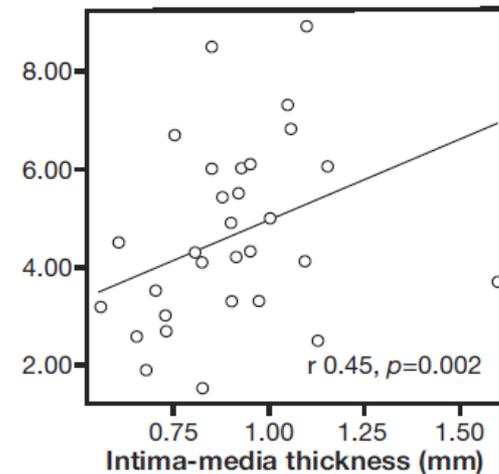
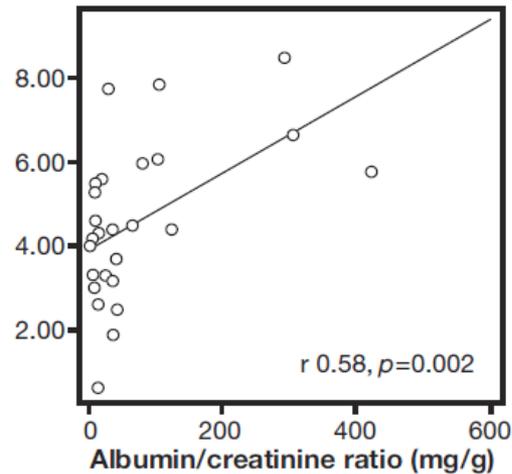
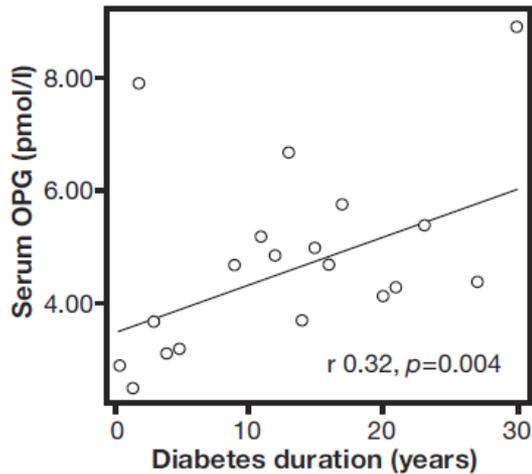
# Serum osteoprotegerin: Bone or cardiovascular marker in Type 2 diabetes males?

P. Rozas Moreno<sup>1,2</sup>, R. Reyes García<sup>1</sup>, A. García-Martín<sup>1</sup>, M. Varsavsky<sup>1</sup>, J.A. García-Salcedo<sup>1</sup>,  
and M. Muñoz-Torres<sup>1</sup>



# Serum osteoprotegerin: Bone or cardiovascular marker in Type 2 diabetes males?

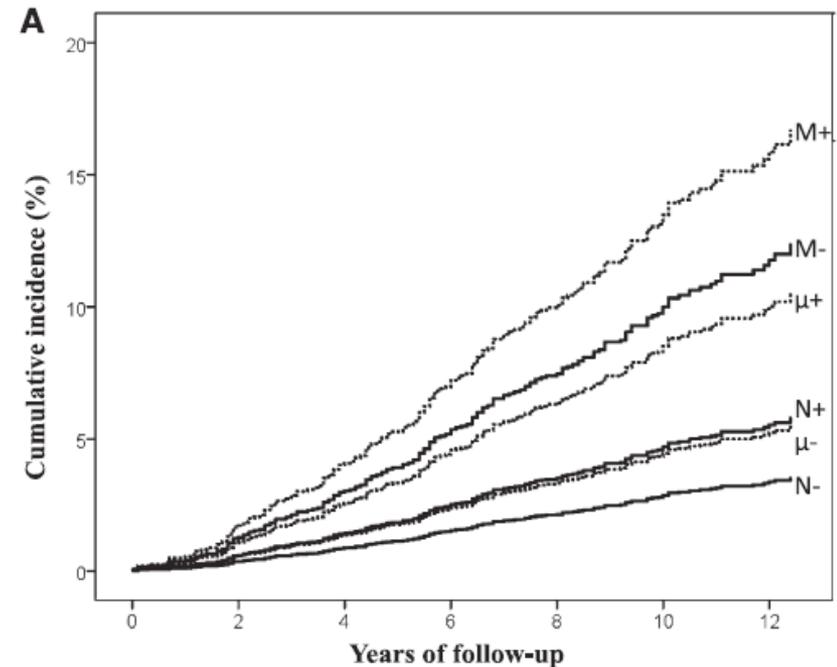
P. Rozas Moreno<sup>1,2</sup>, R. Reyes García<sup>1</sup>, A. García-Martín<sup>1</sup>, M. Varsavsky<sup>1</sup>, J.A. García-Salcedo<sup>1</sup>,  
and M. Muñoz-Torres<sup>1</sup>



# Osteoprotegerin Is an Independent Predictor of Vascular Events in Finnish Adults With Type 1 Diabetes

Table 3—Cox regression analysis for the predictive value of serum OPG for incident CVD, after adjusting for factors associated with serum OPG concentrations, as well as other factors independently associated with the studied event

