Vascular calcification and osteoporosis after menopause

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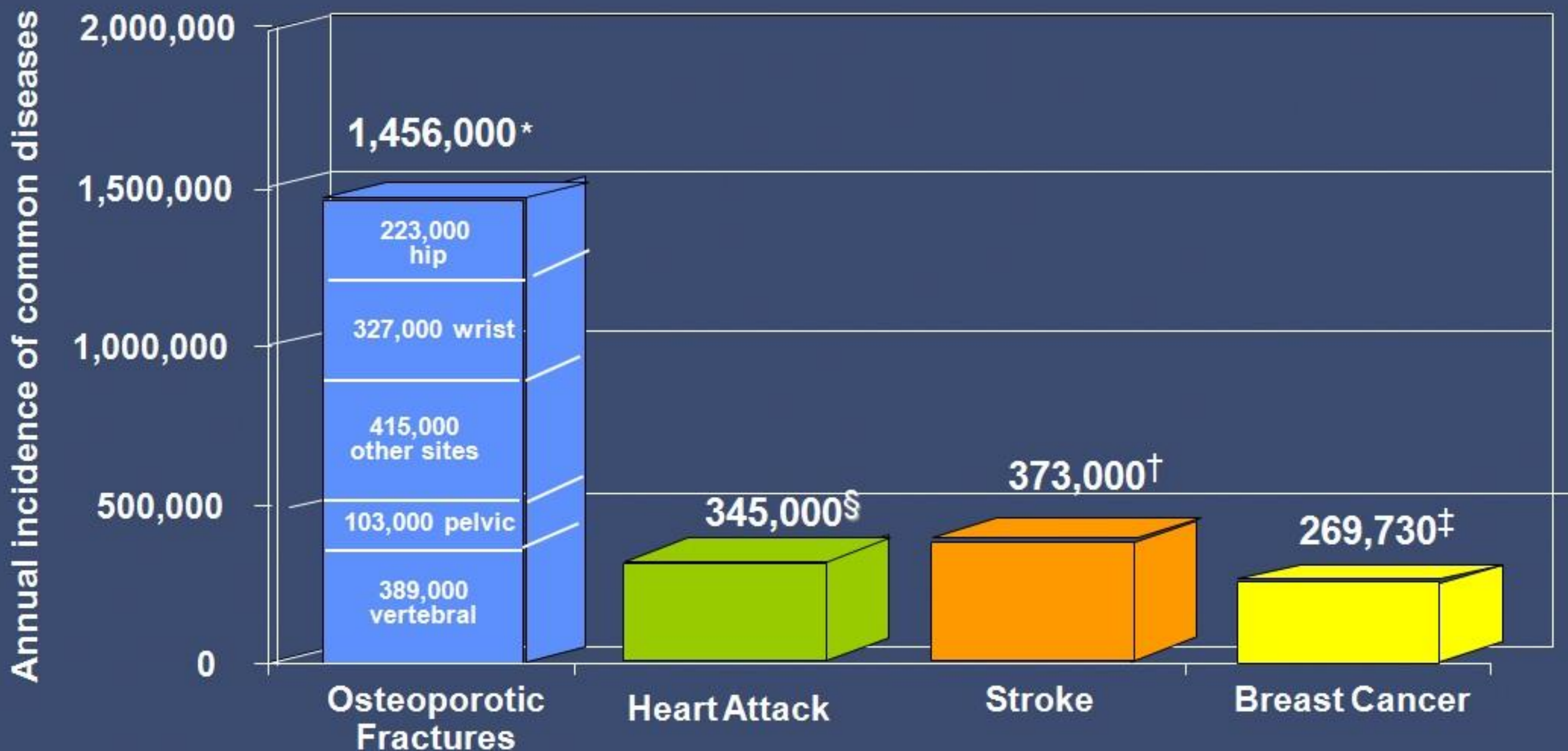
Life of a women…

Osteoporosis…How the life of women is better and worse…

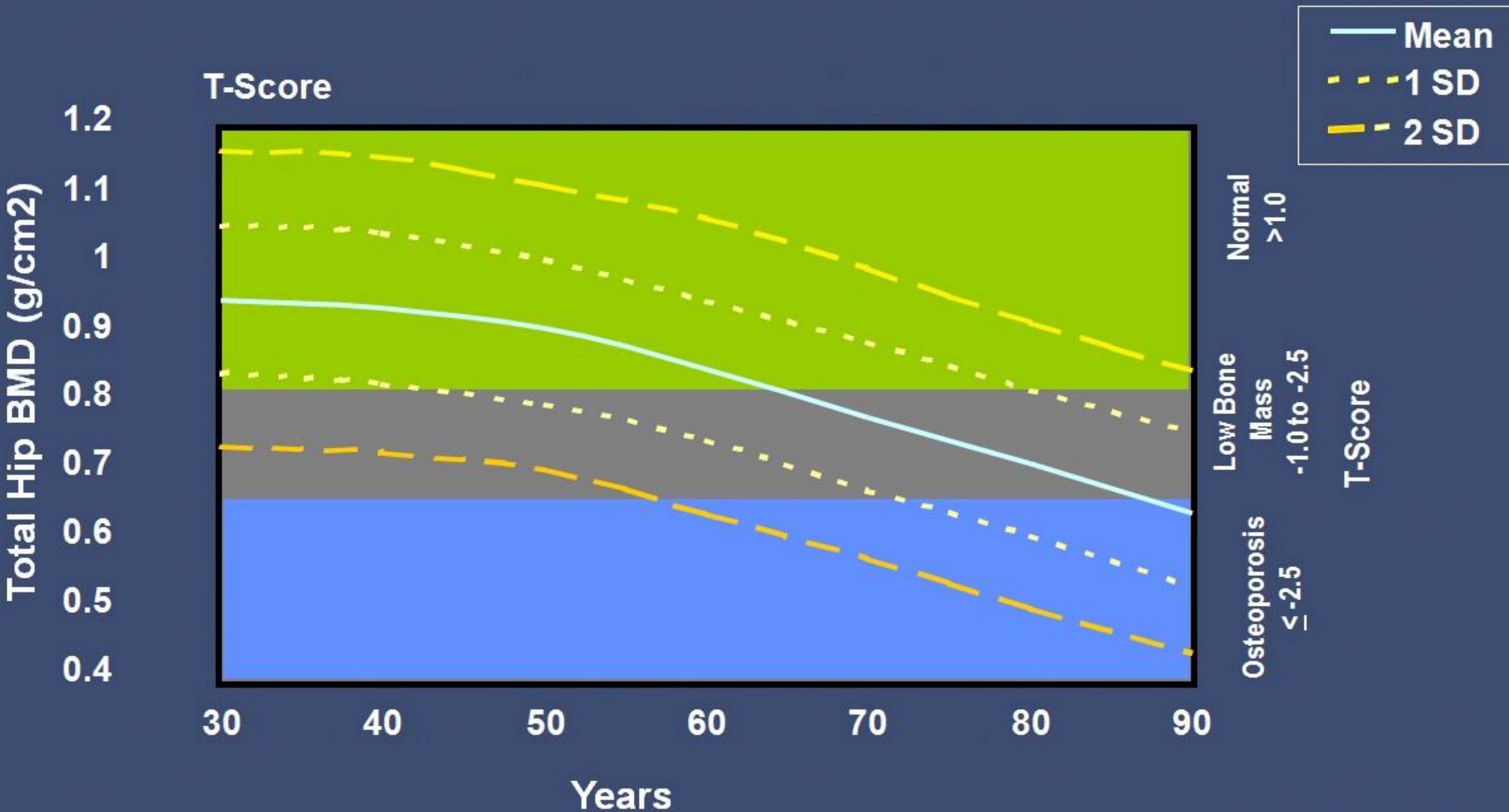
Osteoporosis Fracture Incidence vs. Incidence of Heart Attack, Stroke, Breast Cancer in Women



* Annual fracture incidence all ages
§ Annual estimate new & recurrent MI ages 20+
† Annual estimate new & recurrent stroke in women ages 20+
‡ 2005 new cases in situ & invasive breast cancer all ages

* Burge, et al. *JBMR*. 2007. 465-75.
§† American Heart Association. Heart Disease and Stroke Statistics – 2007 Update. 2007.
‡ American Cancer Society. Surveillance Research. 2005.

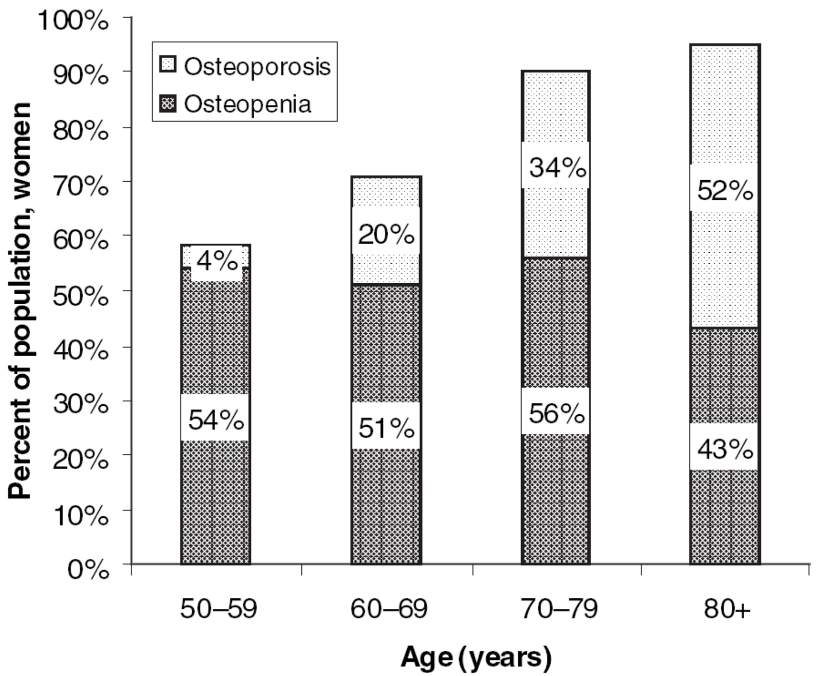
Bone Loss, Aging & Menopause

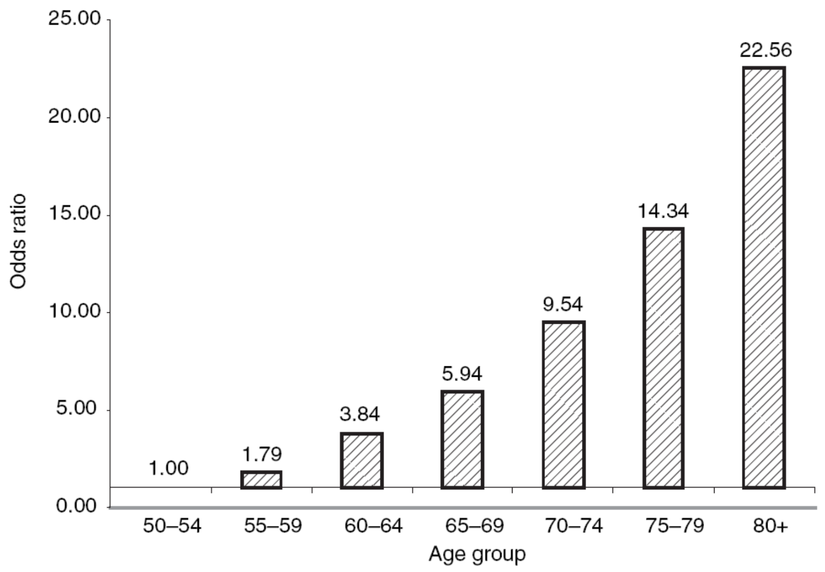


Meunier JP et al. *Clin Ther*. 1999;6:1025–1044.

NATIONAL OSTEOPOROSIS FOUNDATION
Standing Tall For You®

Prevalence of osteoporosis and the odds ratio by different age groups





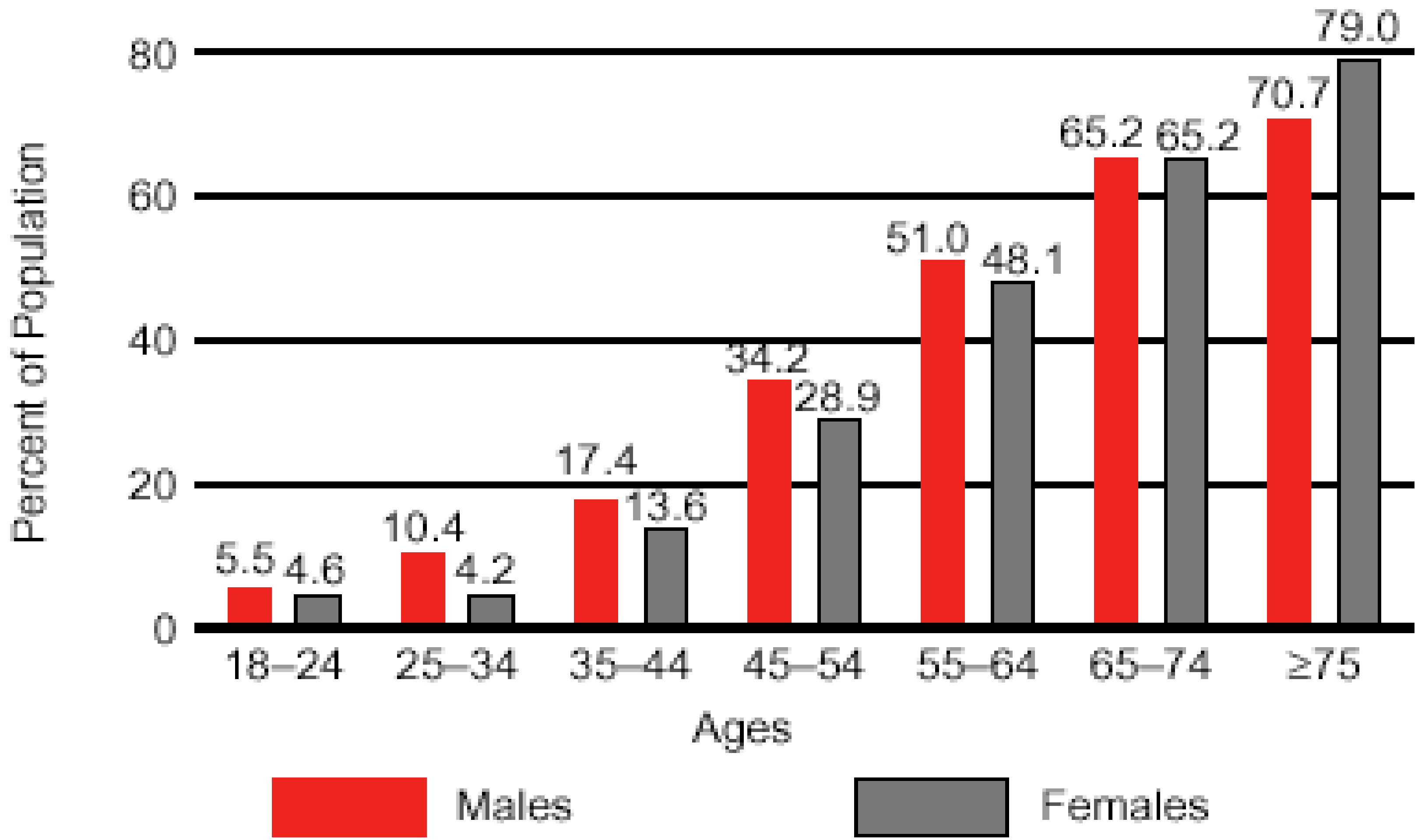
After adjustment for other risk factors, odds ratio increased exponentially 23 times greater for women 80 years of age and older than for 50-55-year-old women

NHANES III. JBMR 10:796, 1995

Siris ES et al. JAMA 286:2815-22, 2001

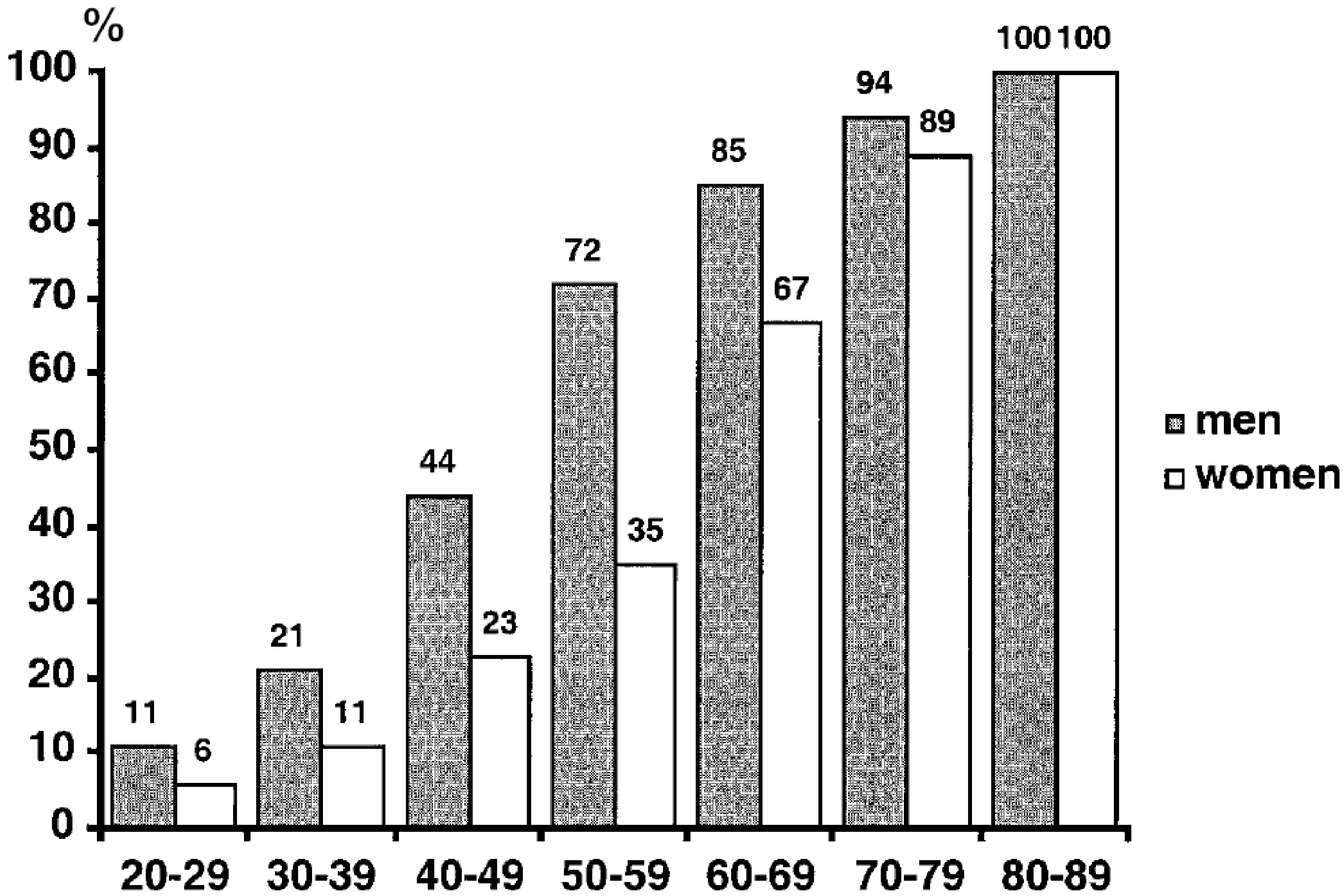
Estimated Prevalence of Cardiovascular Diseases by Age and Sex

