Associazione Medici Endocrinologi

Primo Congresso Interregionale AME Sud - Italia

RELAZIONI TRA METABOLISMO OSSEO OBESITA' VISCERALE E INSULINO-RESISTENZA

Ambulatorio di Nutrizione Clinica

U.O.C. Oncologia Medica

Dipartimento Scienze Biomediche e Oncologia Umana

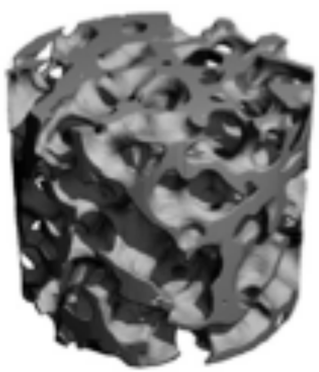
Giovanni De Pergola

Matera, 9-10 Maggio 2014 - HILTON GARDEN INN

Abdominal Fat Is Associated With Lower Bone Formation and Inferior Bone Quality in Healthy Premenopausal Women: A Transiliac Bone Biopsy Study

Trabecular Bone Volume in Subjects from Each Tertile of Trunk Fat by DXA

Lowest Tertile

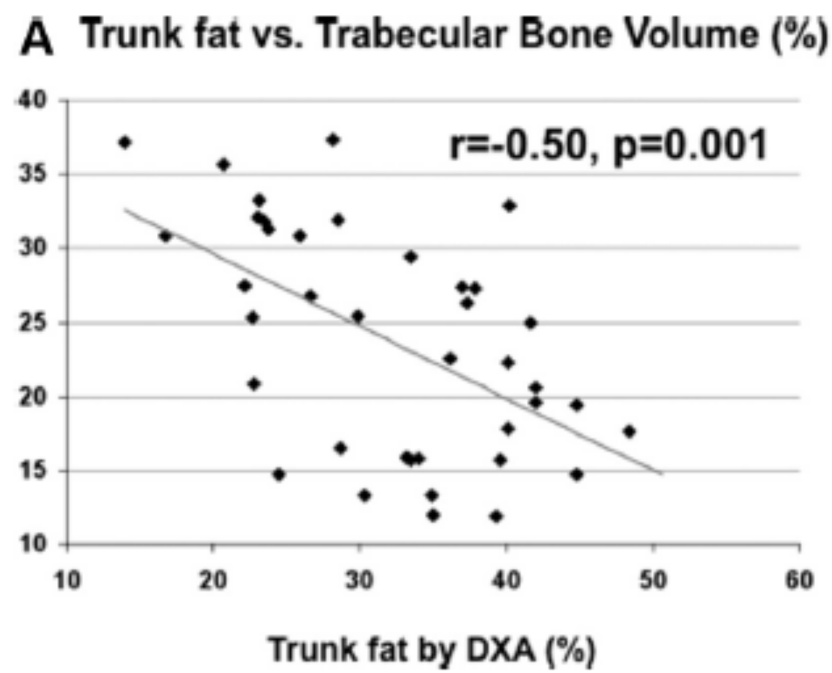


BMI: 22.2 kg/m^2
Trunk Fat: 16.8%
LS Z score: -0.5
BV/TV: 30.8%

Middle Tertile

BMI:28.3 kg/m^2
Trunk Fat: 36.2%
LS Z score: +1.4
BV/TV:22.5%

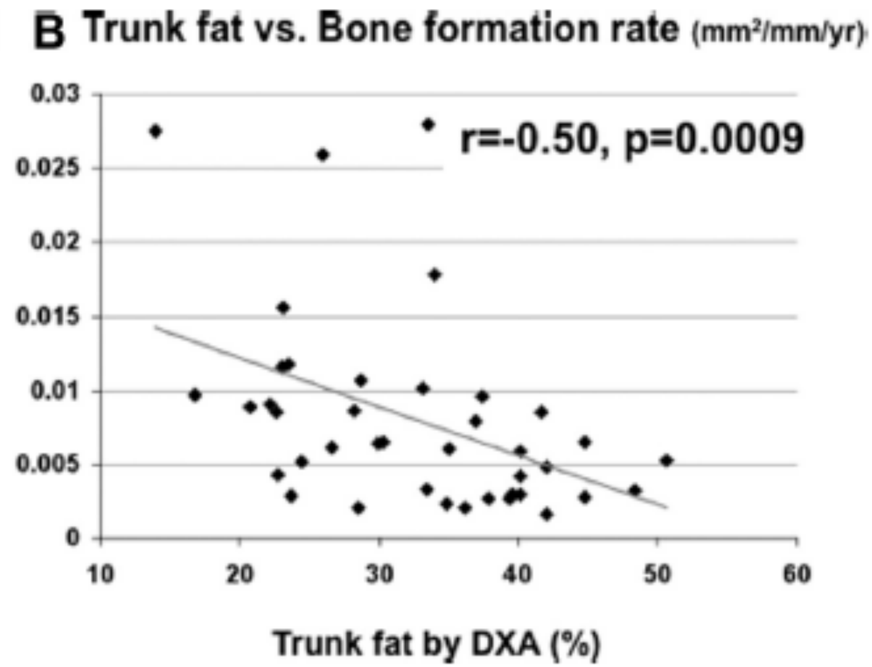
Highest Tertile



Cohen et al, J Clin Endocrinol Metab, 98: 2562-2572, 2013

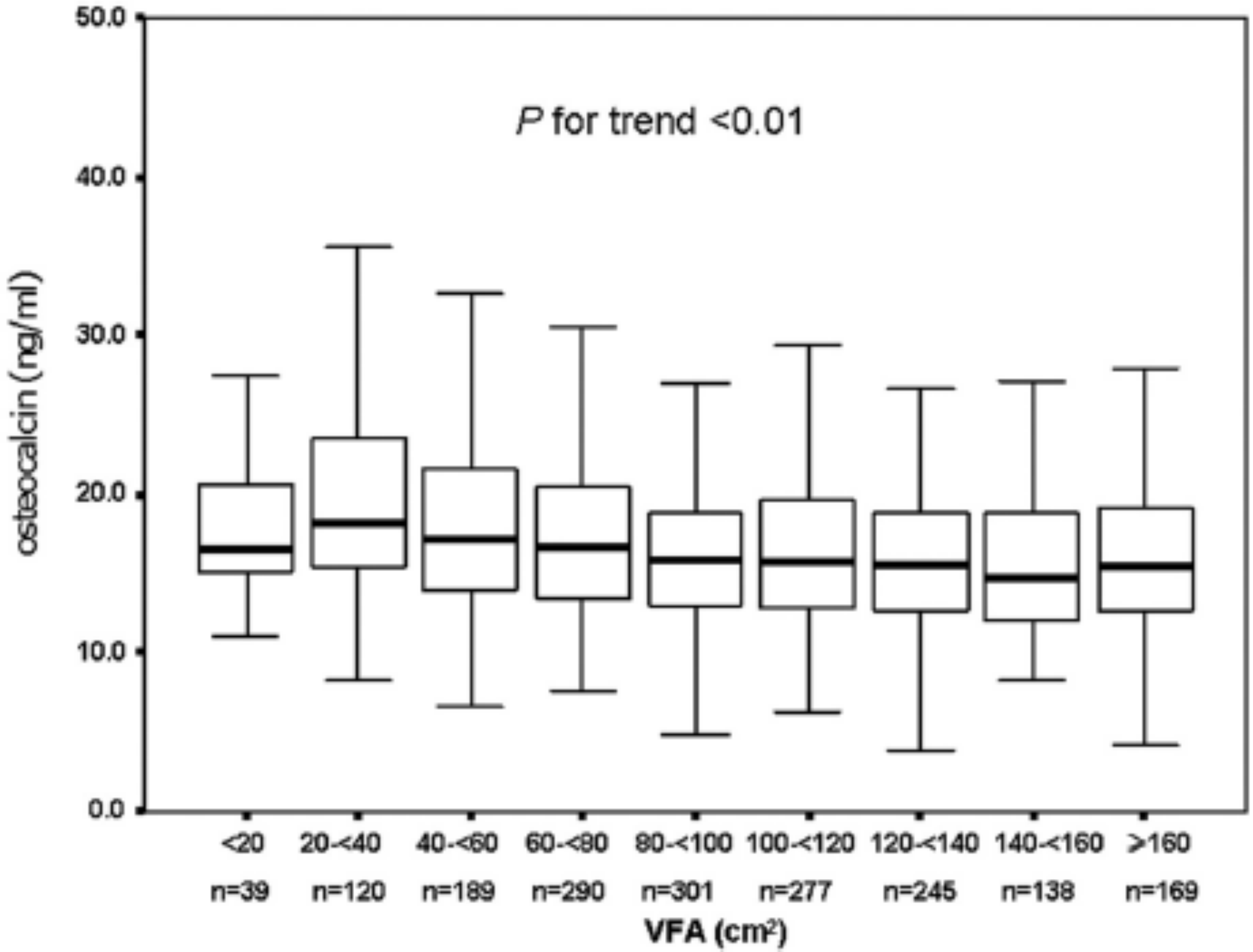
Abdominal Fat Is Associated With Lower Bone Formation and Inferior Bone Quality in Healthy Premenopausal Women: A Transiliac Bone Biopsy Study