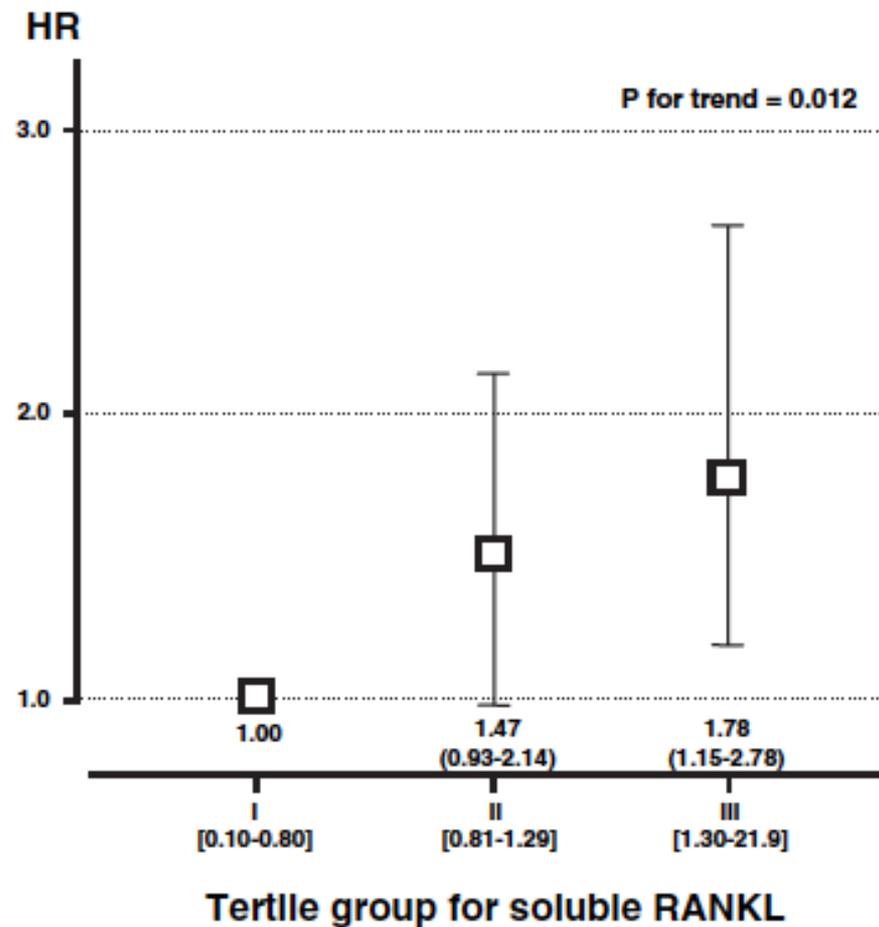
	Incident CVD	P value
Age (years)	1.07 (1.05–1.10)	<0.001
Duration of diabetes (years)	1.04 (1.02–1.06)	<0.001
Waist-to-hip ratio	9.36 (1.05–88.0)	0.045
Triglycerides (log)	3.81 (1.72–8.44)	0.001
Microalbuminuria	1.72 (1.09–2.70)	0.001
Macroalbuminuria	3.35 (2.17–5.16)	<0.001
OPG	1.21 (1.01–1.45)	0.035



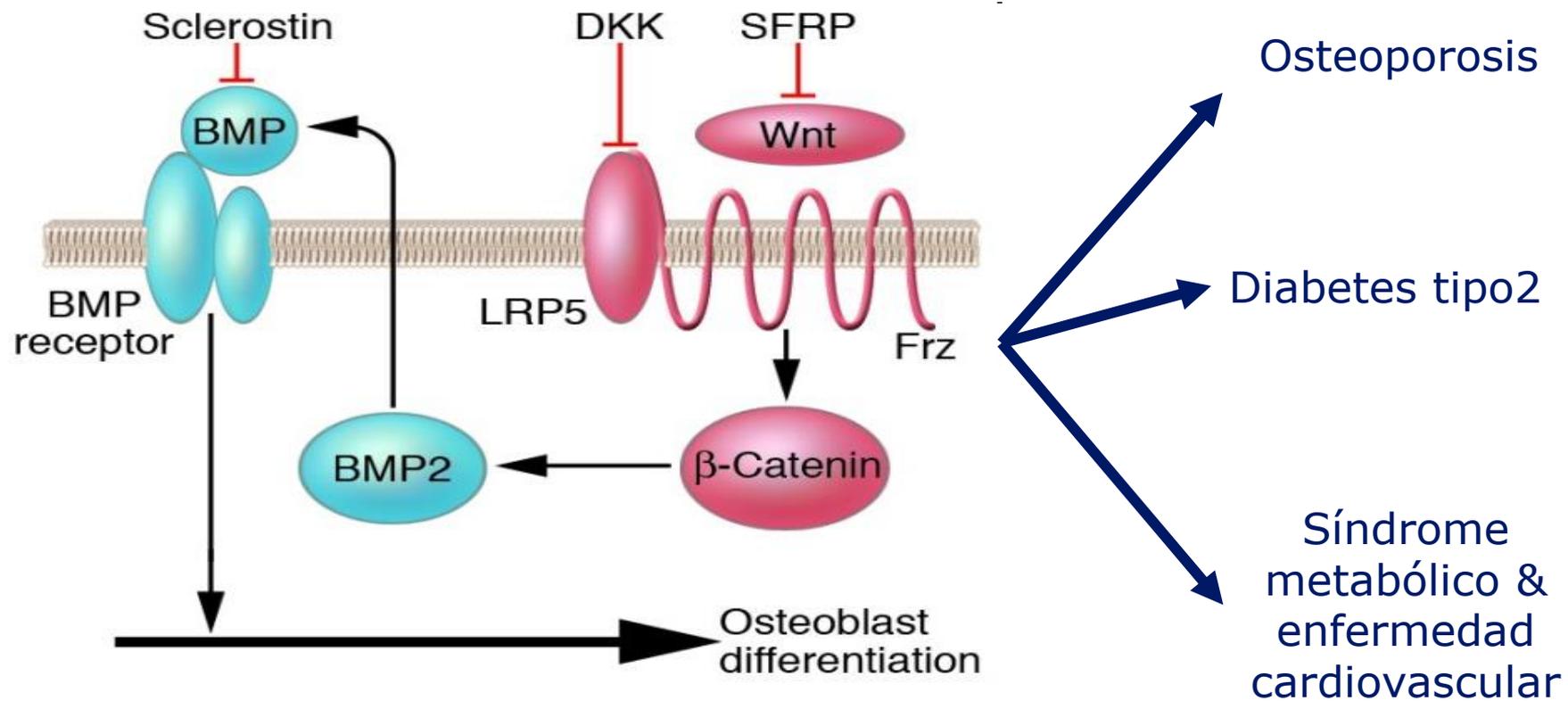
1931 adultos con DM1 seguidos durante 10.5 años