United States: 1988–94



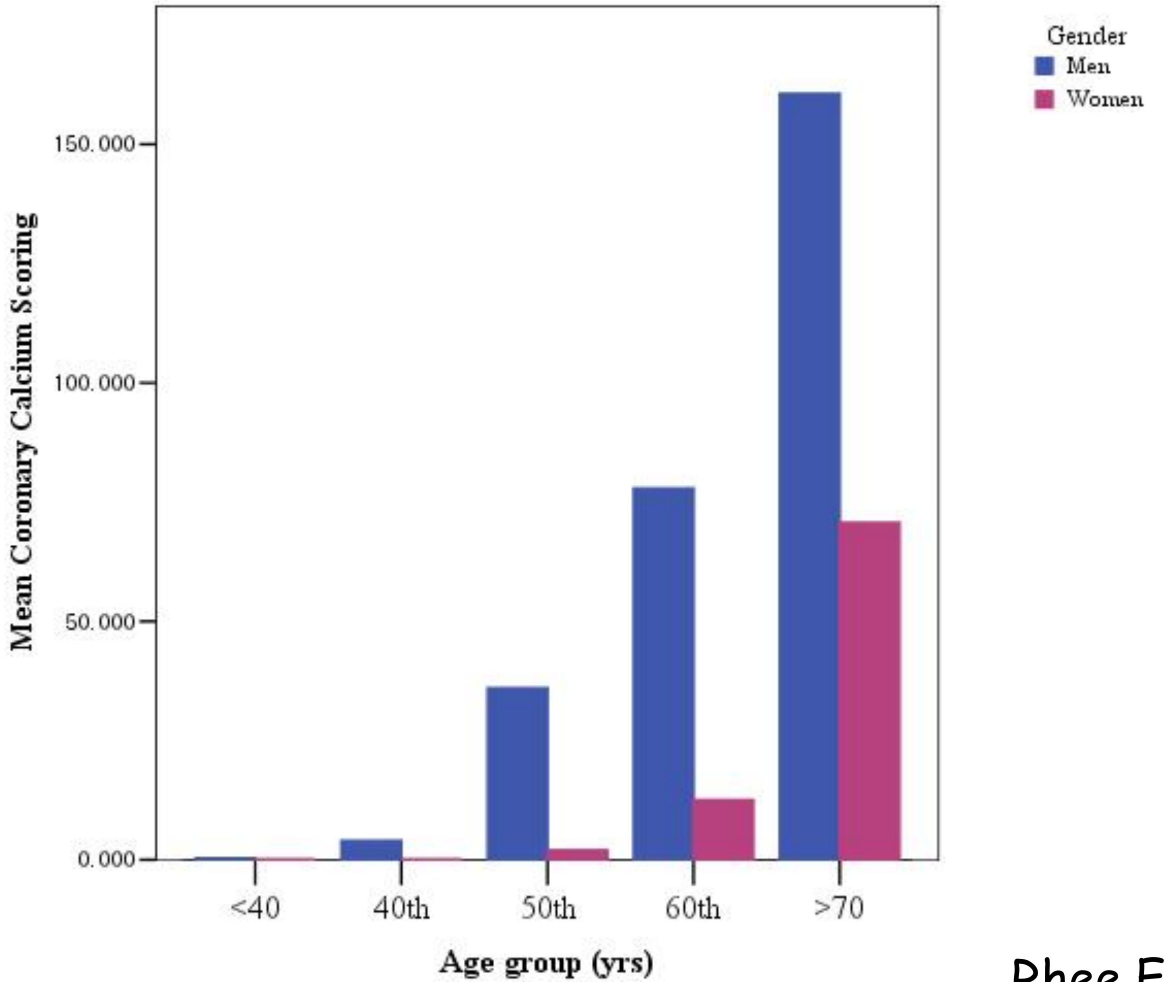
Source: National Health and Nutrition Examination Survey III (NHANES III), 1988–94, CDC/NCHS and the American Heart Association.

Prevalence of coronary calcification detected with EBCT



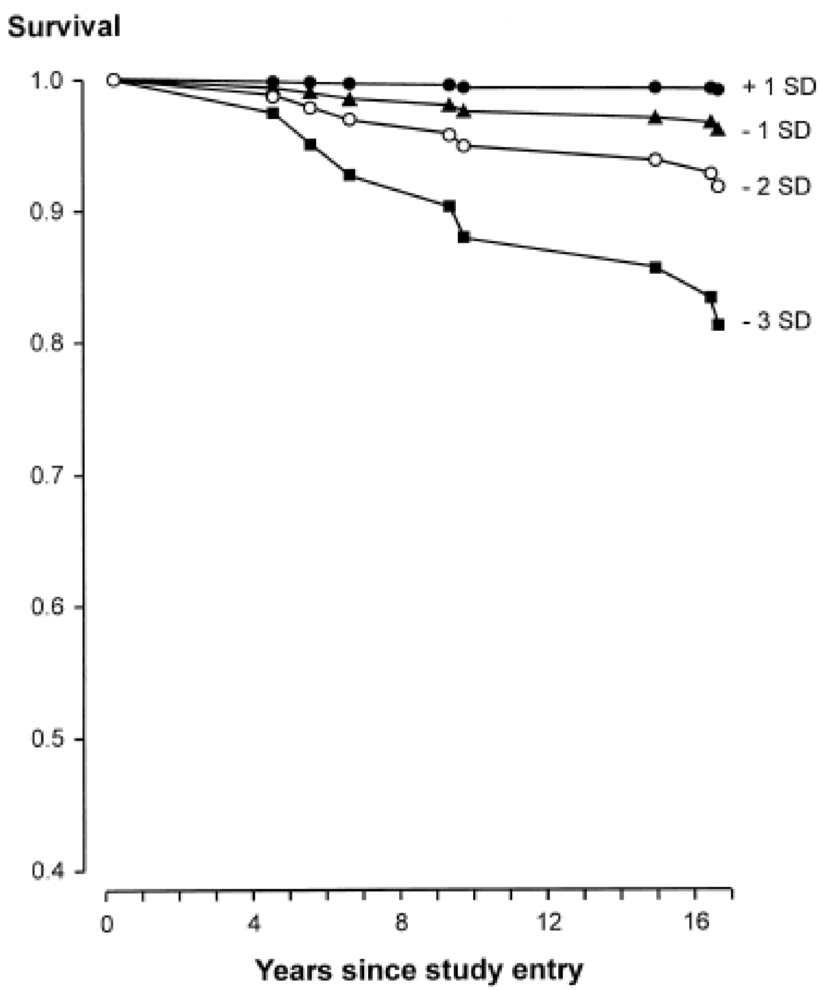
Becker et al., Eur Radiol 10:629-635, 2000

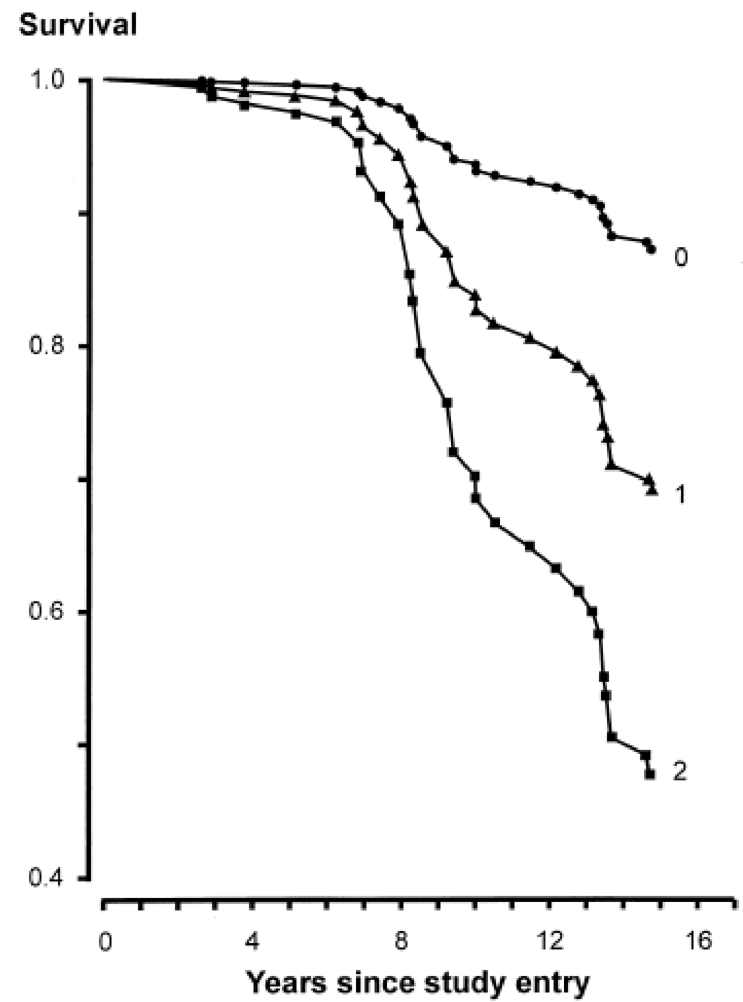
Prevalence of coronary calcification measured by MDCT in Korean subjects by gender and age



Rhee EJ et al.
Unpublished data

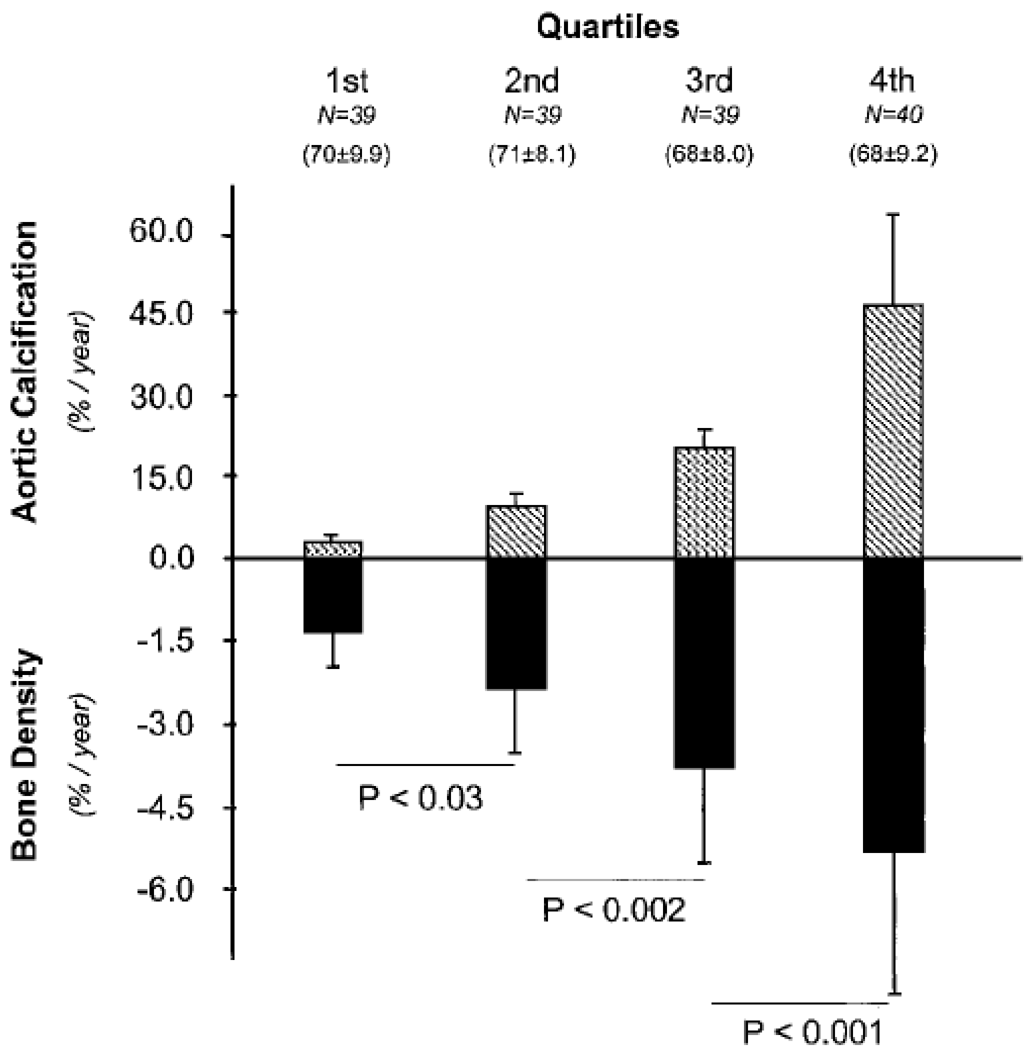
The association between low bone mass at the menopause and cardiovascular mortality





Recke et al., Am J Med 106:273-278, 1999

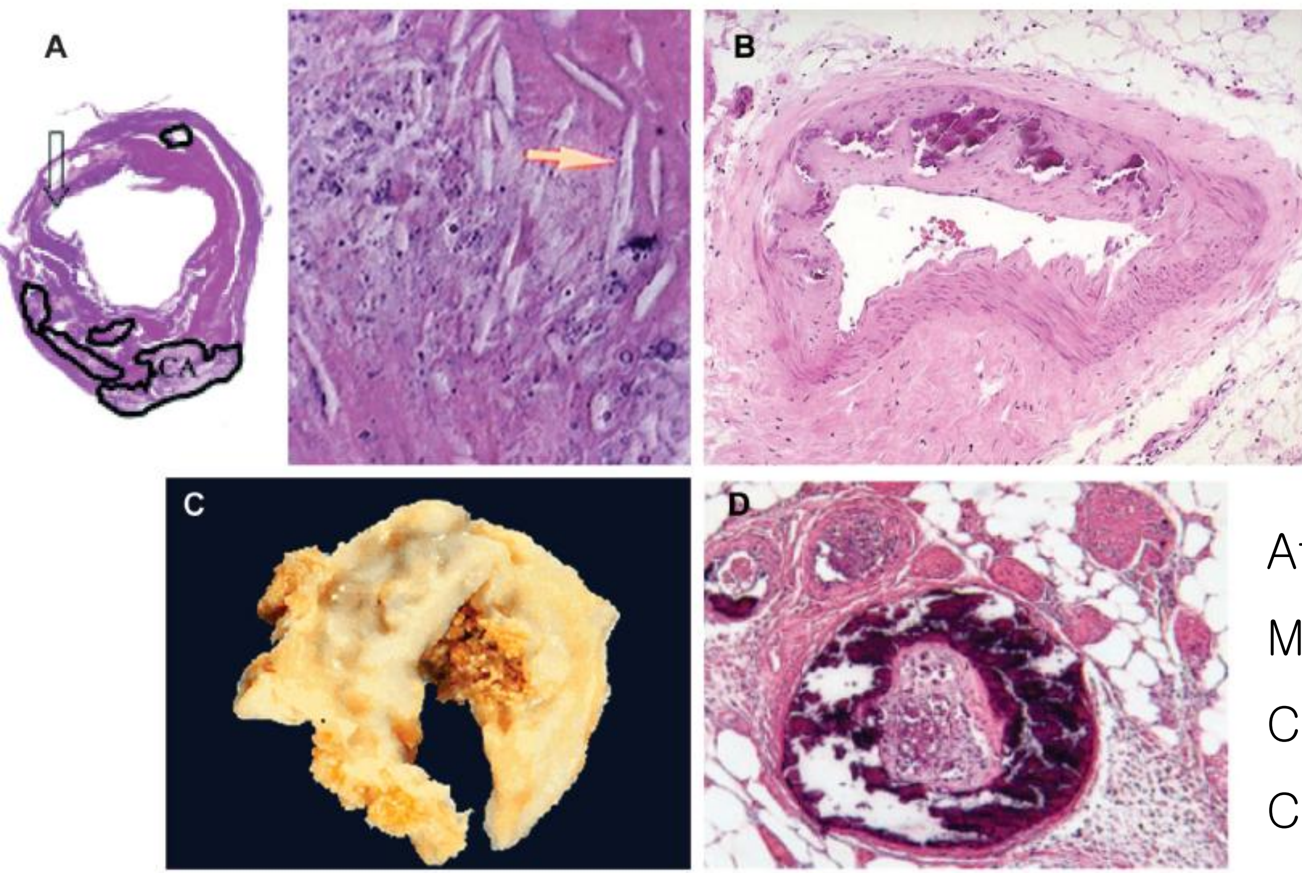
Aortic calcifications are a strong predictor for low bone density and fragility fractures