Women with higher trunk fat mass also had markedly lower static and dynamic indices of bone formation (ostecalcin and P1NP), and lower serum bone formation markers



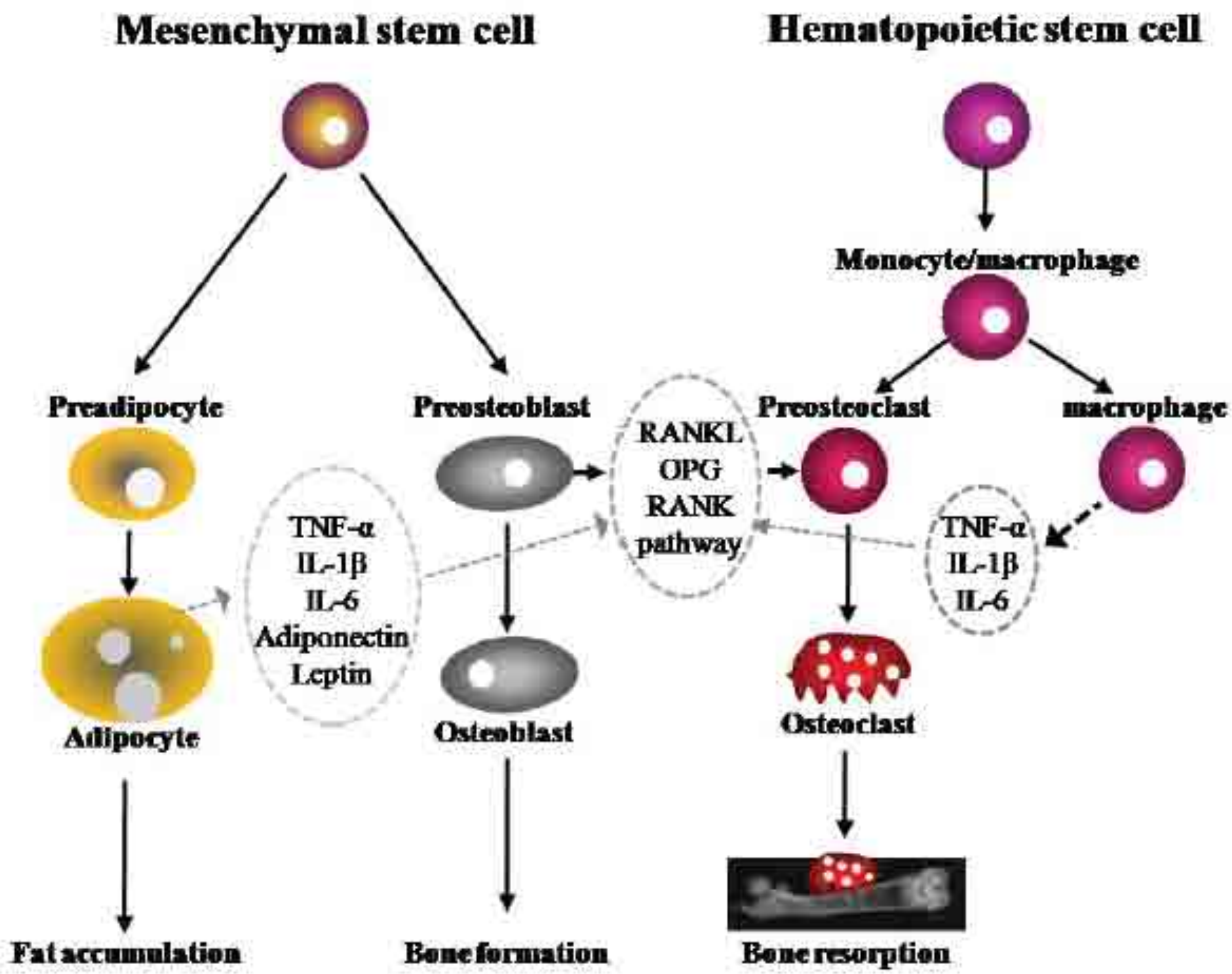
Cohen et al, J Clin Endocrinol Metab, 98: 2562-2572, 2013