# RANKL

## Soluble Receptor Activator of Nuclear Factor- $\kappa$ B Ligand and Risk for Cardiovascular Disease

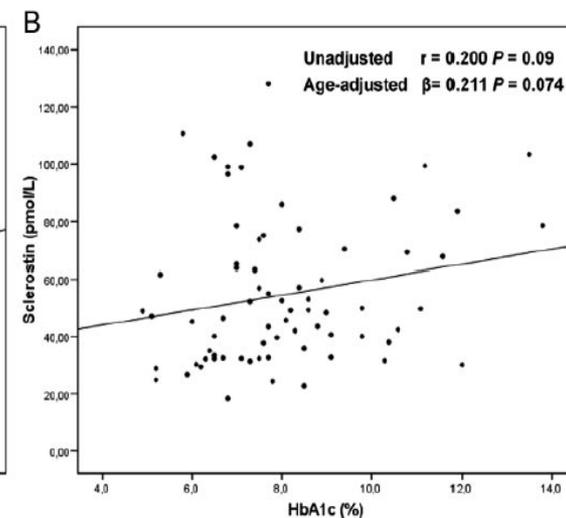
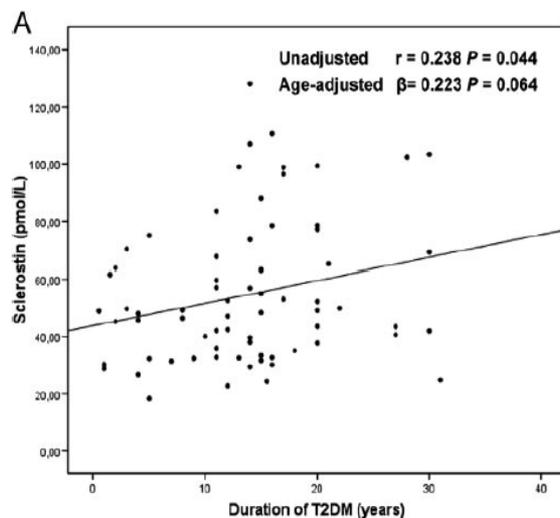
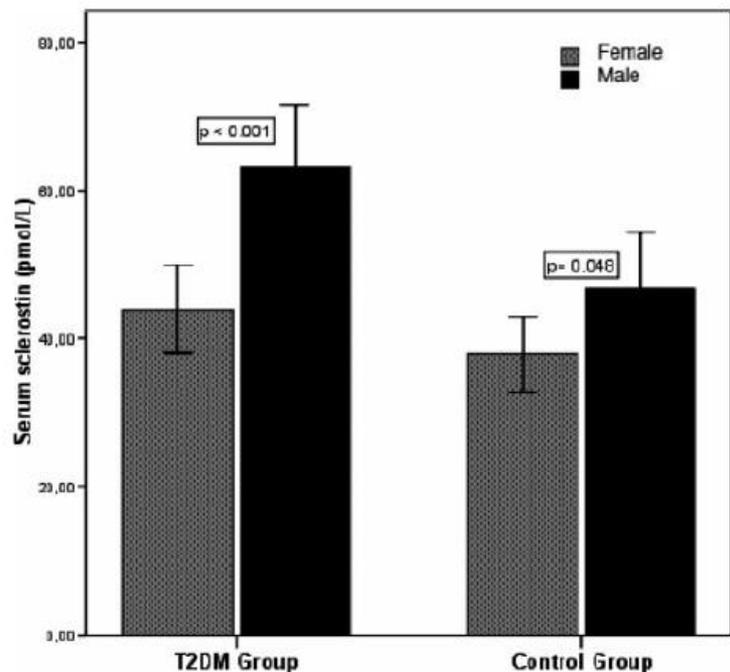


# Via de señalización Wnt/ $\beta$ -catenina y enfermedades metabólicas



# Circulating Levels of Sclerostin Are Increased in Patients with Type 2 Diabetes Mellitus

Antonia García-Martín, Pedro Rozas-Moreno, Rebeca Reyes-García, Sonia Morales-Santana, Beatriz García-Fontana, José A. García-Salcedo, and Manuel Muñoz-Torres