Schulz et al., J Clin Endocrinol Metab 89:4246-4253, 2004

Pathophysiology of vascular calcification

Types of vascular calcification



Atherosclerotic calcification

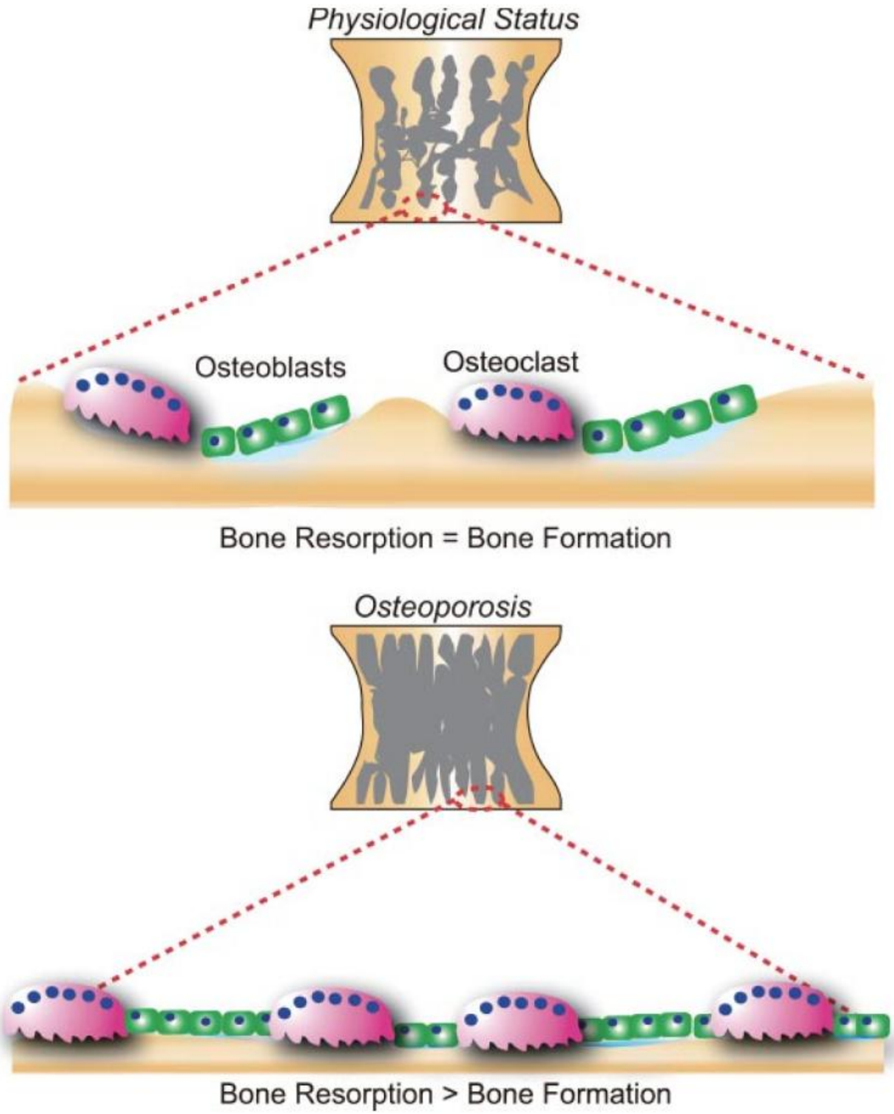
Medial artery calcification

Cardiac valve calcification

Calciphylaxis

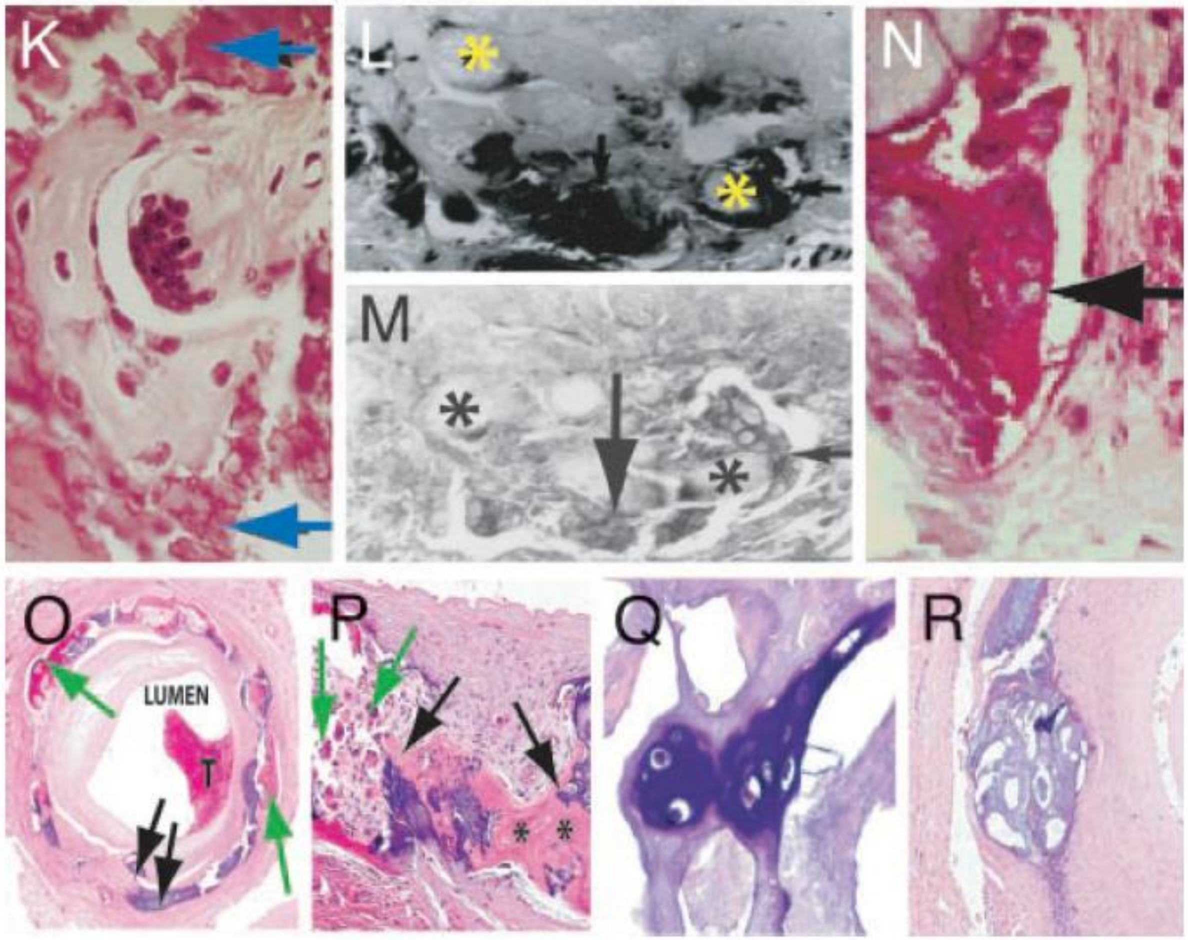
Johnson et al., Circ Res 99:1044-59, 2006

The role of bone cells in bone remodeling



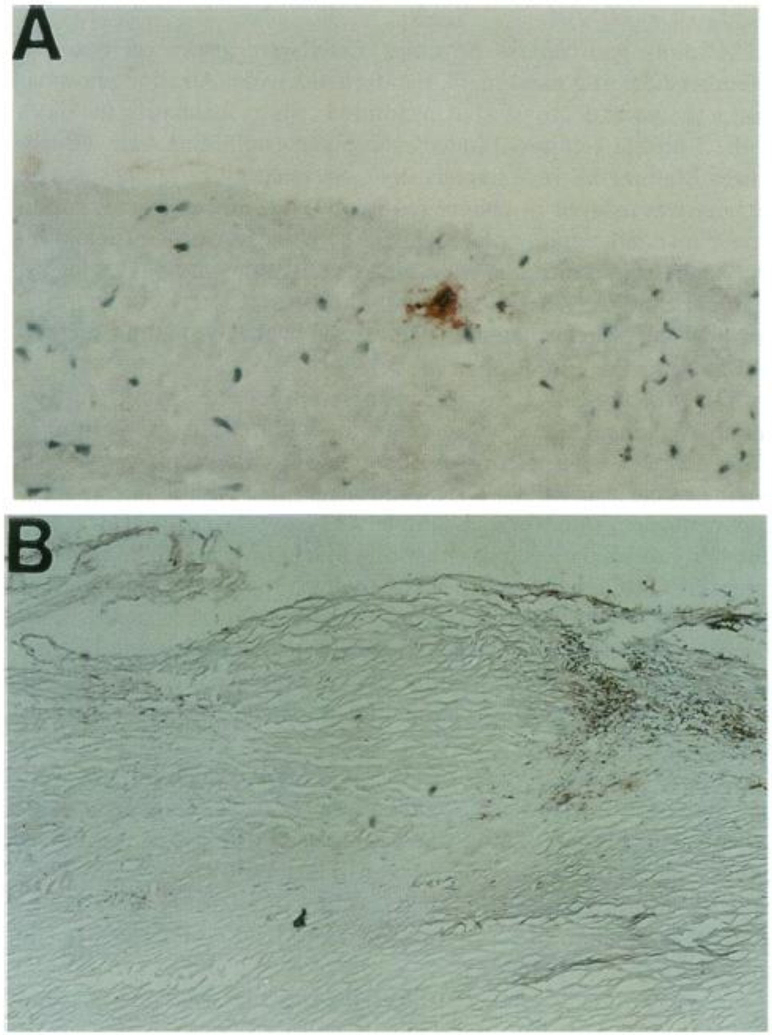
Imai Y et al. Mol Endocrinol, 2010

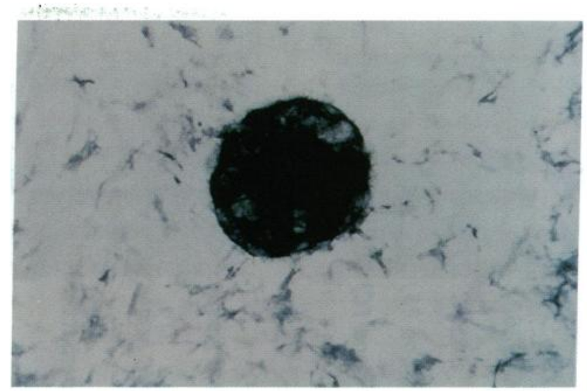
Bone formation in human arteries



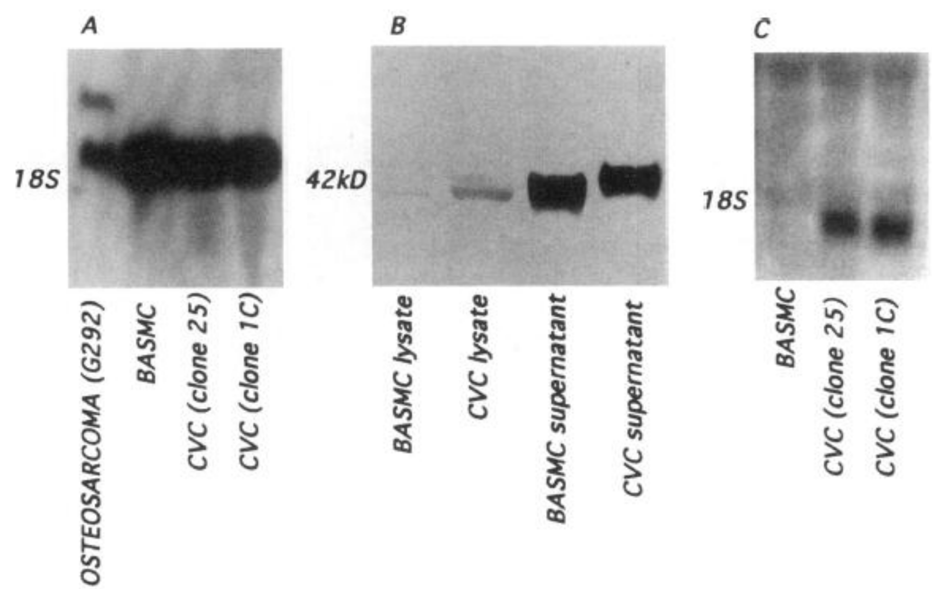
Doherty et al., Endocr Rev 25:629-672, 2004

Existence of a subpopulation of SMCs in the vascular wall – "calcifying vascular cells"



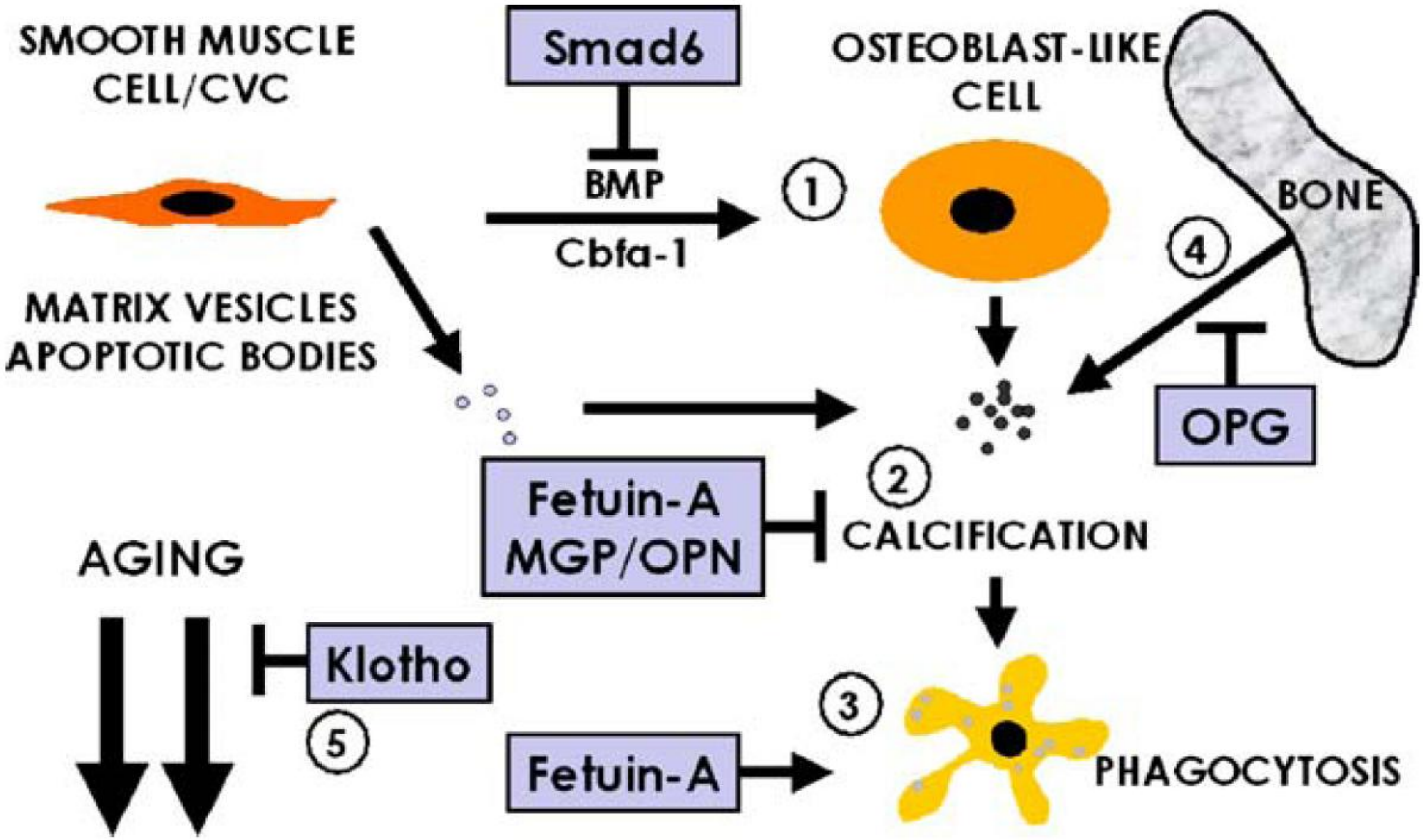


ALP stain



Watson et al., JCI 93:2106-2113, 1994

Unifying hypothesis of arterial calcification and osteoporosis

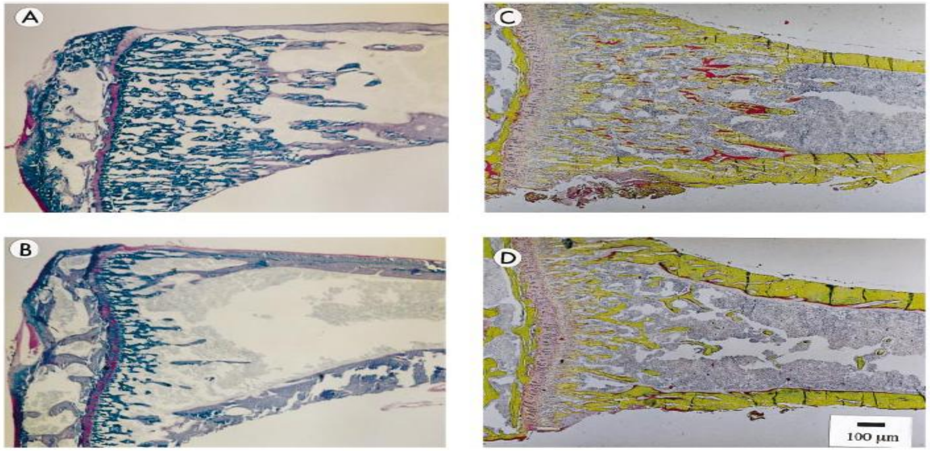


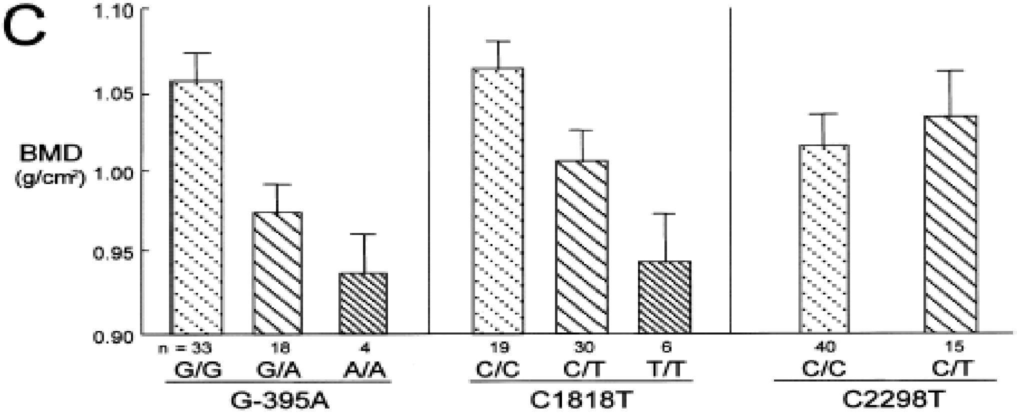
Hofbauer et al., Osteoporos Int 18:251–259, 2007

The Klotho-The Fates..

- The Three fates decided a man's destiny. They assigned a man to good or evil.
- Klotho spun the thread of life, Lachesis measured the thread of life, and Atropos cut the thread.
- They were very dreaded sisters who the even the gods obeyed. They were the most powerful of the minor gods.
- The Three Fates knew the past and future and even Zeus had no power to change their decision. They were the daughters of Themis, who was the goddess of necessity.

Klotho and bone metabolism



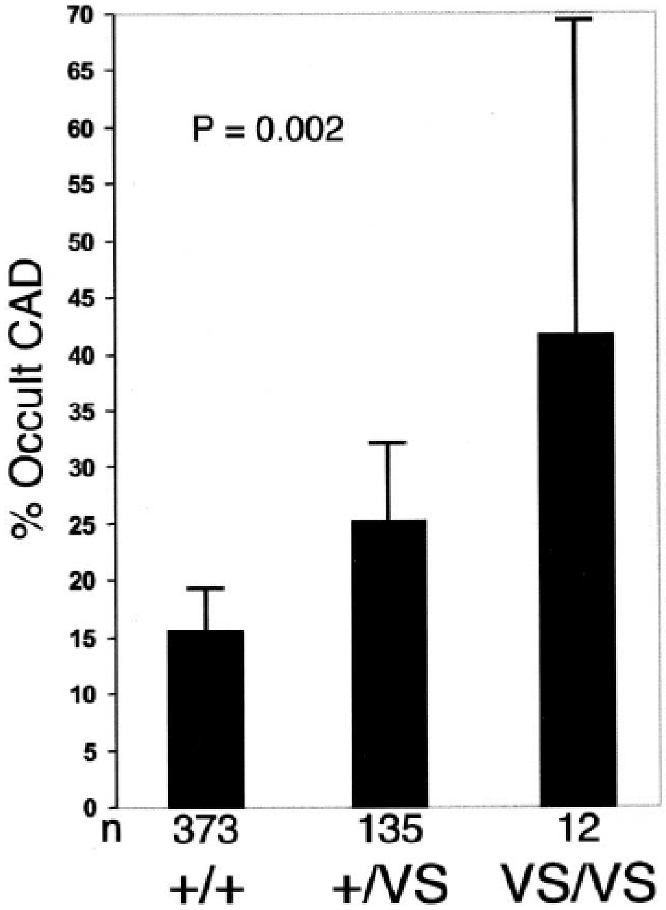


Yamashita et al., J Endorinol 1998;159:1-8
Kawaguchi et al., JCI 199;104:229
Kawano et al., JBMR 2003;17:1744

KLOTHO gene and coronary artery disease

Table 2
Genotype frequencies of the klotho gene G–395A polymorphism in the control, atherosclerotic coronary artery disease (CAD) and vasospastic angina (VSA) groups

	Control, *n* (%)	CAD, *n* (%)	VSA, *n* (%)
GG	268 (81.0)	138 (70.1)	59 (76.6)
AG	62 (18.7)	59 (29.9)	18 (23.4)
AA	1 (0.3)	0 (0.0)	0 (0.0)
AG+AA	63 (19.0)	59 (29.9)	18 (23.4)



Imamura et al., Clin Chim Acta 371:66-70, 2006
Arking et al., Am J hum Genet 72:1154-1161, 2003

The differential effects of age on the association of KLOTHO gene polymorphisms with coronary artery disease in Koreans

Table 4
Association of *KLOTHO* genotypes with CAD

	Promoter G395A (n = 274)		Exon 4 C1818T (n = 273)	
	GG (n = 203)	GA + AA (n = 71)	CC (n = 188)	CT + TT (n = 85)
Without coronary artery stenosis (%)	87 (42.9)	32 (45.1)	74 (39.4)	45 (52.9)
With coronary artery stenosis (%)	116 (57.1)	39 (54.9)	114 (60.6)	40 (47.1)
P	.746		.036	

All percentages are calculated within the same genotype groups. χ^2 Test was used to compare the frequencies of CAD according to different genotypes.