Inverse Relationship between Serum Osteocalcin Levels and Visceral Fat Area in Chinese Men

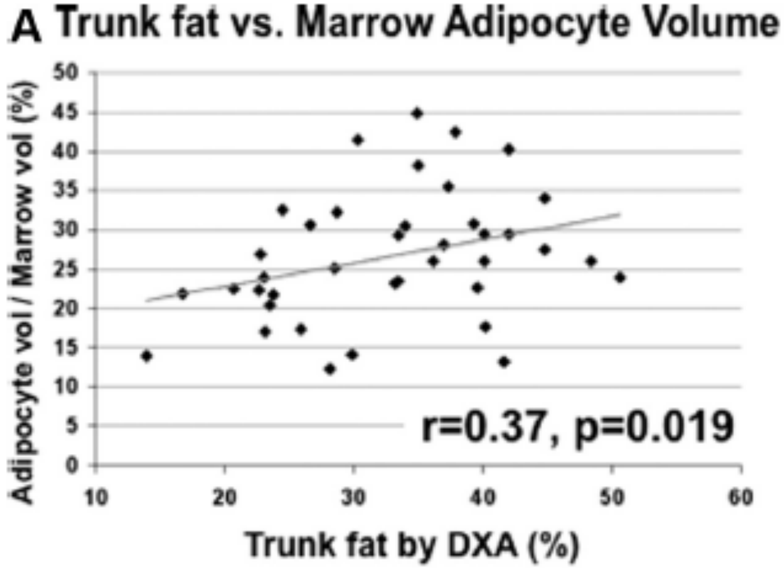


Bao Y et al, J Clin Endocrinol Metab, 98: 345-351, 2013