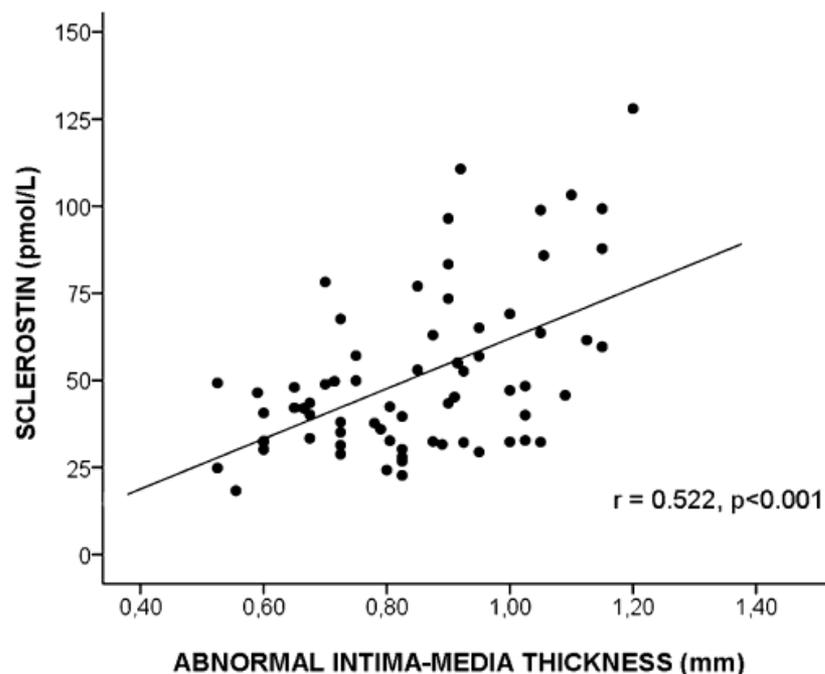
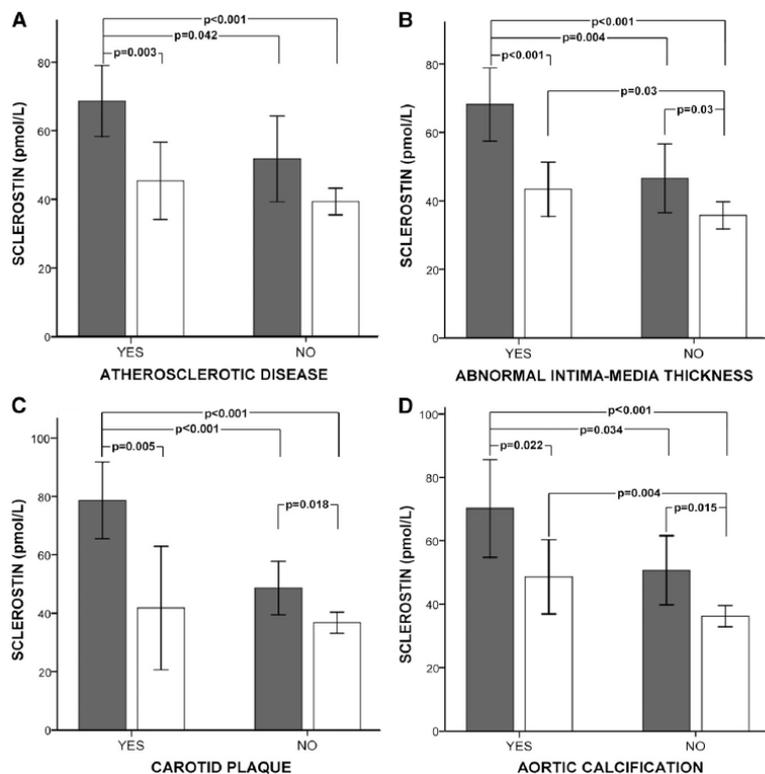


74 pacientes con DM2 y 50 controles (57 años)

# Atherosclerotic Disease in Type 2 Diabetes Is Associated With an Increase of Sclerostin Levels

SONIA MORALES-SANTANA, PHD<sup>1,2</sup>  
 BEATRIZ GARCÍA-FONTANA<sup>1</sup>  
 ANTONIA GARCÍA-MARTÍN, MD, PHD<sup>1</sup>  
 PEDRO ROZAS-MORENO, MD, PHD<sup>3</sup>

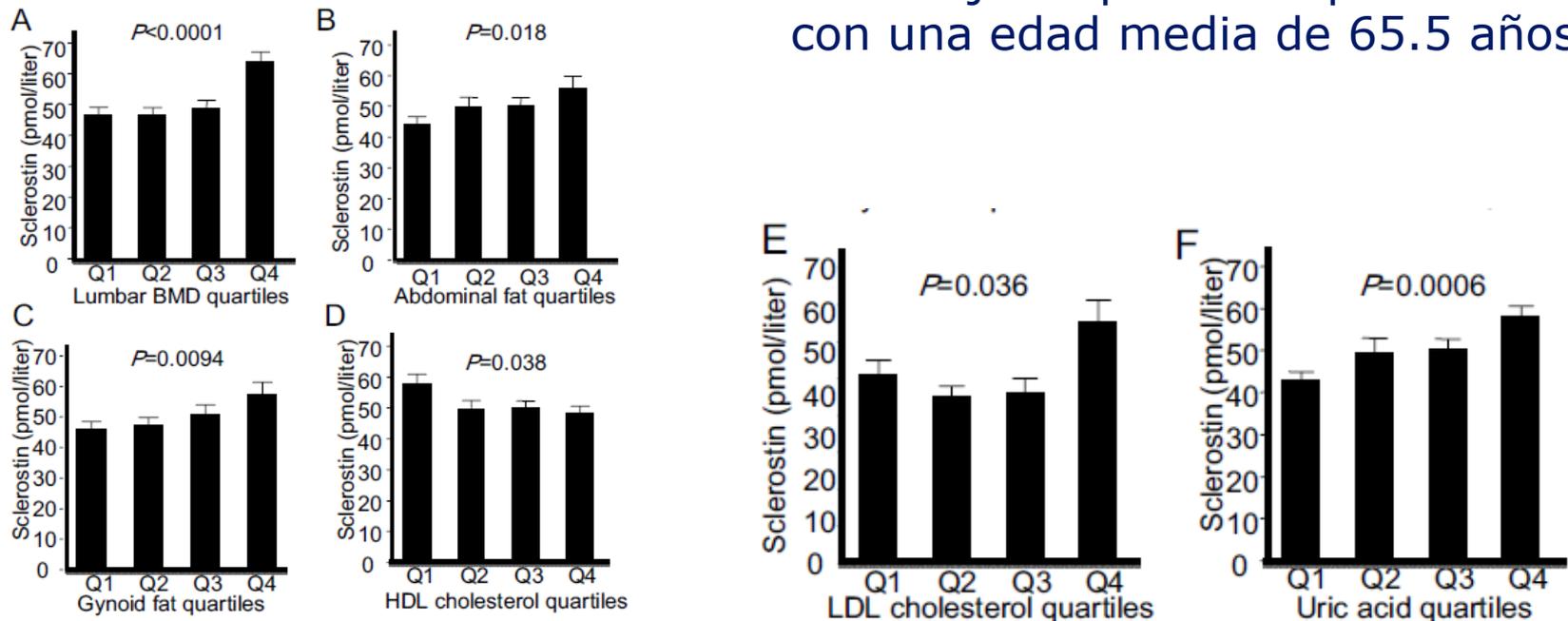
JOSÉ ANTONIO GARCÍA-SALCEDO, PHD<sup>1</sup>  
 REBECA REYES-GARCÍA, MD, PHD<sup>1</sup>  
 MANUEL MUÑOZ-TORRES, MD, PHD<sup>1</sup>