Table 5
Association of *KLOTHO* genotypes with CAD according to different age groups

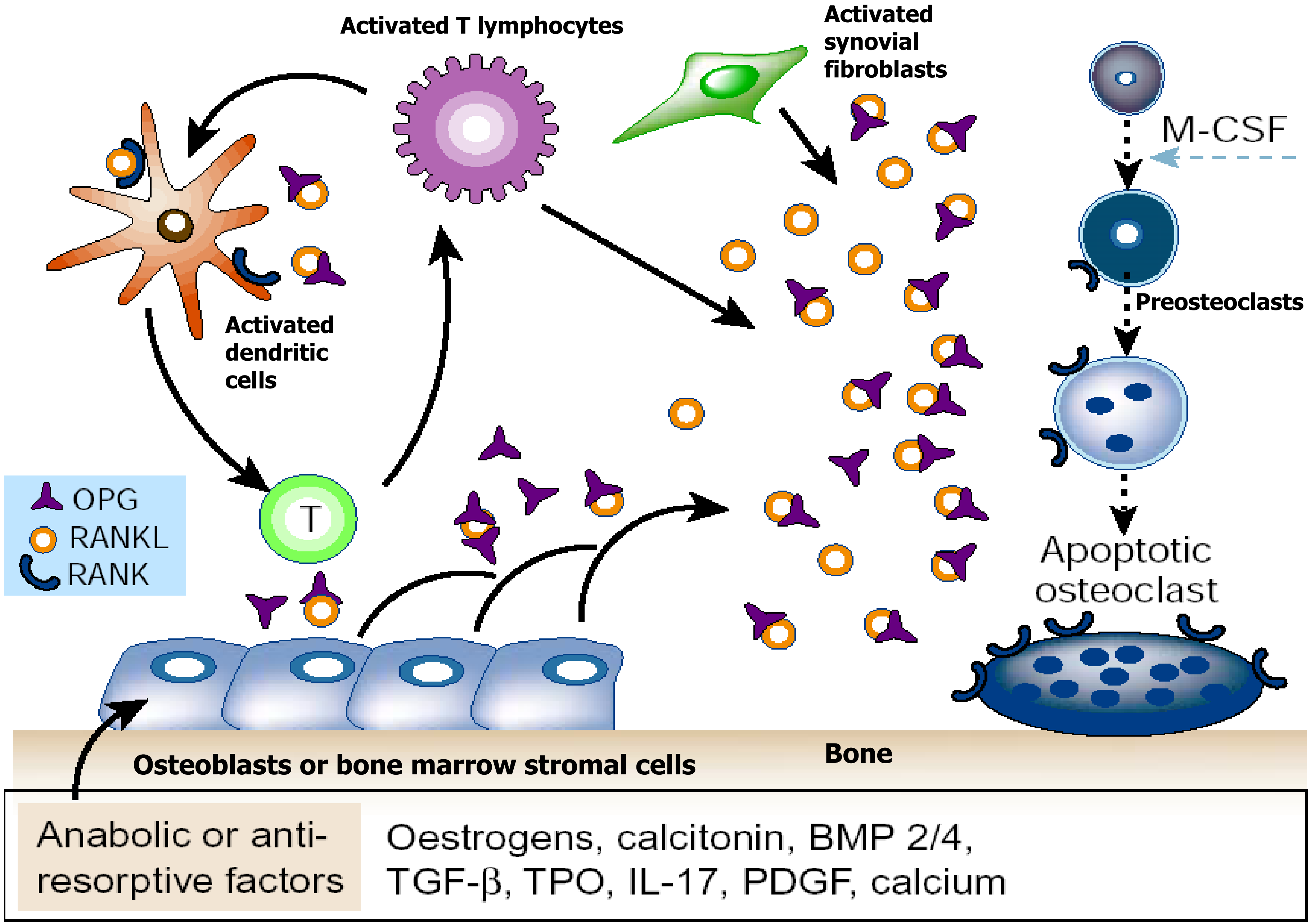
	Promoter G395A (n = 131)		Exon 4 C1818T (n = 130)	
Subjects aged <60 years	GG (n = 99)	GA + AA (n = 32)	CC (n = 92)	CT + TT (n = 39)
Without coronary artery stenosis (%)	57 (57.6)	14 (43.8)	44 (47.8)	27 (69.2)
With coronary artery stenosis (%)	42 (42.4)	18 (56.3)	48 (52.2)	12 (30.8)
P	.172		.025	
	Promoter G395A (143)		Exon 4 C1818T (n = 142)	
Subjects aged ≥60 years	GG (n = 104)	GA + AA (n = 39)	CC (n = 96)	CT + TT (n = 46)
Without coronary artery stenosis (%)	30 (28.8)	18 (46.2)	30 (31.3)	18 (39.1)
With coronary artery stenosis (%)	74 (71.2)	2[illegible] (53.8)	66 (68.8)	28 (60.9)
P	.041		.353	

All percentages are calculated within the same genotype groups. χ^2 Test was used to compare the frequencies of CAD according to different genotypes.

Rhee EJ et al., Metabolism 55:1344-1351,

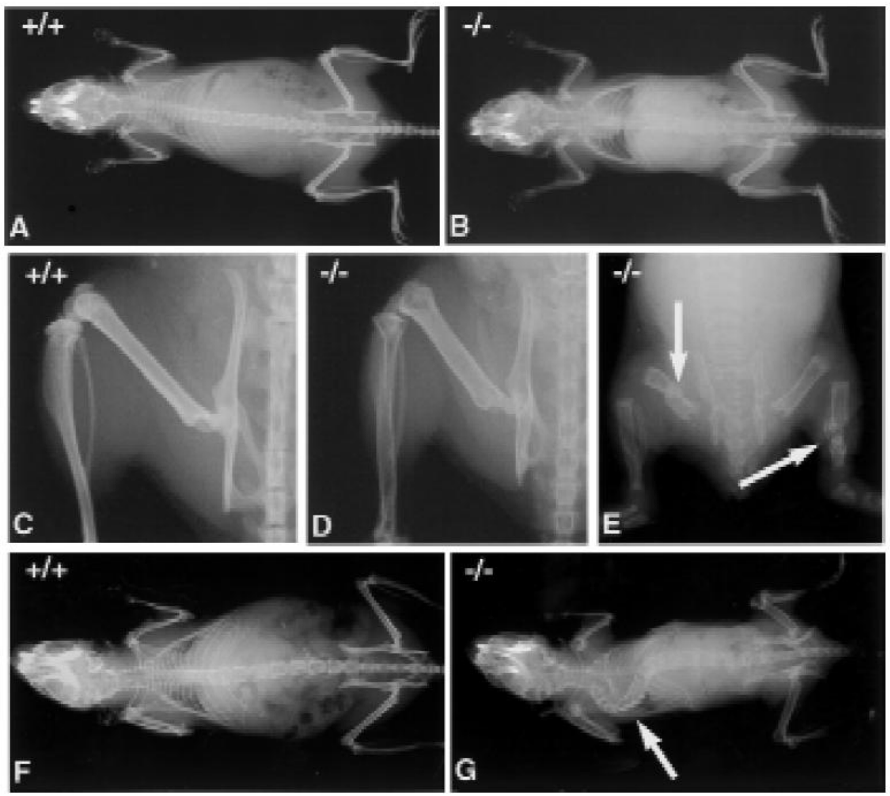
Osteoprotegerin/RANKL

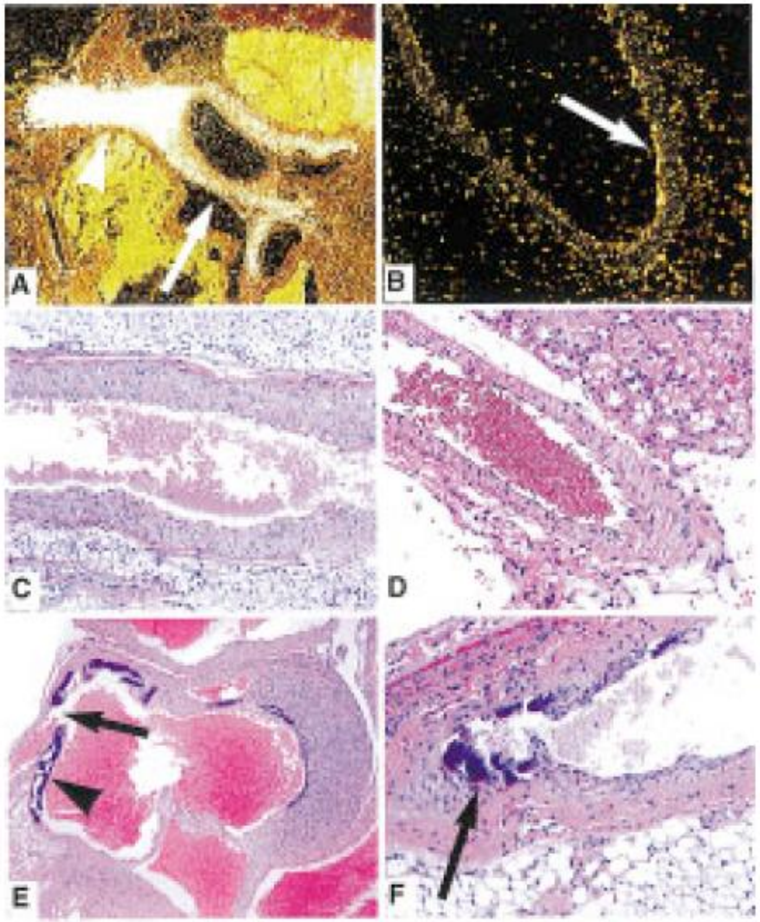
- Decoy receptor of RANKL
- Independently isolated by two laboratories
- Secretory basic glycoprotein that exist in a 60-kd monomeric form and a disulfide-linked homodimeric form of 120 kd.
- Lack of transmembrance domain – **soluble receptor**
- Composed of 401 amino acid residues



Boyle et Simonet, Nature, 2003

Osteoprotegerin-deficient mice develop early onset osteoporosis and arterial calcification





Bucay et al., Genes dev 12:1260-1268, 1998

Relationship of four OPG polymorphisms in the promoter region with aortic calcification or CAD in Korean subjects

Table 5. Association of the genotypic frequencies of the four osteoprotegerin (OPG) polymorphisms with aortic calcification

OPG site	Genotype	Calcification (–)	%	Calcification (+)	%	*P*-value	Age-adjusted *P*-value
A163G	AA	170	79·4	26	72·2	0·108	0·413
	AG + GG	44	20·6	10	27·8		
G209A	GG	174	81·3	25	71·4	0·028	0·201
	GA + AA	40	18·7	10	28·6		
T245G	GG	168	79·6	26	74·3	0·225	0·623
	GA + AA	43	20·4	9	25·7		
T950C	TT	73	34·6	9	24·3	0·016	0·178
	TC + CC	138	65·4	28	75·7		
G209A-T950C	No minor allele	73	65·8	8	44·4	< 0·001	0·127
	All minor alleles	38	34·2	10	55·6		

The frequencies were compared with the χ^2-test.
Age corrections were performed using binary logistic regression analysis.
No minor allele denotes women without the allele and all minor allele denotes those with all minor alleles.

Rhee EJ et al., Clin Endocrinol 64:689-697, 2006

The association of the genotypic frequencies of the two RANKL polymorphisms according to the presence of aortic calcification

	rs2277438		rs9594782	
Genotype	AA (*n*=109)	AG+GG (*n*=128)	TT (*n*=210)	CT+CC (*n*=27)
Calcification (-)	92	112	186	18
Calcification (+)	17	16	24	9
Odds ratio	0.773 (95% CI, 0.37-1.61)		3.875 (95% CI, 1.57-9.59)*	
p-value	0.573		0.005	
Adjusted *p*-value			0.001	

The frequencies were compared with chi-square test.
Corrections were performed using binary logistic regression analysis.
*This significance was persisted after adjustment for age, BMI, blood pressure, fasting plasma glucose, HDL cholesterol, LDL cholesterol

Does vascular calcification increase after menopause?

The impact of menopause on CAC

Table 4 The percentage of fourth quartile CAC* scores (>75%) and mean CAC scores in different age categories according to gender

Age group (years)	*N*		CAC score mean (SD)		Fourth quartile CAC score (%)	
	Males	Females	Males	Females	Males	Females
40–49	140	80	57.9 (143.9)	12.8 (17.6)	25.0	5.0
50–59	138	52	53.1 (98.0)	51.5 (115.7)	31.2	21.2
60–70	50	19	76.3 (105.1)	110.1 (226.2)	42.0	42.2
P value			0.51	0.001	0.08	<0.001

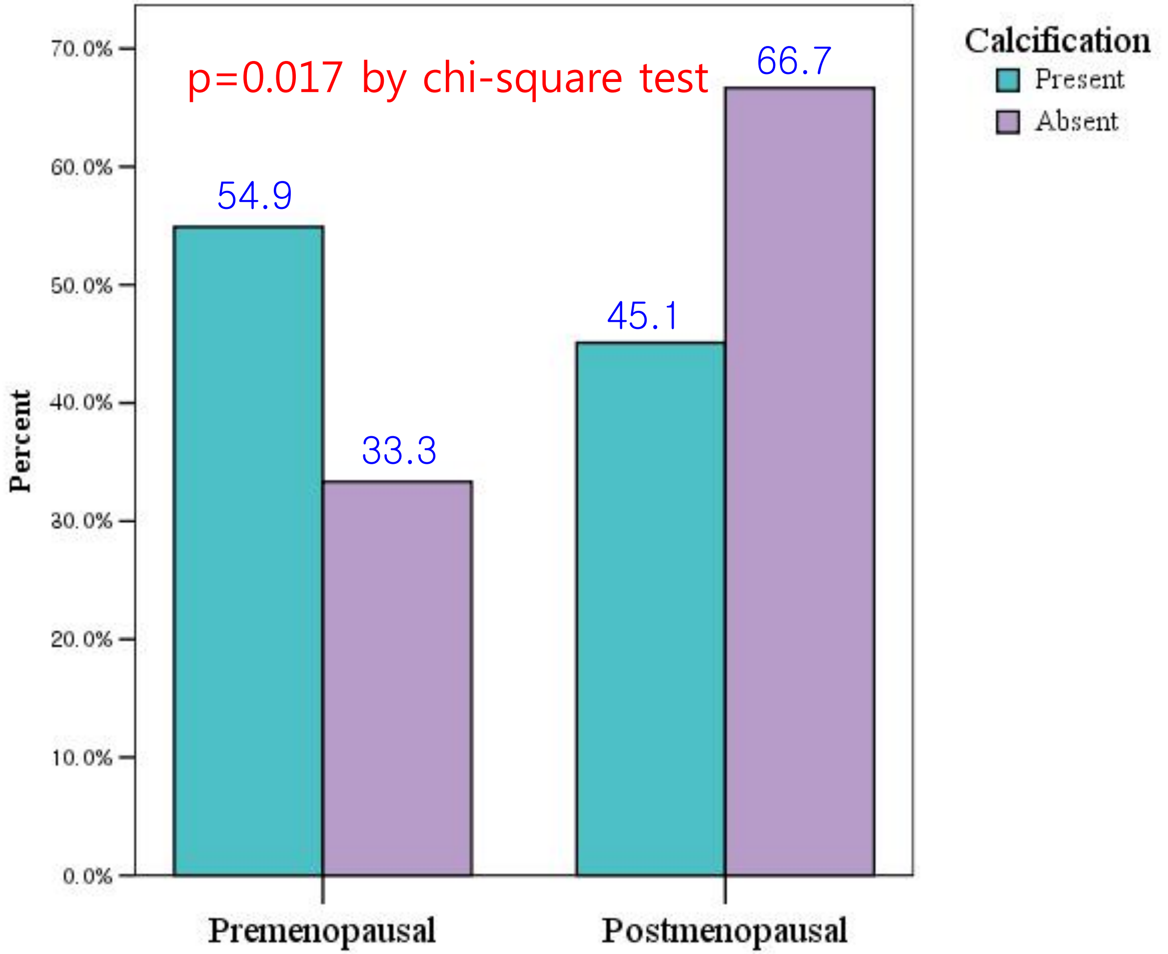
Table 5 Multiple logistic regression analyses for gender, age groups, hypertension, obesity, diabetes, hypercholesterolemia, and hypertriglyceridemia of fourth quartile CAC scores (>75%)

Variables	Odds ratios (95% confidence interval)		
	Males	Females	All
Gender			
Female			Ref
Male			1.7 (0.9–2.9)
Age group (years)			
40–49	Ref	Ref	Ref
50–59	1.4 (0.8–2.4)	4.3 (1.1–15.9)	1.6 (1.0–2.6)
60–70	2.5 (1.2–5.1)	13.4 (2.8–64.5)	3.1 (1.7–6.0)
P value for trend	0.026	<0.001	<0.001
Obesity; body mass index (kg/m^2)			
<27	Ref	Ref	Ref
≥27	1.4 (0.8–2.4)	0.9 (0.2–4.1)	1.3 (0.8–2.1)
Hypertension (mmHg)			
<140/90	Ref	Ref	Ref
≥140/90	2.3 (1.4–3.9)	1.5 (0.5–4.8)	2.2 (1.4–3.5)
Hyperglycemia (mg/dL)			
<126	Ref	Ref	Ref
≥126	0.8 (0.3–1.6)	1.1 (1.7–48.1)	1.1 (0.6–2.2)
Hypercholesterolemia (mg/dL)			
<200	Ref	Ref	Ref
≥200	1.7 (1.0–2.9)	0.6 (0.2–1.8)	1.5 (0.9–2.3)
Hypertriglyceridemia (mg/dL)			
<150	Ref	Ref	Ref
≥150	1.9 (1.1–3.3)	0.6 (0.1–3.7)	1.8 (1.1–2.9)

Hsu CH et al. NMCD 18:306-313, 2008

The proportion of calcification according to menopausal status in perimenopausal Korean women