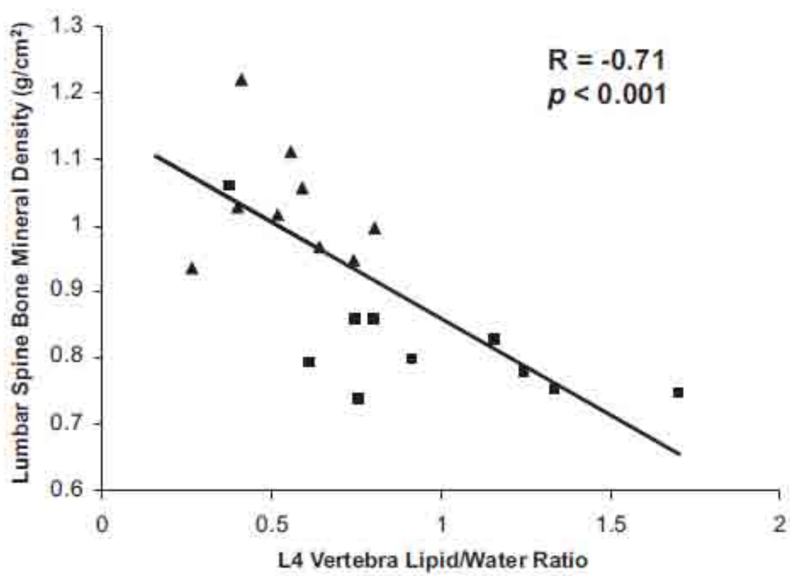
Effects of obesity on bone metabolism



Cao JJ, J Orthopaedic Sugery Res, 6: 30, 2011



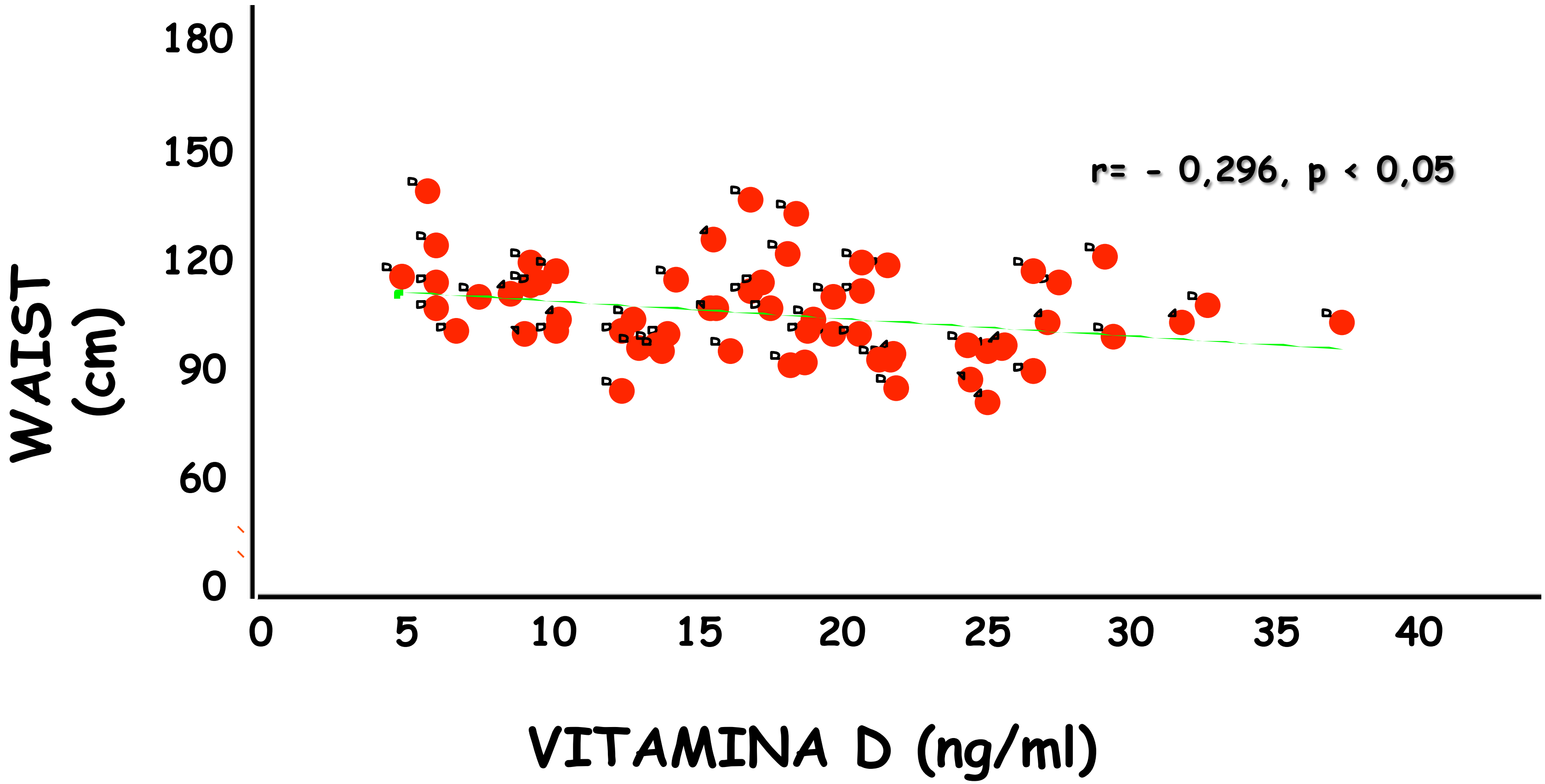
Cohen et al, J Clin Endocrinol Metab, 98: 2562-2572, 2013