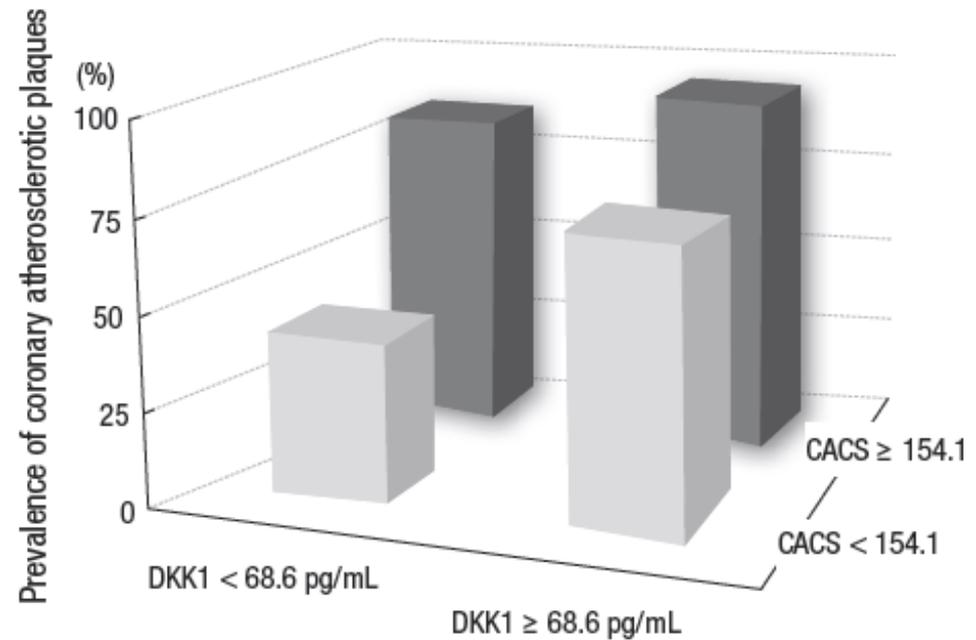
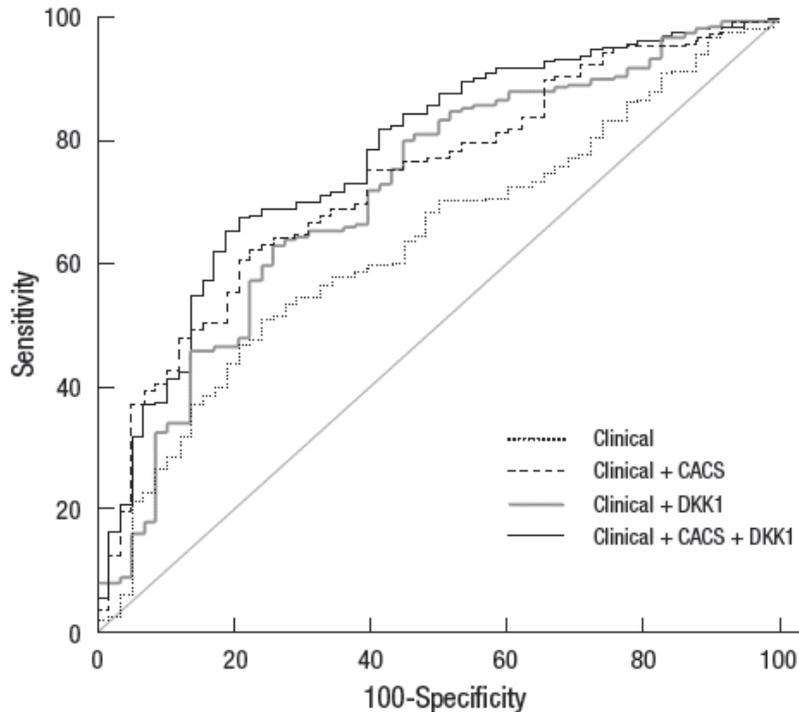
# Association of Circulating Sclerostin Levels with Fat Mass and Metabolic Disease—Related Markers in Japanese Postmenopausal Women