In 237 perimenopausal Korean women



Rhee EJ. Unpublished data

Coronary calcification and osteoporosis after menopause

vBMD and vascular calcification in middle-aged women: The Study of Women's Health Across the Nation

490 caucasian women aged 45-58 years, with 64% white

TABLE 3. RESULTS OF THE MULTINOMIAL LOGISTIC REGRESSION MODELS FOR AC AND CAC. UNADJUSTED, AGE-ADJUSTED, AND RISK FACTOR–ADJUSTED ORs (95% CI) PER 1 SD* DECREASE IN vBMD

	AC level			*CAC level*		
	No AC (0)	*Moderate AC (1–74)*	*High AC (≥75)*	*No CAC (0)*	*Moderate CAC (1–7.54)*	*High CAC (≥7.55)*
vBMD (unadjusted)	1.00 146	1.05 (0.86, 1.30) 221	1.73[‡] (1.33, 2.25) 123	1.00 256	0.94 (0.75, 1.17) 111	1.35[§] (1.08, 1.70) 123
vBMD (adjusted for age)	1.00 146	0.98 (0.78, 1.22) 221	1.54[§] (1.17, 2.03) 123	1.00 256	0.88 (0.70, 1.10) 111	1.19 (0.94, 1.51) 123
vBMD (adjusted for age + shared risk factors)[†]	1.00 109	1.33 (0.93, 1.90) 171	1.68[¶] (1.06, 2.68) 84	1.00 211	1.09 (0.77, 1.53) 91	1.19 (0.81, 1.74) 98

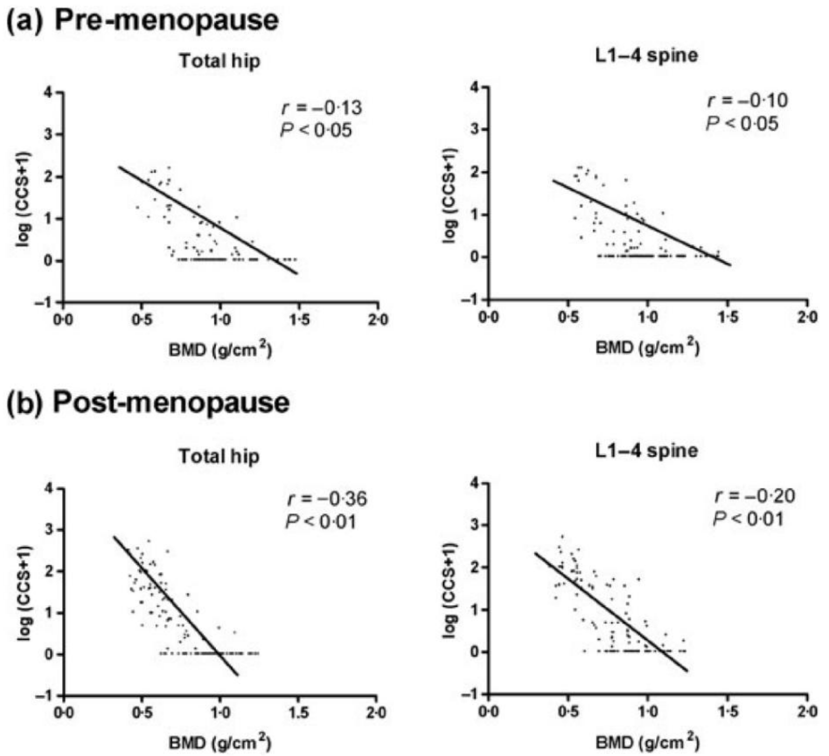
Farhat GN et al. JBMR 21:1839-1846, 2006

Low BMD is associated with higher CAC and coronary plaque burden in pre- and postmenopausal women

467 women with 160 premenopausal women, 179 postmenopausal Korean women

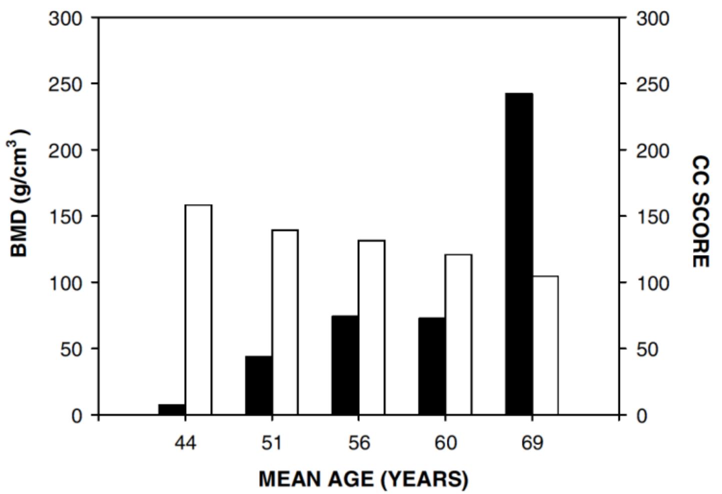
Table 2. Correlations between coronary calcium score (CCS) and various parameters

Variable	Correlation coefficient			
	Male	Female	Premenopause	Postmenopause
BMD				
Total hip	–0·03	–0·27**	–0·13*	–0·36**
Femur neck	–0·09	–0·26**	–0·18*	–0·35**
Trochanter	0·03	–0·23**	–0·16*	–0·33**
L-spine 1–4	0·05	–0·19**	–0·10*	–0·20**
Age	0·29*	0·30**	0·02	0·37**
BMI	0·04	0·04	0·03	0·03
SBP	0·02	0·12	0·10	0·09
DBP	0·13	0·05	0·08	0·05
FBS	0·21	0·02	0·07	0·01
HbA1c	0·15	0·08	0·06	0·09
TC	0·06	0·07	0·01	0·03
LDL-C	0·09	0·09	0·01	0·02
HDL-C	0·05	–0·01	–0·06	–0·04
TG	0·07	0·05	0·06	0·04
Smoking	0·02	0·03	0·02	0·04
Years since menopause				0·22*



Choi SH et al. Clin Endocrinol 71:644-651, 2009

Coronary calcification and osteoporosis in postmenopausal women are independent process associated with aging



In 313 postmenopausal women and 167 men

Table 4. Correlations among age, CC scores, and BMD determined for men and women separately: values of correlation coefficients and partial coefficients of correlation are shown

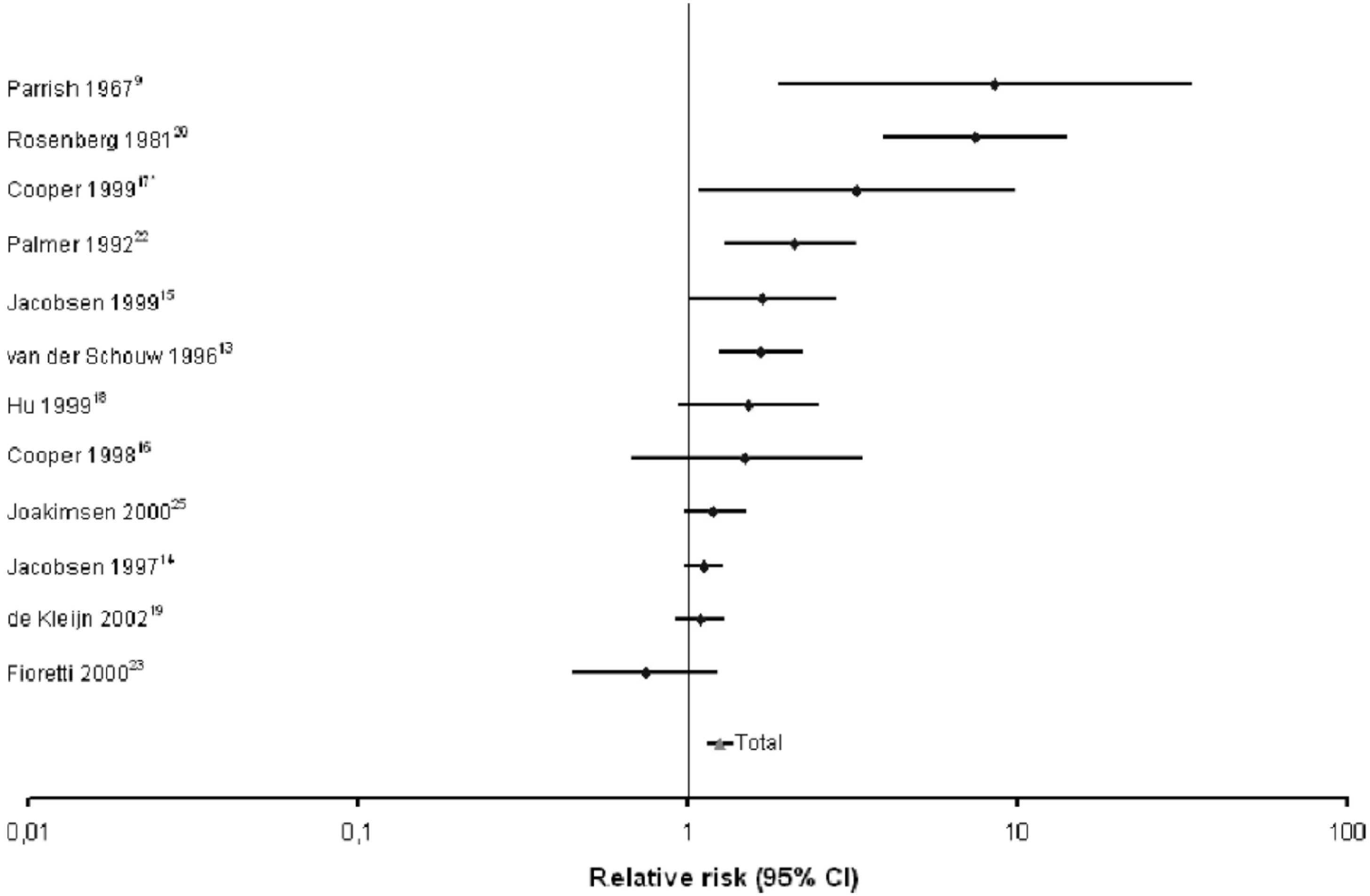
Variable 1	Variable 2	Control variable	Women	Men
Age	BMD spine	None	−0.62*	−0.42*
Age	CC score	None	0.33*	0.35*
BMD	CC score	None	−0.23*	−0.13
BMD	CC score	Age	−0.04	0.02

[a] $P \leq 0.001$ by Pearson's correlation

Sinnott B et al. Calcif Tissue Int 78:195-202, 2006

Premature menopause and vascular calcification

The effects of early menopause vs. usual menopause on CVD risk



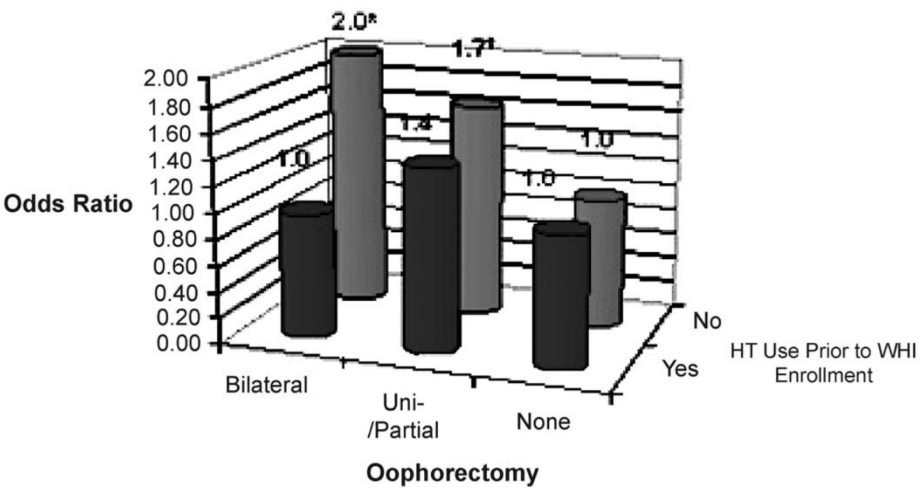
Atsma F et al. Menopause 13:265-279, 2006

Oophorectomy, HRT and coronary calcification

TABLE 1. *Cohort characteristics by the presence and absence of coronary calcium*

Variable	CAC score > 0 (n = 499)	CAC score = 0 (n = 565)	P^a
Age at WHI enrollment, y[b]	55.6 (2.8)	54.8 (2.9)	<0.01
Age at CAC scan, y[b]	65.3 (2.8)	64.4 (2.9)	<0.01
Ethnicity[c]			0.24
White	377 (75.6)	422 (74.7)	
Black	73 (14.6)	104 (18.4)	
Hispanic	33 (6.6)	32 (5.7)	
American Indian	8 (1.6)	1 (0.2)	
Asian/Pacific Islander	2 (0.4)	1 (0.2)	
Unknown	6 (1.2)	5 (1.0)	
Body mass index (kg/m^2)[b]	31.5 (6.0)	29.8 (6.1)	<0.01
Waist circumference (cm)[b]	94.9 (14.0)	88.8 (13.9)	<0.01
Waist-to-hip ratio[b]	0.84 (0.1)	0.80 (0.01)	<0.01
Cigarette smoking, pack-years[b]	13.6 (19.9)	7.1 (14.4)	<0.01
Physical activity, METs[b]	9.0 (12.2)	11.0 (13.8)	0.06
Education[c]			<0.01
0-8 y	6 (1.2)	10 (1.8)	
Some high school	22 (4.5)	12 (2.1)	
High school diploma/GED	124 (25.1)	99 (17.7)	
School after high school	219 (44.3)	247 (44.1)	
College degree or higher	123 (24.9)	192 (34.3)	
Smoking status[c]			<0.01
Never smoked	212 (42.6)	303 (54.0)	
Past smoker	200 (40.2)	216 (38.5)	
Current smoker	85 (17.1)	42 (7.5)	
Hypertension[c]	218 (48.3)	176 (33.9)	<0.01
High cholesterol[c]	62 (14.8)	36 (7.3)	<0.01
Diabetes mellitus[c]	35 (7.0)	18 (3.2)	0.01
Oophorectomy[c]			0.15
None	195 (39.3)	264 (47.1)	
Part of an ovary removed	10 (2.0)	8 (1.4)	
One ovary removed	85 (17.1)	73 (13.0)	
Both ovaries removed	184 (37.1)	194 (34.6)	
Do not know	13 (2.6)	11 (2.0)	
Years since bilateral oophorectomy[b]	14.1 (7.3)	12.8 (7.0)	0.26
Years since hysterectomy[b]	16.2 (6.9)	15.5 (6.8)	0.57
Reported previous HT use[c]			0.88
Never used	236 (47.3)	267 (47.3)	
Past user	161 (32.3)	173 (30.6)	
Current user	102 (20.4)	125 (22.1)	
Duration of previous HT use, y[b]	3.0 (5.0)	3.2 (5.2)	0.40
Years of no HT after hysterectomy[b]	13.3 (7.9)	12.5 (7.9)	0.39

Women's Health Initiative
Coronary Artery Calcium Study



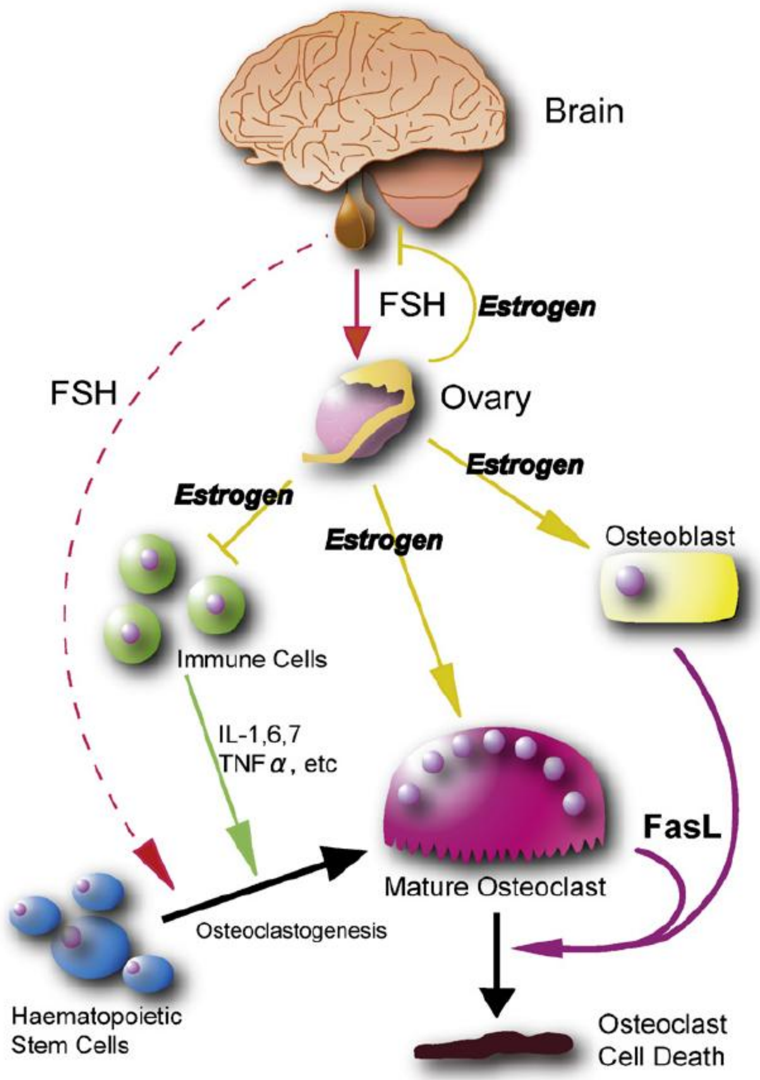
Menopause 15:639-647, 2008

The relationship of estrogen with vascular calcification and osteoporosis

Common mechanisms in the pathogenesis of osteoporosis and vascular disease

- Age-related mechanisms
- Chronic inflammation (e.g. in rheumatoid arthritis)
- Cigarette smoking
- Diabetes Mellitus
- Estrogen deficiency
- Hypovitaminosis C,D, and K
- Oxidized lipids and free radicals
- Renal failure