Fazeli PK et al, J Clin Endocrinol Metab, 98: 935-945, 2013

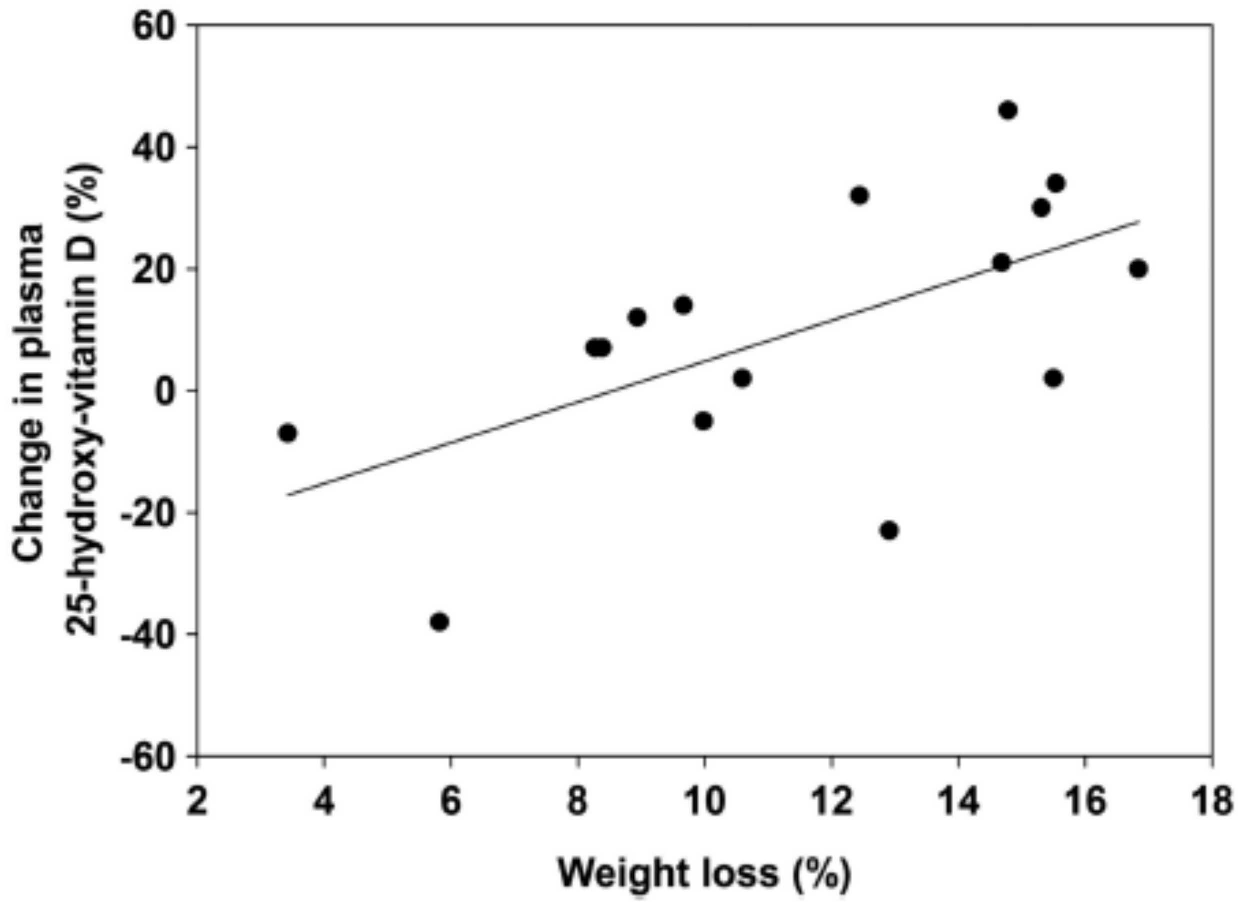
Possible Role of Hyperinsulinemia and Insulin Resistance in Lower Vitamin D Levels in Overweight and Obese Patients