Tomohiko Urano,\* Masataka Shiraki,\* Yasuyoshi Ouchi, and Satoshi Inoue

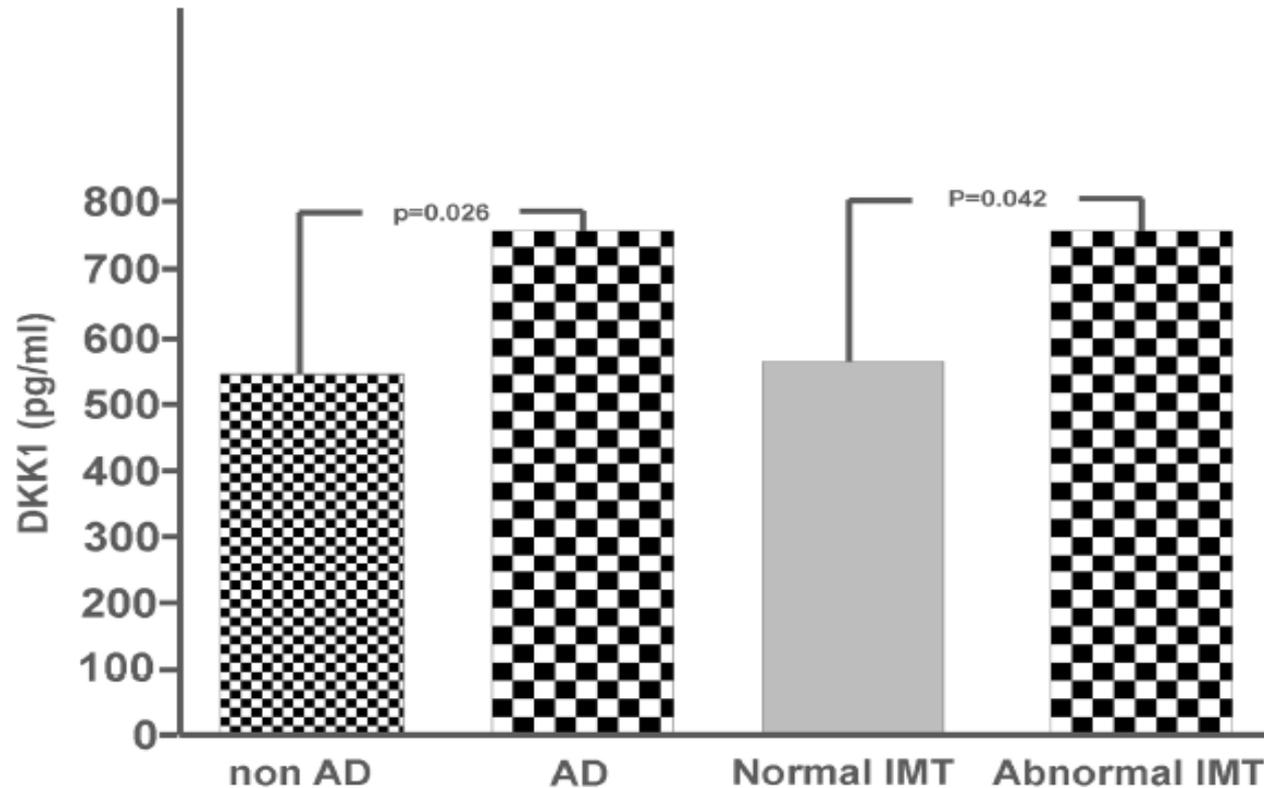
352 mujeres postmenopáusicas con una edad media de 65.5 años



# A Novel Biomarker of Coronary Atherosclerosis: Serum DKK1 Concentration Correlates with Coronary Artery Calcification and Atherosclerotic Plaques