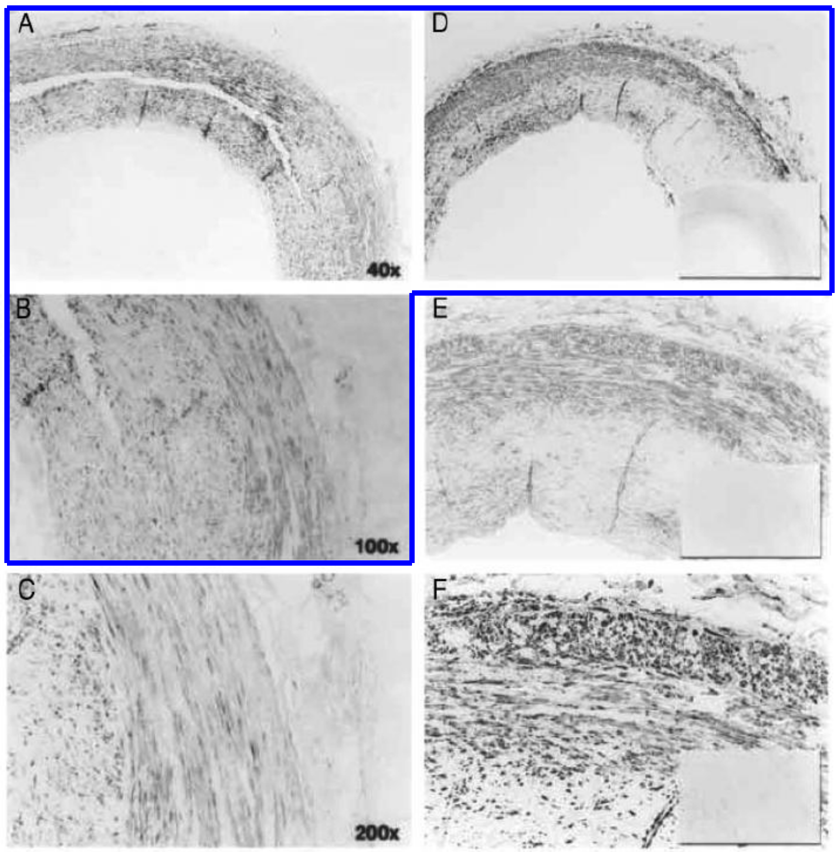
Schematic outline of estrogen regulated pathways in the bone mass control



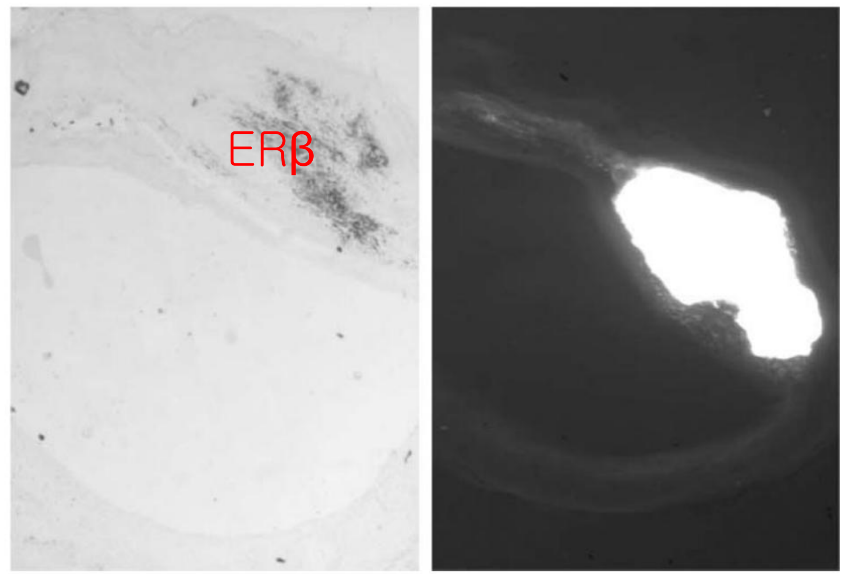
Imai Y et al. Mol Cell Endocrinol 310 (2009) 3–10

ERα,β are expressed on coronary artery of pre- and postmenopausal women

ERα



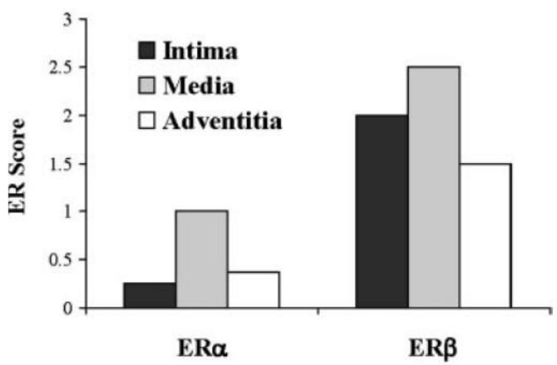
ERβ

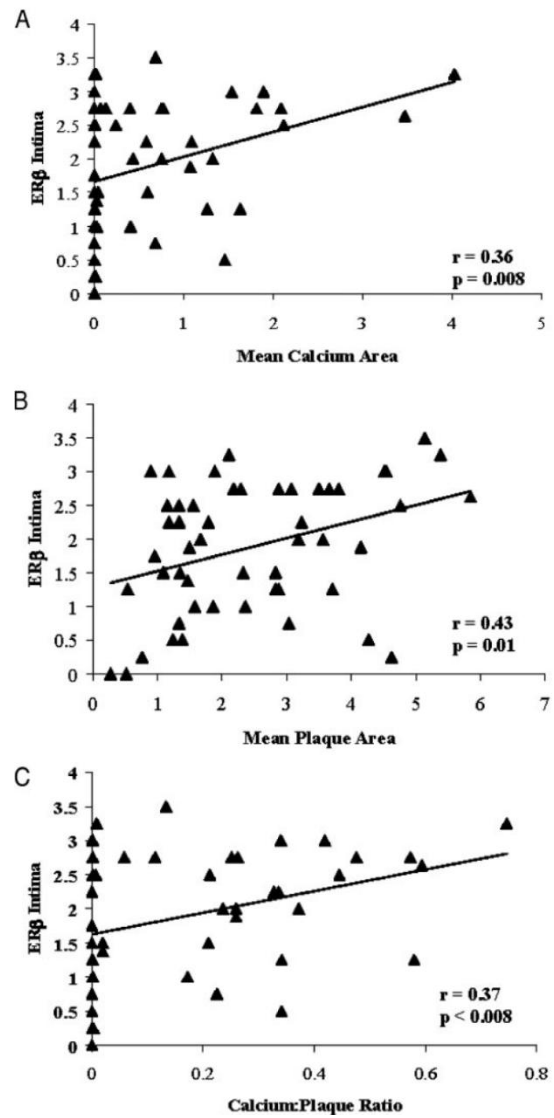


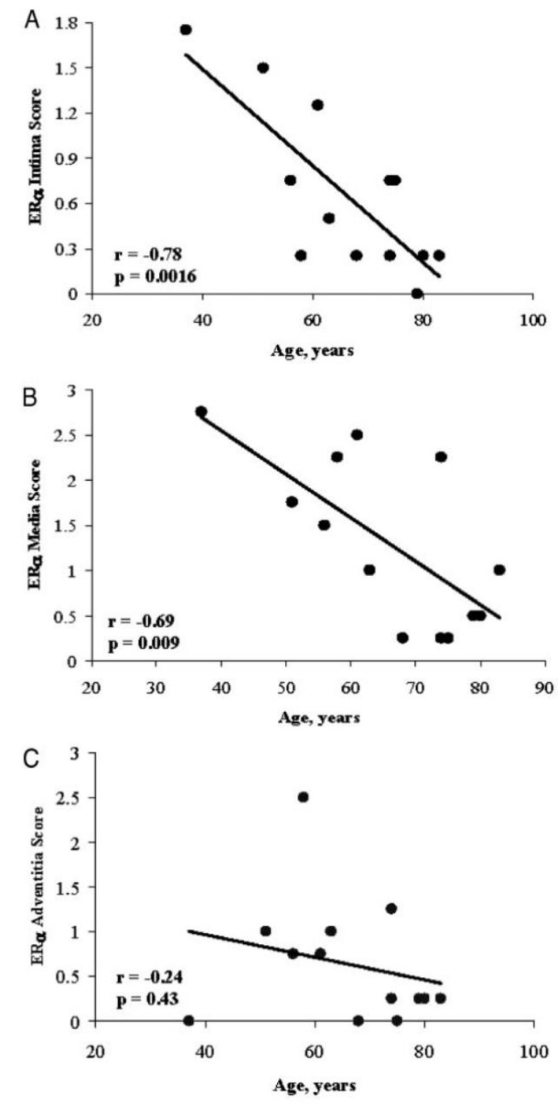
Rose CC et al. JCEM 91:2713-2720, 2006

ERβ expression was correlated with calcification and ERα expression was correlated with age in pre- and postmenopausal women

Autopsy from 55 women







Rose CC et al. JCEM 91:2713-2720, 2006

Serum OPG level is higher in postmenopausal women compared with premenopausal women

Table III Comparisons of mean BMD, bone turnover markers, and serum OPG levels between groups differentiated by the presence of the T allele in premenopausal and postmenopausal women

	Premenopausal (n = 138)			Postmenopausal (n = 125)		
	All (n = 138)	CC (n = 83)	CT+TT (n = 55)	All (n = 125)	CC (n = 88)	CT+TT (n = 37)
Age (y)*	49.07 ± 6.75	49.23 ± 6.22	48.84 ± 7.54	54.18 ± 5.85	54.63 ± 5.71	53.14 ± 6.12
BMI (kg/m^2)	24.13 ± 2.91	24.20 ± 2.80	24.02 ± 3.10	24.12 ± 3.01	24.15 ± 3.17	24.06 ± 2.62
OPG (pg/mL)†	1258.56 ± 398.57	1307.56 ± 393.12	1184.61 ± 398.85	1365.61 ± 375.54	1411.46 ± 399.38‡	1256.56 ± 287.98‡
ALP (IU/L)*	54.00 ± 15.61	55.20 ± 16.68	52.18 ± 13.79	67.78 ± 20.42	67.59 ± 22.19	68.22 ± 15.70
Ca (mmol/L)*	2.23 ± 0.08	2.22 ± 0.08	2.23 ± 0.09	2.28 ± 0.08	2.27 ± 0.08	2.29 ± 0.08
P (mmol/L)*	1.16 ± 0.14	1.15 ± 0.14	1.17 ± 0.14	1.29 ± 0.14	1.28 ± 0.14	1.30 ± 0.14
DPD (nmol/L per mol/L)*	6.44 ± 1.77	6.37 ± 1.79	6.55 ± 1.74	7.86 ± 2.14	7.65 ± 2.16	8.37 ± 2.01
Uca (mmol/L/d)*	4.53 ± 2.43	4.43 ± 2.24	4.69 ± 2.73	4.64 ± 2.92	4.70 ± 3.15	4.48 ± 2.32
Up (mg/d)*	513.56 ± 173.55	504.16 ± 162.42	528.38 ± 190.96	444.81 ± 189.05	442.73 ± 206.03	449.91 ± 141.59
Lumbar spine BMD (g/cm^2)*	1.02 ± 0.16	1.03 ± 0.17	1.00 ± 0.15	0.90 ± 0.15	0.90 ± 0.15	0.91 ± 0.14
Lumbar spine T-score*	−0.89 ± 1.45	−0.80 ± 1.52	−1.03 ± 1.34	−1.95 ± 1.36	−1.99 ± 1.39	−1.84 ± 1.30
Femoral neck BMD (g/cm^2)*	0.83 ± 0.12	0.83 ± 0.11	0.82 ± 0.13	0.77 ± 0.12	0.77 ± 0.12	0.78 ± 0.11
Femoral neck T-score*	−1.04 ± 0.86	−1.02 ± 0.80	−1.08 ± 0.94	−1.39 ± 0.83	−1.42 ± 0.85	−1.33 ± 0.79

Values are presented as means ± SD.

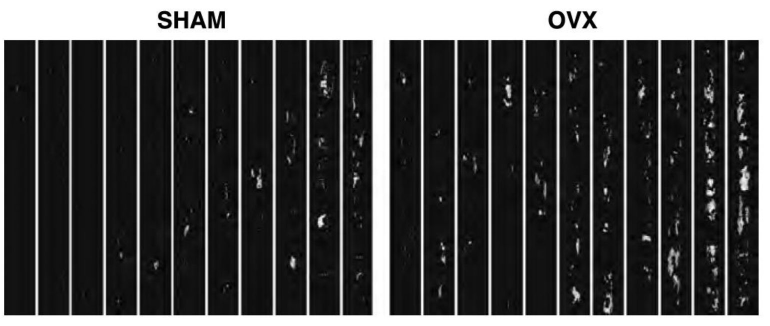
* $P < .01$ for comparison between premenopausal and postmenopausal groups as a whole.

† $P = .026$ for comparison between premenopausal and postmenopausal groups.

‡ $P < .05$ for comparison between CC and CT+TT genotype groups before and after adjustment for age and FSH with ANCOVA test.

Rhee EJ et al. Am J OBGY 192:1087-93, 2005

Ovariectomy increases vascular calcification via OPG/RANKL cytokine signalling pathway



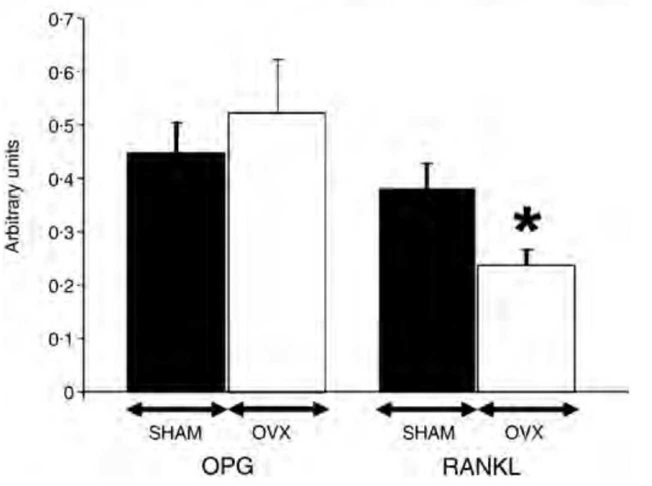


Table 3 Quantitative analysis of vessel calcification by μCT and osteoprotegerin (OPG) and receptor activator of nuclear factor κB ligand (RANKL) expression by Western blot analysis

	Mineral density (mg cm^{-3})	Particle density (particles cm^{-3})	Calcific arc angle	OPG/RANKL (Arbitrary unit ratio)
OVX	8·4 ± 2·8*	94 ± 26*	33 ± 7°	1·81 ± 1·06*
SHAM	1·9 ± 0·6	33 ± 7	33 ± 5°	1·09 ± 0·81

Choi BG et al. Eur J Clin Invest 38:211-217, 2008

The role of OPG/RANKL on association of bone and CAC

TABLE 1. Mean RANKL and OPG among postmenopausal estrogen-using women with and without coronary artery calcification

	CACS		
	Mean ± SE		
	≤10	**<10**	***P* value**
RANKL	n = 52	n = 40	
Crude	1.15 ± 1.21	1.32 ± 1.25	0.643
Multiply adjusted[a]	0.79 ± 1.42	1.21 ± 1.37	0.225
OPG	n = 50	n = 37	
Crude	102.9 ± 1.07	126.8 ± 1.08	0.033
Multiply adjusted[a]	99.8 ± 1.12	107.2 ± 1.10	0.508

TABLE 2. Association of BMD at each skeletal site with CACS (≤10 *vs.* <10) before and after adjustment for RANKL and OPG

	Women, current estrogen users (n = 92)	
	OR (95% CI)	***P* value**
Total hip		
Age-adjusted	0.62 (0.36–1.05)	0.075
Multiply adjusted[a]	0.52 (0.29–0.93)	0.029
Multiply adjusted[a] + RANKL	0.49 (0.27–0.90)	0.022
Multiply adjusted[a] + OPG	0.51 (0.78–0.95)	0.035
Multiply adjusted[a] + RANKL + OPG	0.49 (0.26–0.91)	0.025
Femoral neck		
Age-adjusted	0.68 (0.42–1.12)	0.128
Multiply adjusted[a]	0.61 (0.36–1.03)	0.064
Multiply adjusted[a] + RANKL	0.59 (0.34–1.01)	0.055
Multiply adjusted[a] + OPG	0.58 (0.34–1.01)	0.056
Multiply adjusted[a] + RANKL + OPG	0.56 (0.32–0.98)	0.042
Lumbar spine		
Age-adjusted	0.60 (0.35–1.05)	0.072
Multiply adjusted[a]	0.55 (0.31–1.00)	0.050
Multiply adjusted[a] + RANKL	0.51 (0.28–0.93)	0.029
Multiply adjusted[a] + OPG	0.59 (0.32–1.09)	0.090
Multiply adjusted[a] + RANKL + OPG	0.54 (0.29–1.00)	0.050

Bakhireva LN et al. JCEM 93:2009–2012, 2008

Hormone replacement therapy and vascular calcification

Estrogen therapy and coronary artery calcification-WHI-CACS

Table 3. Coronary-Artery Calcium Scores after Trial Completion, According to Score Category.*

Coronary-Artery Calcium Score	Conjugated Equine Estrogens	Placebo	Odds Ratio (95% CI)		Multivariate P Value
			Unadjusted	Multivariate	
	no. (%)				
Intention-to-treat analyses†	**N=537**	**N=527**			
0 (referent)	299 (55.7)	266 (50.5)	1.00	1.00	
>0	238 (44.3)	261 (49.5)	0.81 (0.64–1.03)	0.78 (0.58–1.04)	0.09
<10 (referent)	348 (64.8)	302 (57.3)	1.00	1.00	
≥10	189 (35.2)	225 (42.7)	0.73 (0.57–0.93)	0.74 (0.55–0.99)	0.04
<100 (referent)	448 (83.4)	408 (77.4)	1.00	1.00	
≥100	89 (16.6)	119 (22.6)	0.68 (0.50–0.93)	0.69 (0.48–0.98)	0.04
Analyses restricted to participants with ≥80% adherence to study medication‡	**N=387**	**N=352**			
0 (referent)	227 (58.7)	172 (48.9)	1.00	1.00	
>0	160 (41.3)	180 (51.1)	0.67 (0.50–0.90)	0.64 (0.46–0.91)	0.01
<10 (referent)	262 (67.7)	191 (54.3)	1.00	1.00	
≥10	125 (32.3)	161 (45.7)	0.57 (0.42–0.76)	0.55 (0.39–0.79)	<0.001
<100 (referent)	333 (86.0)	269 (76.4)	1.00	1.00	
≥100	54 (14.0)	83 (23.6)	0.53 (0.36–0.77)	0.46 (0.29–0.73)	0.001

Manson JE et al. NEJM 356:2591-602, 2007

HRT and CAC in asymp. Postmenopausal women: the Rancho Bernardo Study

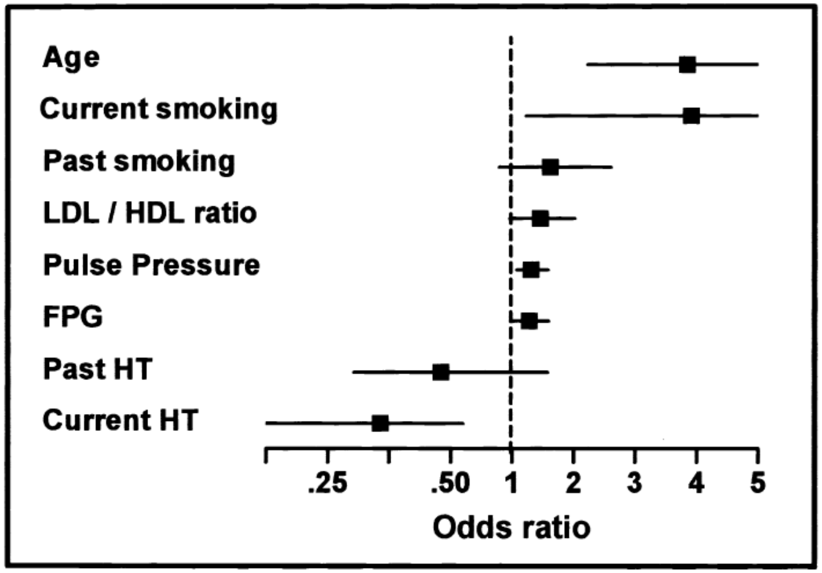


FIG. 1. Odds ratios for the association of *current* and *past* vs *never* HT and other CHD risk factors with increasingly severe coronary artery calcification among 204 asymptomatic postmenopausal women. Units: age = 10 y; LDL/HDL ratio = 1; pulse pressure = 10 mm Hg; FPG (fasting plasma glucose) = 20 mg/dL; current smoking = *yes* vs *no*.