PAZIENTI OBESI NON IPERTESI NON DIABETICI



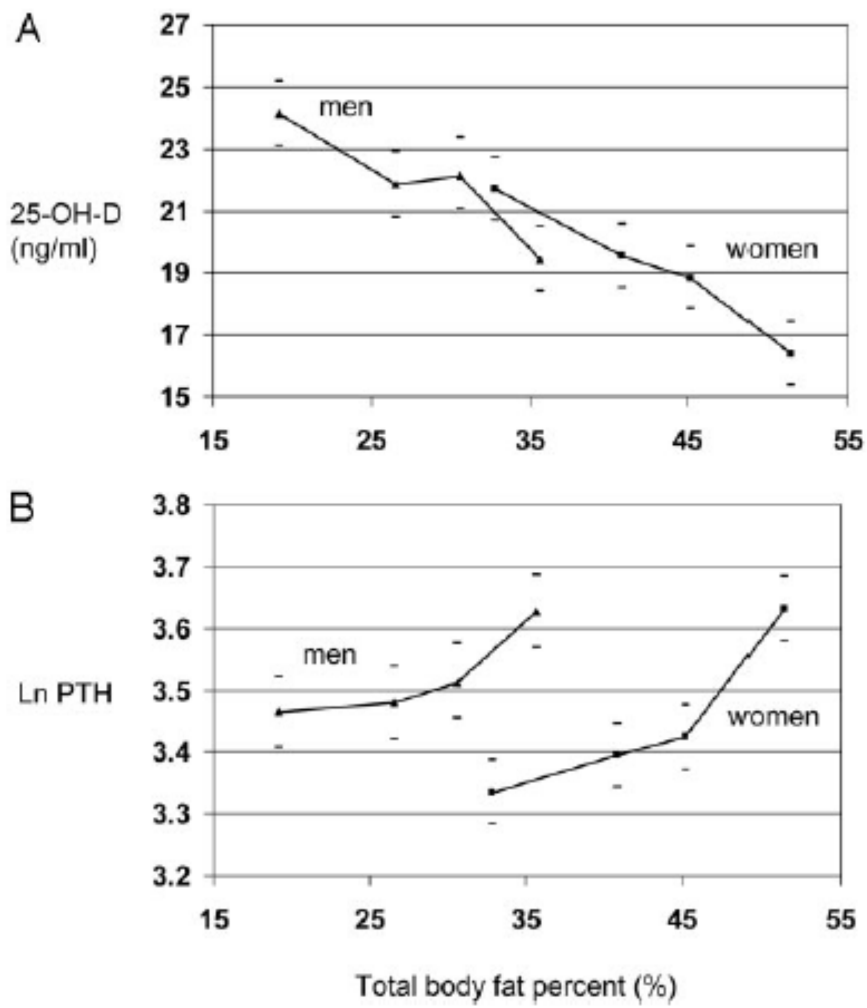
De Pergola et al, BioMed Research, 2013

EFFETTO DELLA PERDITA DI PESO SULLA VITAMINA D



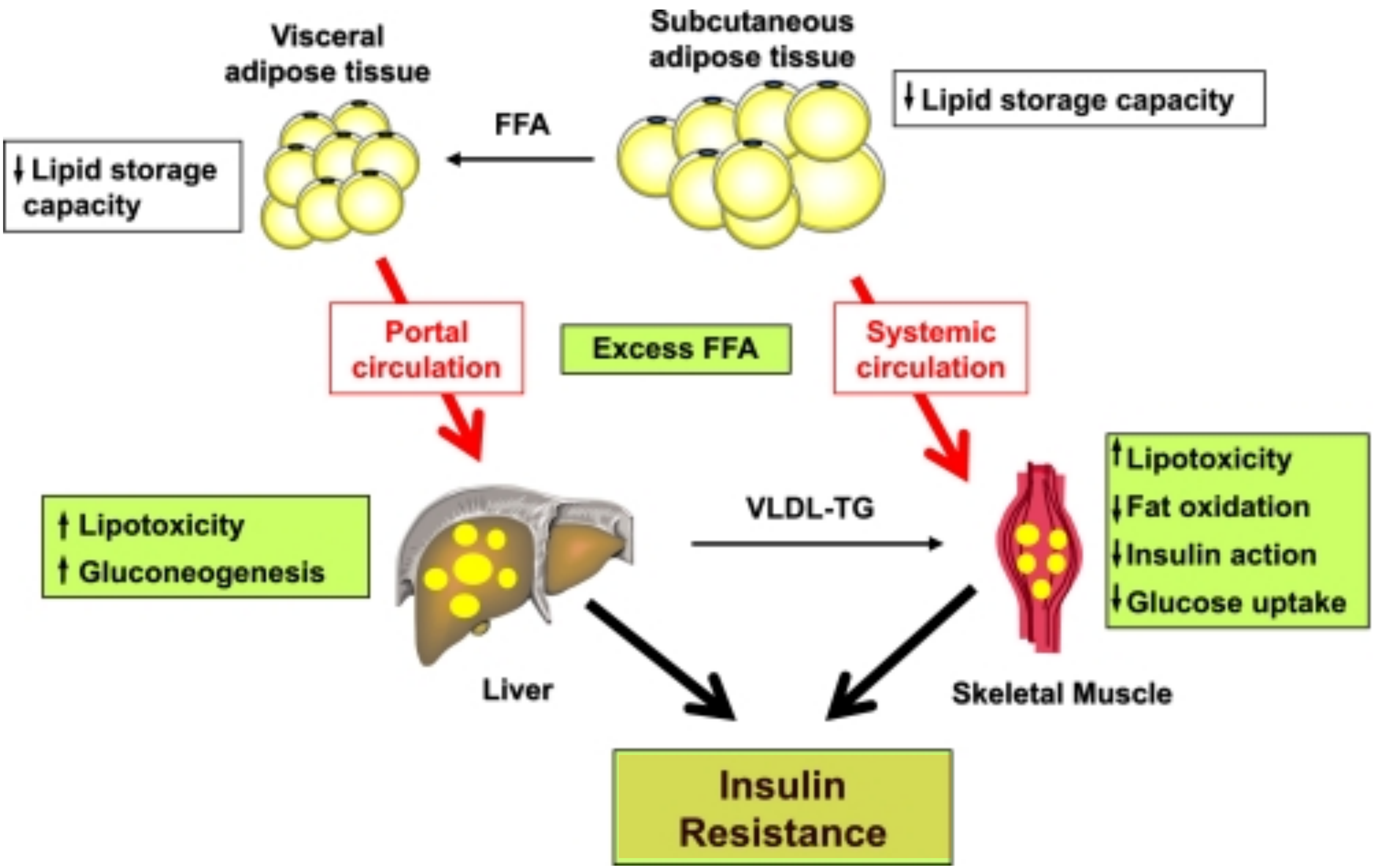
Wamberg L et al, Int J Obesity, 37: 651-657, 2013