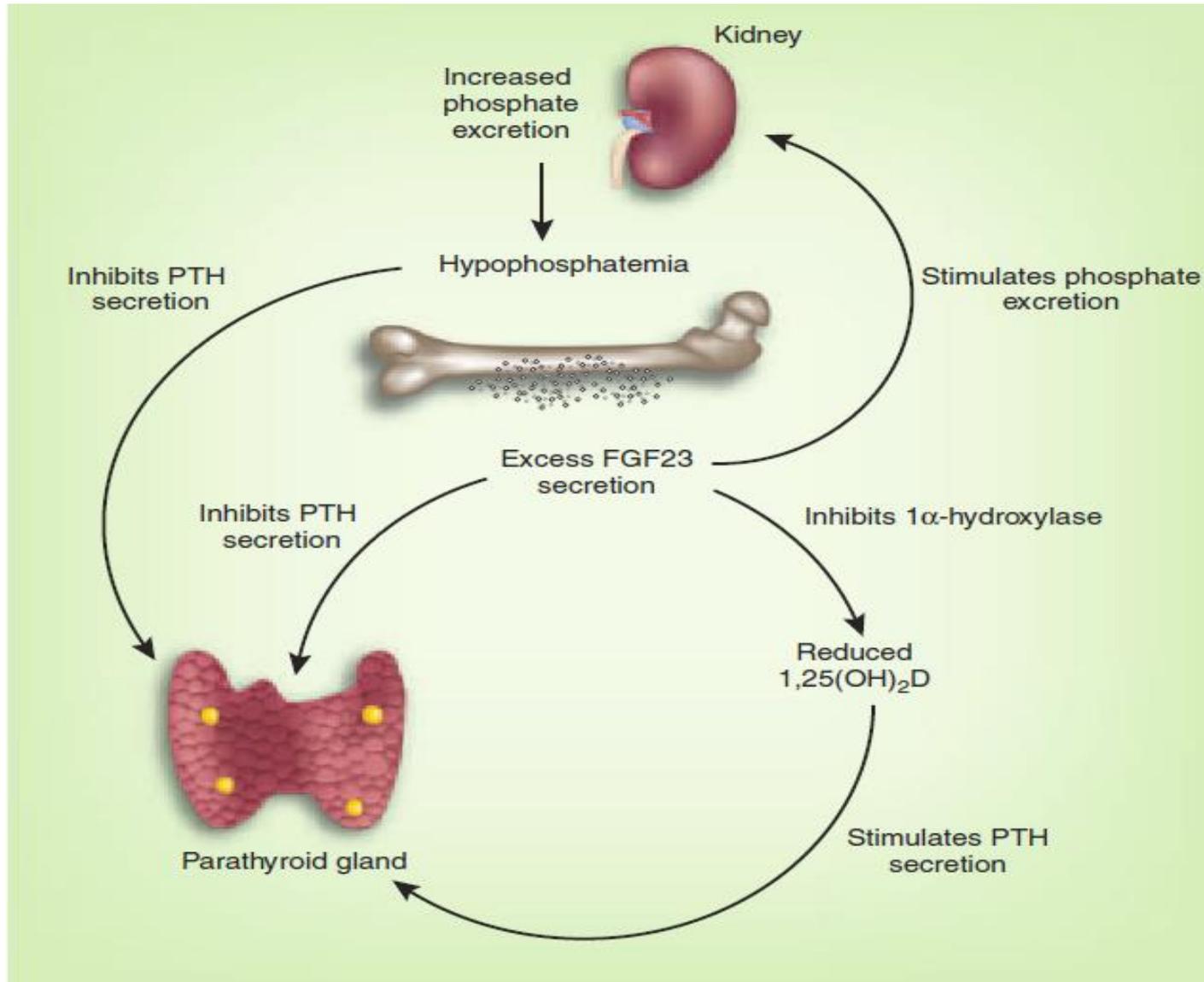


# RELATIONSHIP OF DICKKOPF1 (DKK1) WITH ATHEROSCLEROTIC DISEASE AND BONE METABOLISM IN TYPE 2 DIABETES MELLITUS

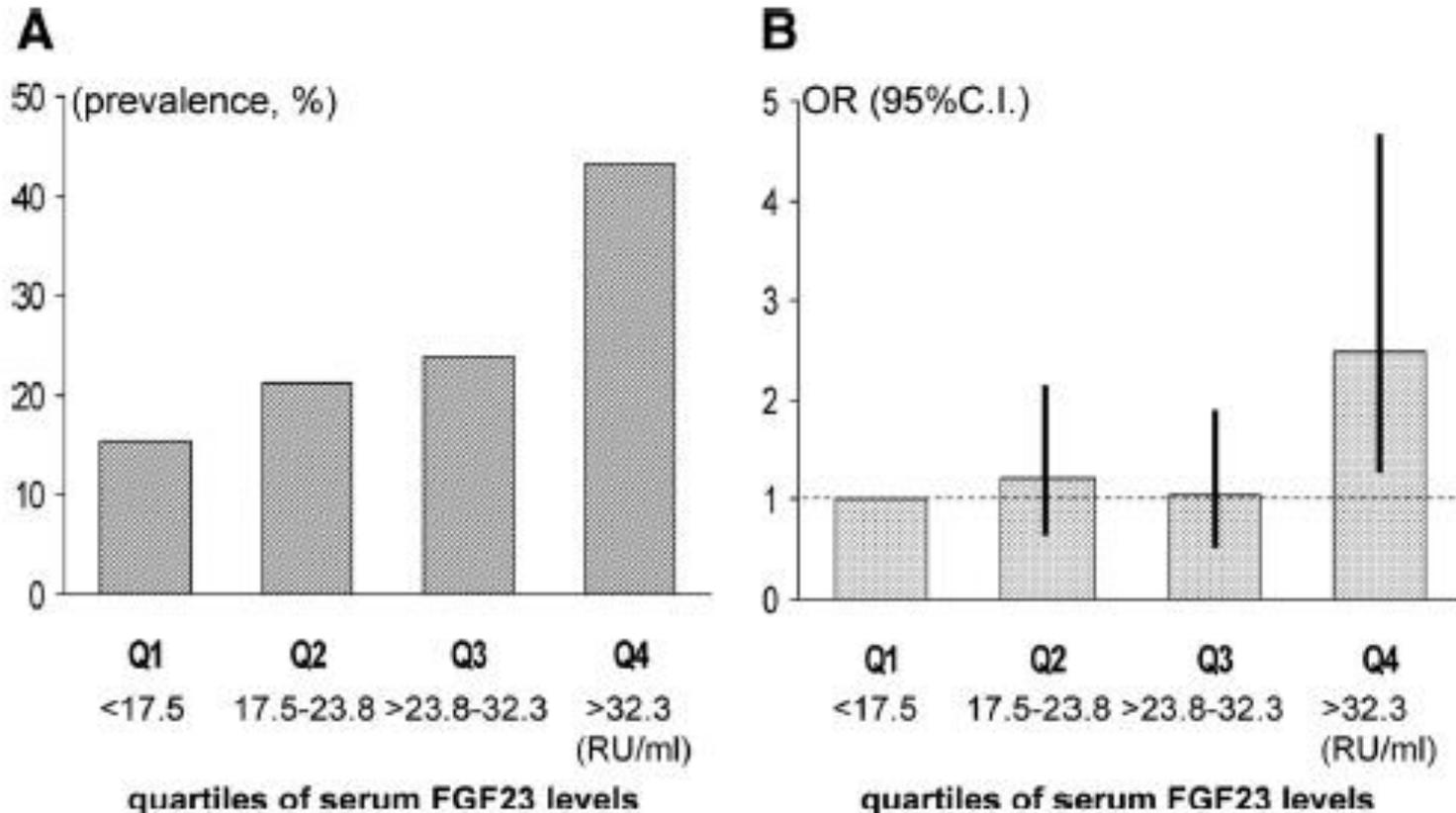


72 pacientes con DM2 con y sin enfermedad cardiovascular

# FGF23: Nuevo sistema de regulación del metabolismo del fosfato



# Serum Level of the Phosphaturic Factor FGF23 Is Associated with Abdominal Aortic Calcification in Men: The STRAMBO Study