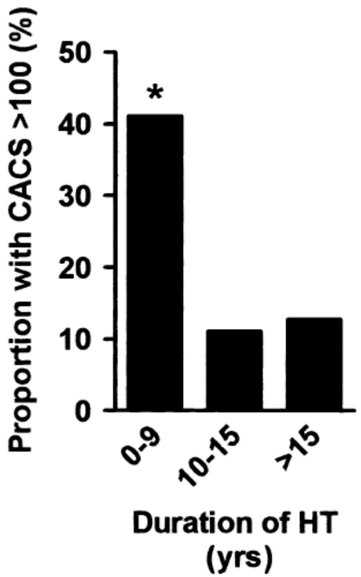
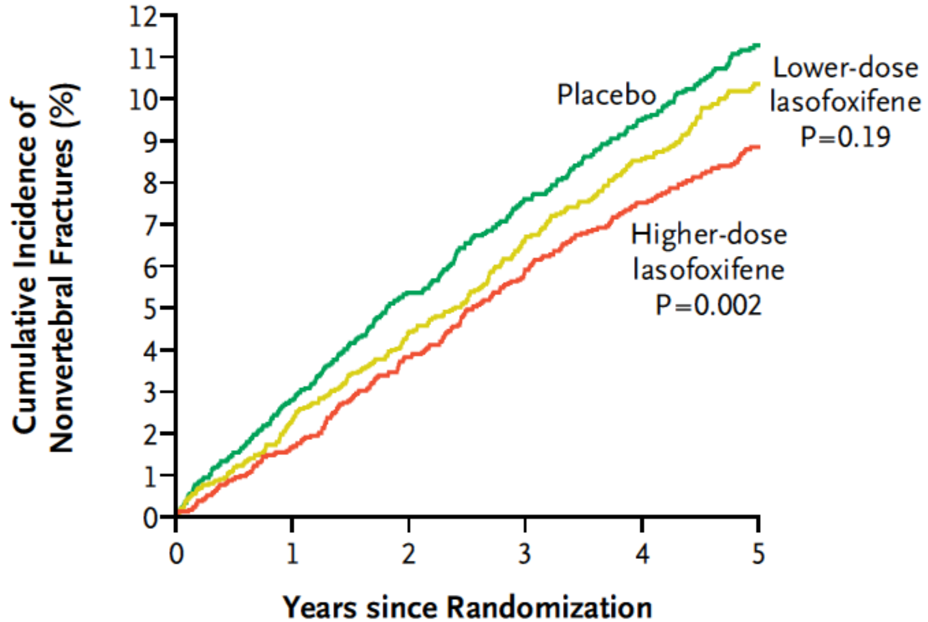


FIG. 2. Age-adjusted proportions of women with CACS (coronary artery calcification score) >100 by duration of HT use among 127 asymptomatic postmenopausal women. $*P < 0.01$ vs 10-15 y and >15 y.

Barrett-Connor E et al. Menopause 12:40-48, 2005

Lasofoxifene in postmenopausal women with osteoporosis - PEARL Study



No. at Risk

Lasofoxifene, 0.25 mg	2852	2745	2639	2520	2139	2002
Lasofoxifene, 0.5 mg	2852	2763	2647	2531	2150	2053
Placebo	2852	2731	2598	2479	2093	1979

Figure 1. Cumulative Incidence of Nonvertebral Fractures, According to Study Group.

Cummings SR et al. NEJM 362:686-696, 2010

Lasofoxifene in postmenopausal women with osteoporosis – PEARL Study

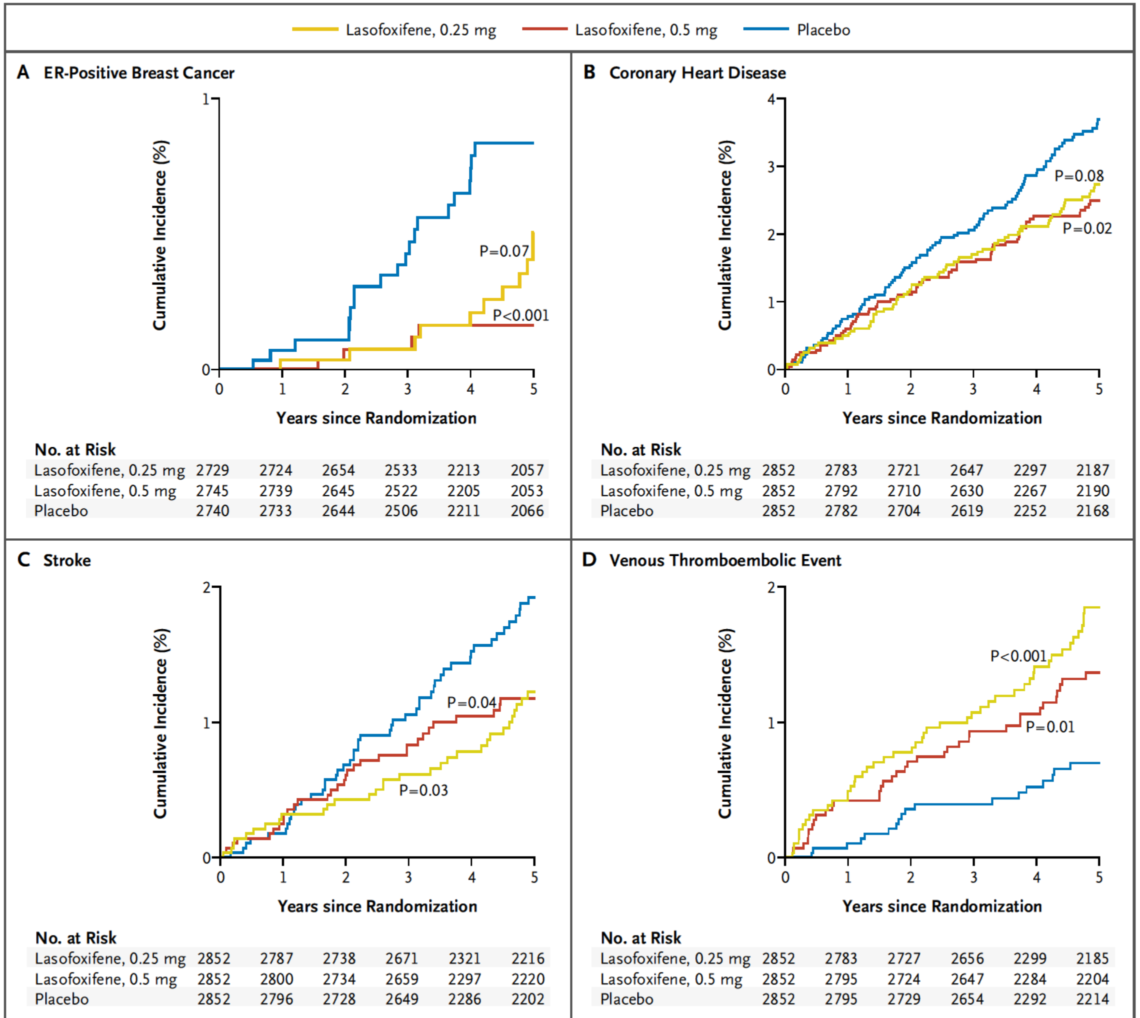


Figure 2. Cumulative Incidence of Events Other than Fracture, According to Study Group.
The cumulative incidence of estrogen-receptor (ER)–positive breast cancer (Panel A), major coronary heart disease (Panel B), stroke (not including transient ischemic attacks) (Panel C), and venous thromboembolic events (Panel D) is shown.

Cummings SR et al. NEJM 362:686-696, 2010

What should we do?

- Atherosclerosis and osteoporosis:

→ applying one treatment and treating two diseases?

Statin

Bisphosphonate

Metformin

Estrogen

SERM

Vitamin D

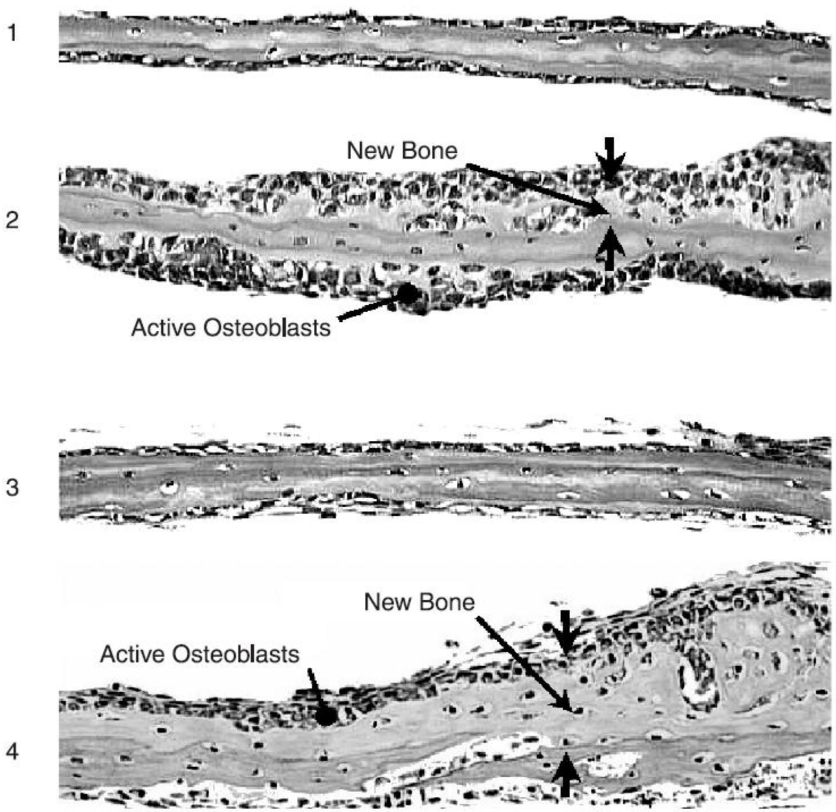
Relationship between premenopausal dietary intake and postmenopausal subclinical atherosclerosis

The relative risks of subclinical atherosclerosis by quartiles of baseline macronutrients intake, keys score, and fiber intake for 401 HWS participants

	Coronary calcification ($N=357$)		Aortic calcification ($N=346$)		Carotid plaque index ($N=382$)	
	Unadjusted RR (95% CI)	Adjusted RR (95% CI)[a]	Unadjusted RR (95% CI)	Adjusted RR (95% CI)[a]	Unadjusted RR (95% CI)	Adjusted RR (95% CI)[a]
Calories (kcal)						
Q 1	1	1	1	1	1	1
Q 2	1.45 (0.80, 2.64)	1.89 (0.95, 3.74)	0.90 (0.45, 1.78)	0.98 (0.44, 2.18)	0.90 (0.51, 1.59)	1.11 (0.58, 2.12)
Q 3	1.86 (1.02, 3.37)	1.90 (0.96, 3.75)	0.80 (0.41, 1.58)	0.64 (0.29, 1.41)	0.94 (0.53, 1.66)	0.87 (0.45, 1.66)
Q 4	1.99 (1.09, 3.62)	2.47 (1.25, 4.88)	1.41 (0.68, 2.94)	1.58 (0.68, 3.66)	1.29 (0.73, 2.29)	1.92 (0.99, 3.73)
Protein % energy						
Q 1	1	1	1	1	1	1
Q 2	1.00 (0.56, 1.80)	1.15 (0.59, 2.23)	1.55 (0.78, 3.08)	1.78 (0.82, 3.86)	0.56 (0.32, 1.00)	0.52 (0.28, 1.01)
Q 3	1.02 (0.57, 1.84)	1.33 (0.68, 2.62)	1.36 (0.70, 2.67)	1.84 (0.85, 3.98)	0.61 (0.34, 1.09)	0.58 (0.30, 1.11)
Q 4	1.20 (0.67, 2.16)	2.20 (1.07, 4.53)	1.53 (0.77, 3.04)	2.25 (0.98, 5.18)	0.68 (0.38, 1.21)	0.74 (0.37, 1.50)
Carbohydrate % energy						
Q 1	1	1	1	1	1	1
Q 2	0.48 (0.26, 0.88)	0.47 (0.24, 0.92)	1.02 (0.49, 2.09)	1.10 (0.49, 2.51)	0.59 (0.33, 1.05)	0.59 (0.30, 1.15)
Q 3	0.47 (0.26, 0.86)	0.44 (0.22, 0.88)	0.63 (0.32, 1.25)	0.60 (0.27, 1.34)	0.79 (0.45, 1.40)	0.98 (0.50, 1.92)
Q 4	0.35 (0.19, 0.64)	0.37 (0.18, 0.74)	0.94 (0.46, 1.91)	1.20 (0.52, 2.79)	0.84 (0.48, 1.50)	1.08 (0.55, 2.15)
Fat % energy						
Q 1	1	1	1	1	1	1
Q 2	0.96 (0.53, 1.73)	0.90 (0.46, 1.74)	0.79 (0.39, 1.59)	0.72 (0.33, 1.57)	0.62 (0.35, 1.09)	0.63 (0.33, 1.20)
Q 3	1.17 (0.65, 2.11)	0.99 (0.51, 1.92)	0.67 (0.34, 1.32)	0.44 (0.20, 0.97)	1.06 (0.60, 1.89)	0.95 (0.50, 1.82)
Q 4	1.57 (0.87, 2.84)	1.24 (0.63, 2.45)	1.15 (0.55, 2.40)	0.78 (0.33, 1.87)	0.71 (0.40, 1.26)	0.47 (0.24, 0.93)
Saturated fat % energy						
Q 1	1	1	1	1	1	1
Q 2	1.82 (1.00, 3.30)	1.74 (0.89, 3.40)	1.15 (0.57, 2.31)	1.05 (0.48, 2.29)	0.94 (0.53, 1.66)	0.97 (0.51, 1.85)
Q 3	1.49 (0.82, 2.70)	1.32 (0.68, 2.59)	0.76 (0.39, 1.48)	0.61 (0.29, 1.29)	0.79 (0.45, 1.40)	0.75 (0.39, 1.43)
Q 4	1.99 (1.09, 3.62)	1.70 (0.87, 3.32)	1.50 (0.73, 3.11)	1.27 (0.57, 2.86)	1.04 (0.59, 1.85)	0.86 (0.45, 1.65)
Cholesterol (mg/1000 kcal)						
Q 1	1	1	1	1	1	1
Q 2	1.67 (0.91, 3.04)	1.69 (0.86, 3.31)	1.08 (0.55, 2.13)	0.92 (0.43, 1.97)	1.06 (0.60, 1.88)	1.25 (0.66, 2.38)
Q 3	2.23 (1.22, 4.06)	2.53 (1.27, 5.04)	1.15 (0.58, 2.28)	0.88 (0.40, 1.94)	1.02 (0.58, 1.80)	0.94 (0.49, 1.82)
Q 4	1.74 (0.96, 3.17)	1.73 (0.87, 3.42)	1.29 (0.64, 2.59)	1.20 (0.55, 2.65)	1.00 (0.57, 1.77)	0.99 (0.52, 1.88)
Keys score[b]						
Q 1	1	1	1	1	1	1
Q 2	1.21 (0.66, 2.20)	1.16 (0.59, 2.28)	1.08 (0.55, 2.11)	1.03 (0.48, 2.19)	0.70 (0.40, 1.24)	0.78 (0.41, 1.47)
Q 3	2.12 (1.16, 3.84)	2.21 (1.12, 4.34)	1.02 (0.52, 1.98)	0.75 (0.35, 1.61)	0.90 (0.51, 1.59)	0.80 (0.42, 1.53)
Q 4	1.73 (0.95, 3.14)	1.65 (0.84, 3.24)	1.99 (0.95, 4.18)	2.05 (0.89, 4.72)	1.04 (0.59, 1.85)	0.94 (0.49, 1.81)
Fiber (g/1000 kcal)						
Q 1	1	1	1	1	1	1
Q 2	0.58 (0.32, 1.05)	0.53 (0.27, 1.05)	0.80 (0.40, 1.58)	0.73 (0.33, 1.59)	0.90 (0.51, 1.59)	1.04 (0.54, 2.00)
Q 3	0.54 (0.30, 0.98)	0.58 (0.30, 1.13)	0.80 (0.40, 1.58)	0.89 (0.41, 1.94)	1.21 (0.68, 2.13)	1.92 (0.99, 3.68)
Q 4	0.44 (0.24, 0.80)	0.49 (0.24, 0.98)	1.23 (0.59, 2.55)	2.00 (0.84, 4.75)	1.18 (0.67, 2.10)	1.71 (0.86, 3.40)

Park HA et al. Atherosclerosis 186:420-427, 2006

Stimulation of bone formation in vitro and in rodents by statins



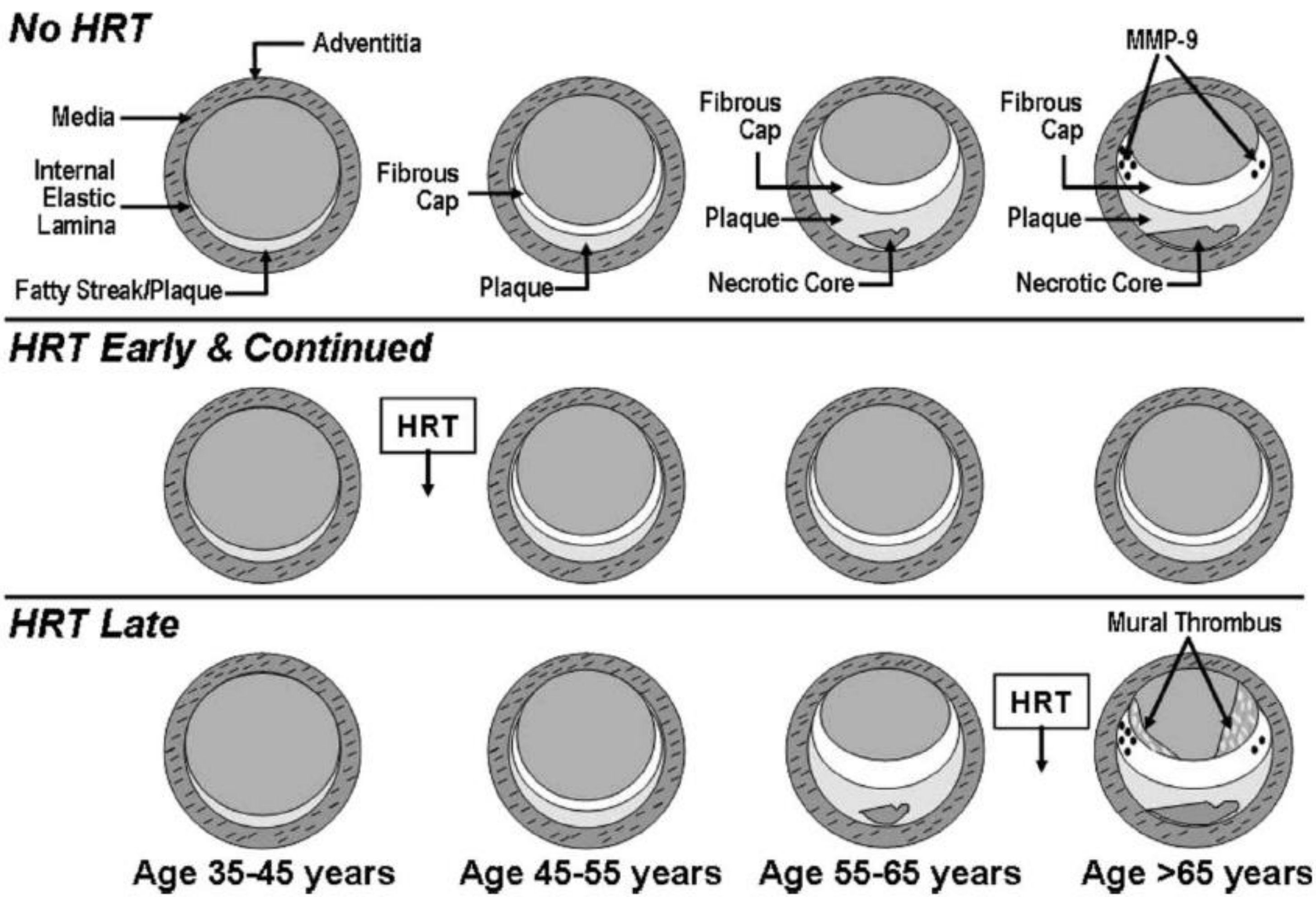
Effects of simvastatin (1 mM) added to cultures of explanted murine calvaria for 4 or 7 days.