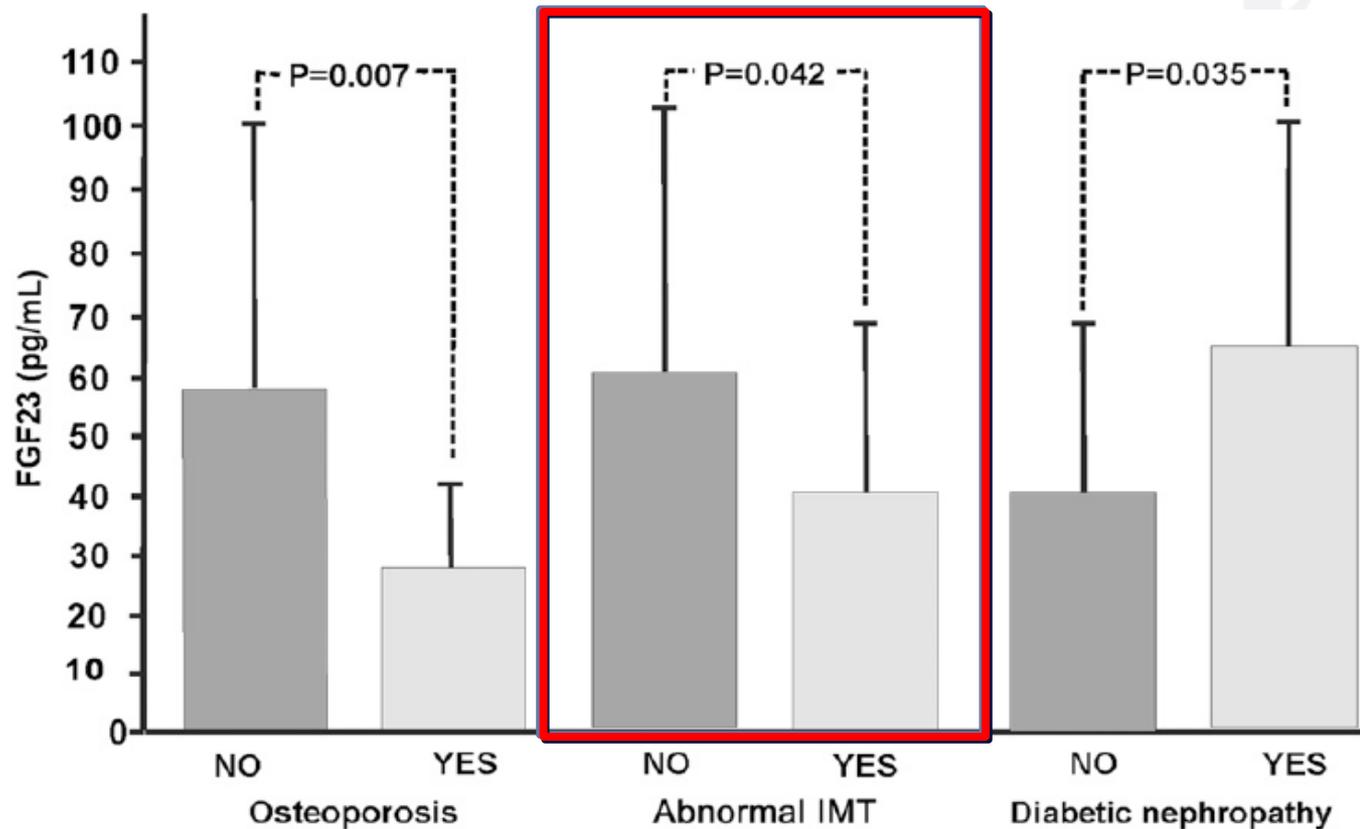


Estudio poblacional con 1130 varones (20-87 años)

# FGF23 in Type 2 Diabetic Patients: Relationship With Bone Metabolism and Vascular Disease

Rebeca Reyes-Garcia,<sup>1,2</sup>  
Antonia Garcia-Martín,<sup>1,3</sup>  
Beatriz García-Fontana,<sup>1</sup>  
Sonia Morales-Santana,<sup>1,4</sup>  
Pedro Rozas-Moreno,<sup>1,5</sup> and  
Manuel Muñoz-Torres<sup>1</sup>

*Diabetes Care* 2014;37:e1–e2 | DOI: 10.2337/dc13-2235



# Conclusiones

- Datos epidemiológicos sustentan una relación entre la OP y la ECV.
- Factores de riesgo comunes a ambas enfermedades.
- Existe una relación bidireccional entre el tejido óseo y el sistema cardiovascular.
- Mecanismos biológicos compartidos entre ambas entidades.

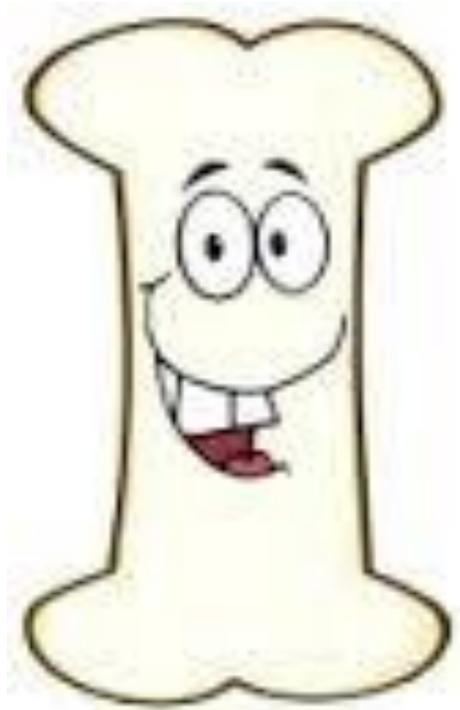
# ¿APLICABILIDAD CLÍNICA?



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**¡GRACIAS  
POR  
VUESTRA  
ATENCIÓN!**