Table. Frequency of Reported Fractures in the Scandinavian Simvastatin Survival Study

Type of Fracture	Placebo Group: Patients Aged ≤60 y, No. (%) (n = 1223)	Placebo Group: Patients Aged >60 y, No. (%) (n = 1000)	Simvastatin Group: Patients Aged ≤60 y, No (%) (n = 1177)	Simvastatin Group: Patients Aged >60 y, No. (%) (n = 1044)
Hip or femur	2 (0.16)	8 (0.80)	1 (0.08)	9 (0.86)
Vertebral	4 (0.33)	4 (0.40)	1 (0.08)	2 (0.19)
Other	30 (2.45)	23 (2.30)	34 (2.89)	37 (3.54)
All	36 (2.94)	35 (3.50)	36 (3.06)	48 (4.60)
All, any age	71 (3.19)		84 (3.78)	

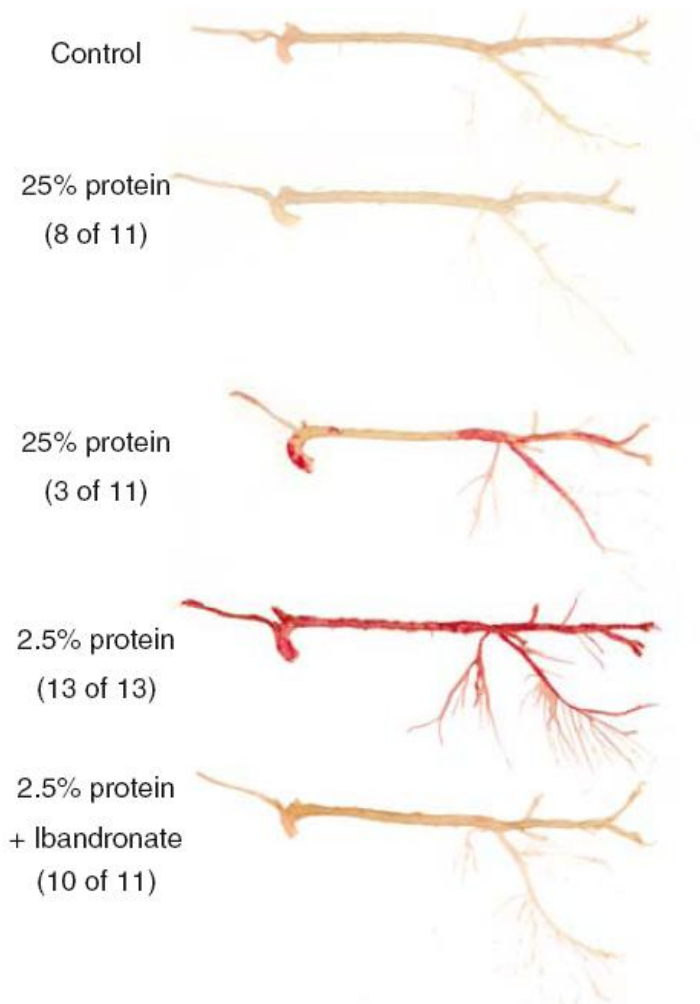
Mundy et al., Science 286:1946-1949, 1999

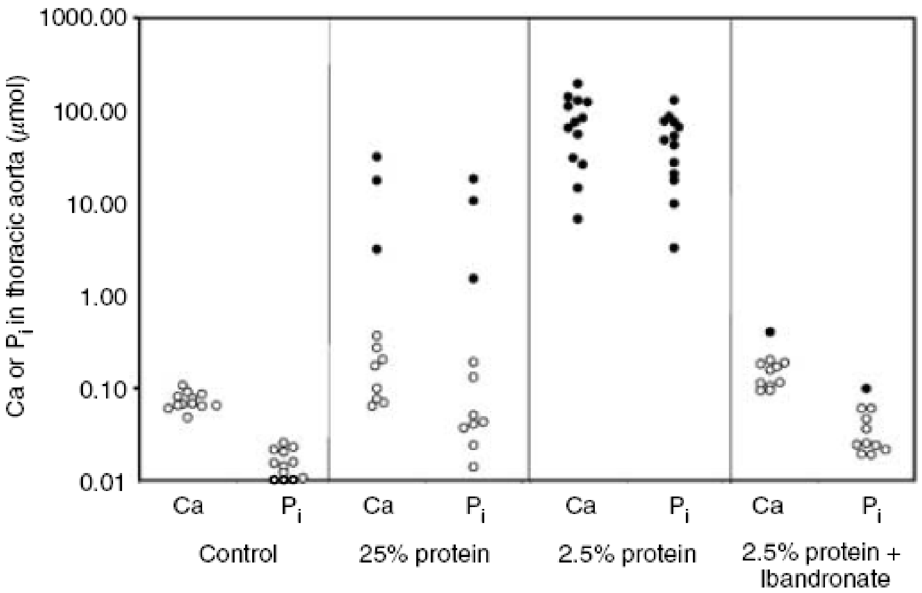
"Window of opportunity"



Archer DF. Climacteric 12:26-31, 2009

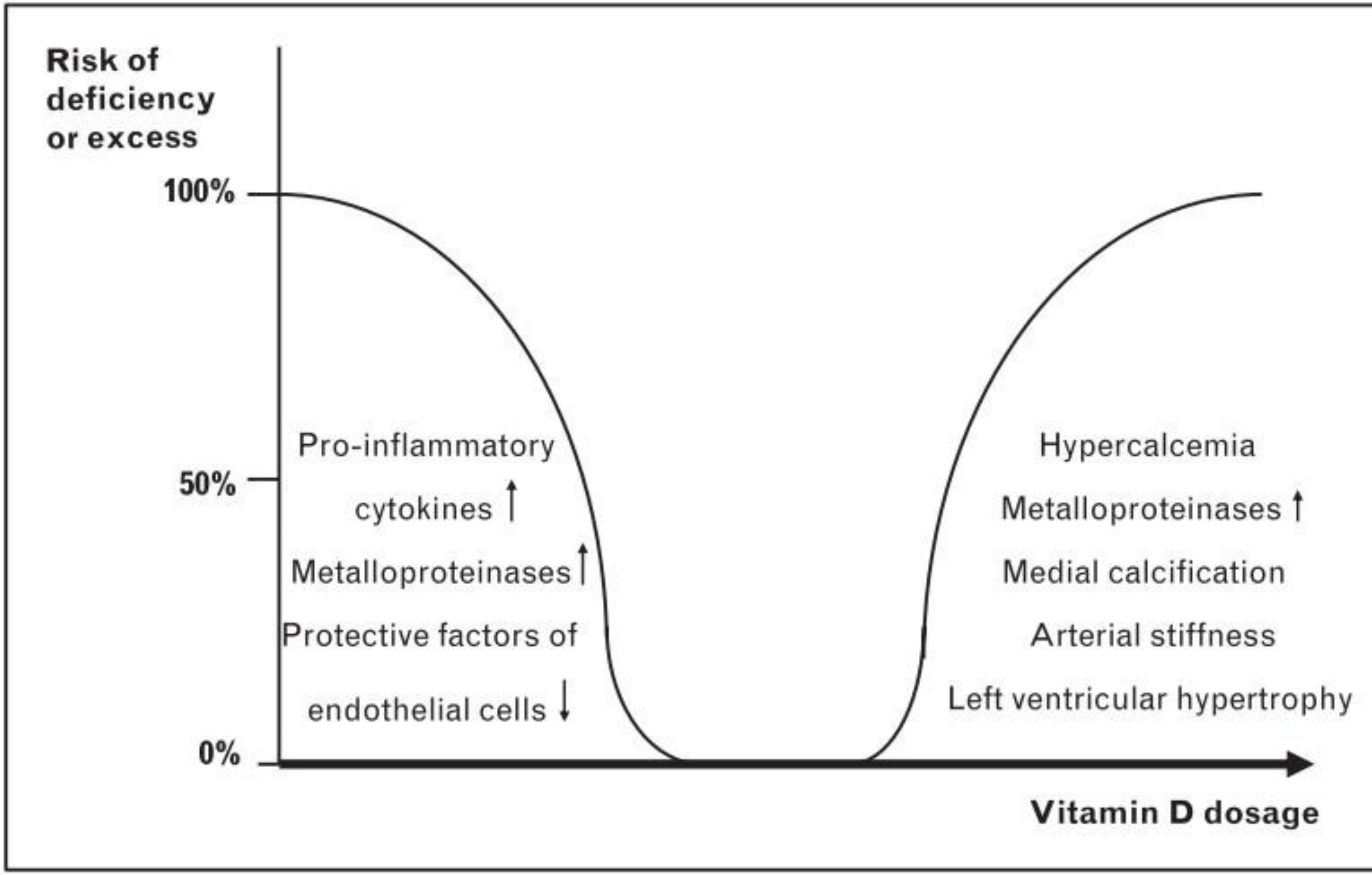
Artery calcification in uremic rats is increased by low protein diet and prevented by treatment with ibandronate





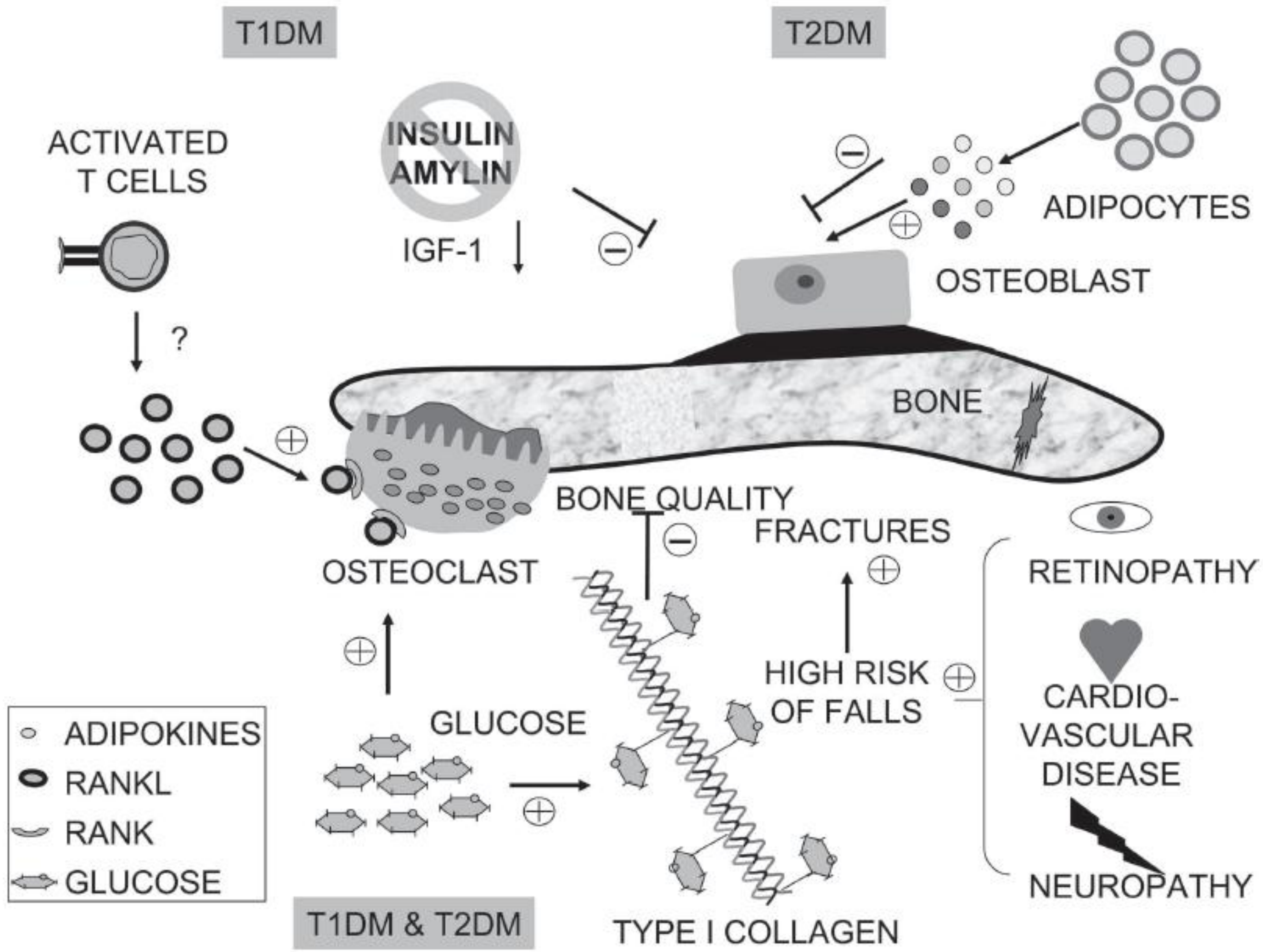
Price et al., Kidney Int 70:1577-1583, 2006

Biphasic dose-response curve for vitamin D in vascular calcification



Zitterman A et al. Curr Opin Lipidol 18:41-46, 2007

Potential mechanisms contributing to low bone mass and increased fracture susceptibility in diabetes mellitus

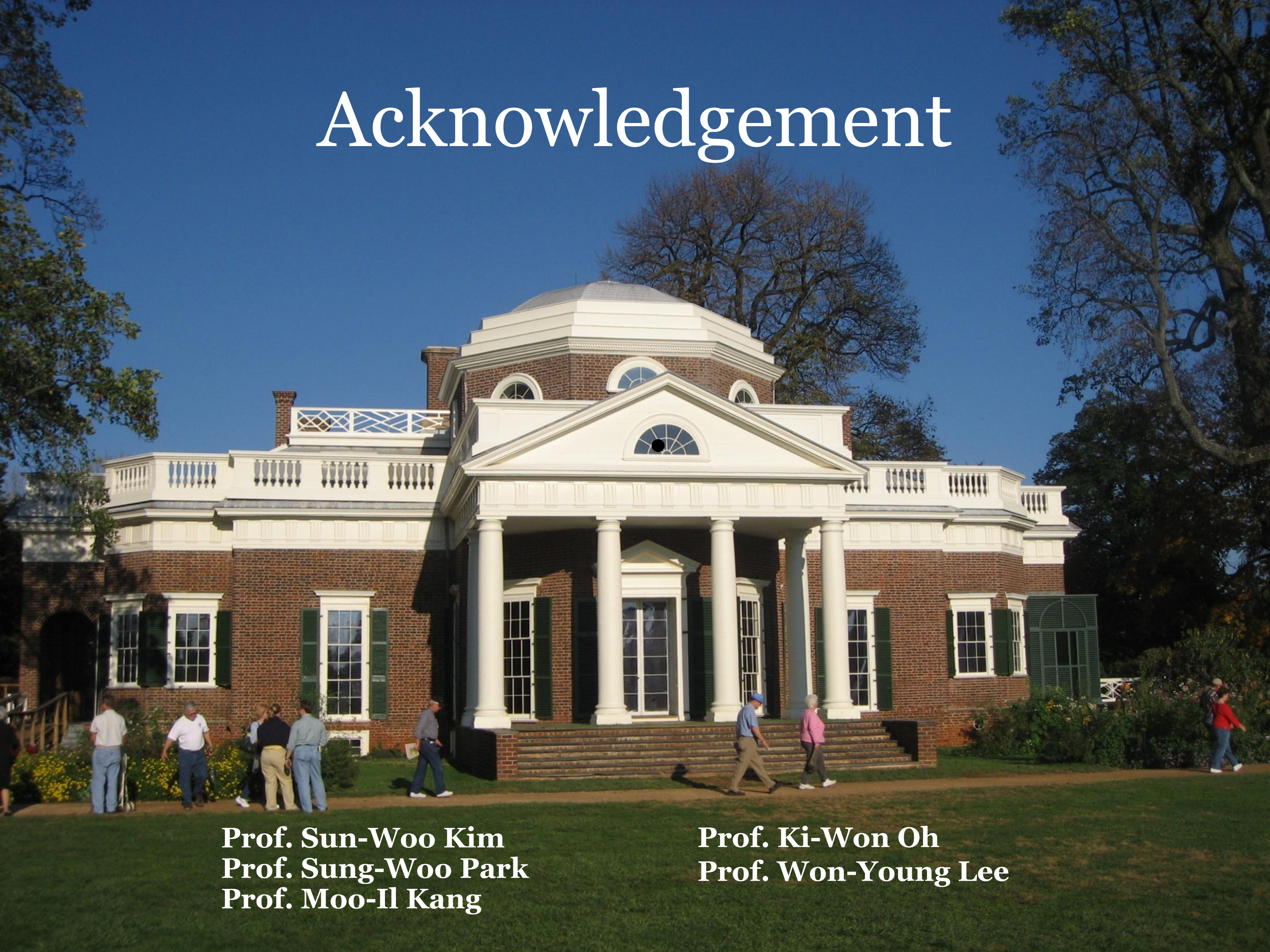


Hofbauer LC et al., JBMR 22:1317-1328, 2007

The way to go..

- Postmenopausal women are at risk for osteoporosis and vascular calcification simultaneously.
- Although there are a few specific strategies for the risk reduction of the two diseases, conventional interventions for the management of chronic diseases of aging could benefit.
- Life style interventions, such as appropriate diet and exercise and the preventive habits for the CVDs might help.
- The awareness of the physicians for the possibility of the two diseases in postmenopausal women is important.

Acknowledgement



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