Adiposity in Relation to Vitamin D Status and Parathyroid Hormone Levels: A Population-Based Study in Older Men and Women



Snijder MB et al, J Clin Endocrinol Metab, 90: 4119-4123, 2005

OBESITA' VISCERALE E INSULINO-RESISTENZA



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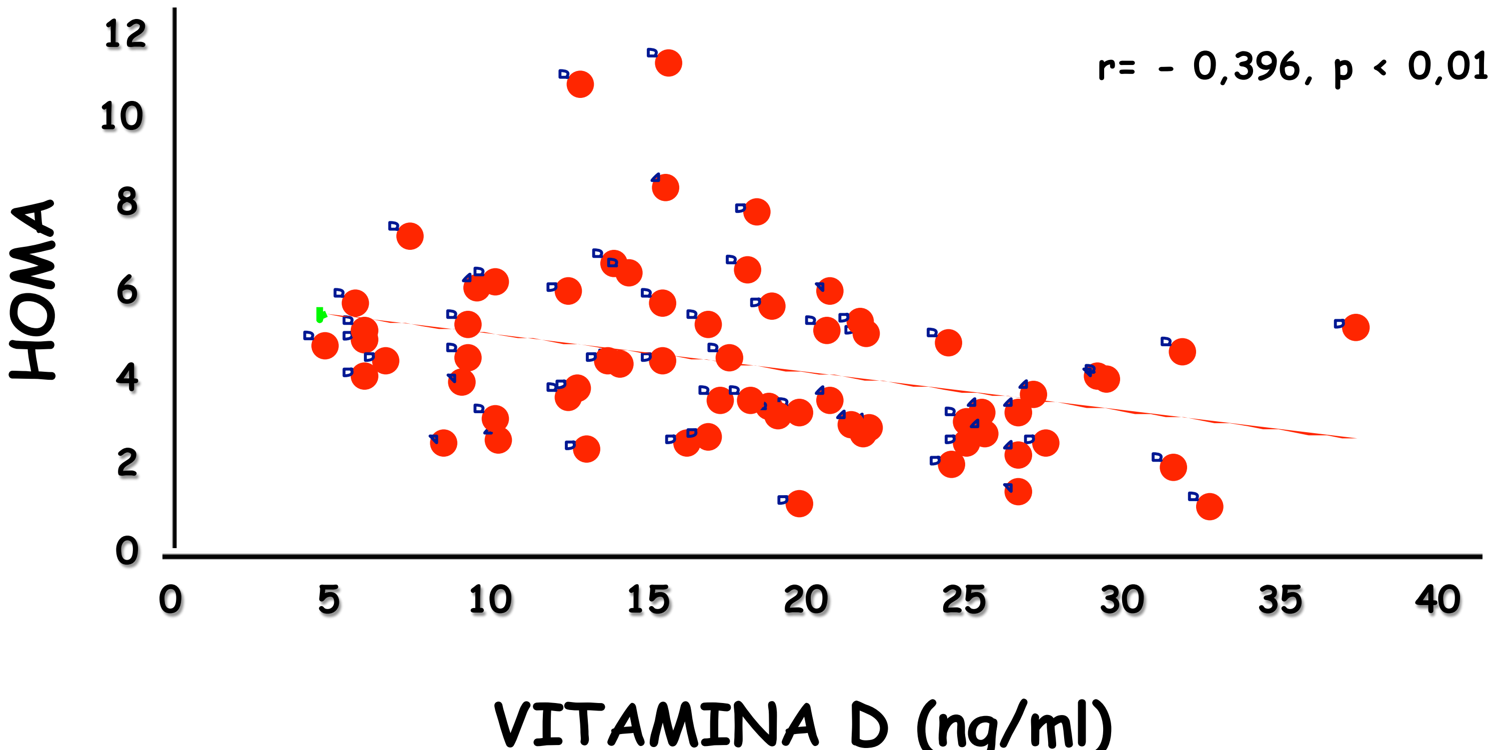


De Pergola et al, BioMed Research, 2013

Serum 25(OH)D and Type 2 Diabetes Association in a General Population

A prospective study

Low 25(OH)D status was significantly associated with unfavorable longitudinal changes in continuous markers of glucose homeostasis, indicating that low vitamin D status could be related to deterioration of glucose homeostasis

Husemoen LLN et al, Diabetes Care, 2012

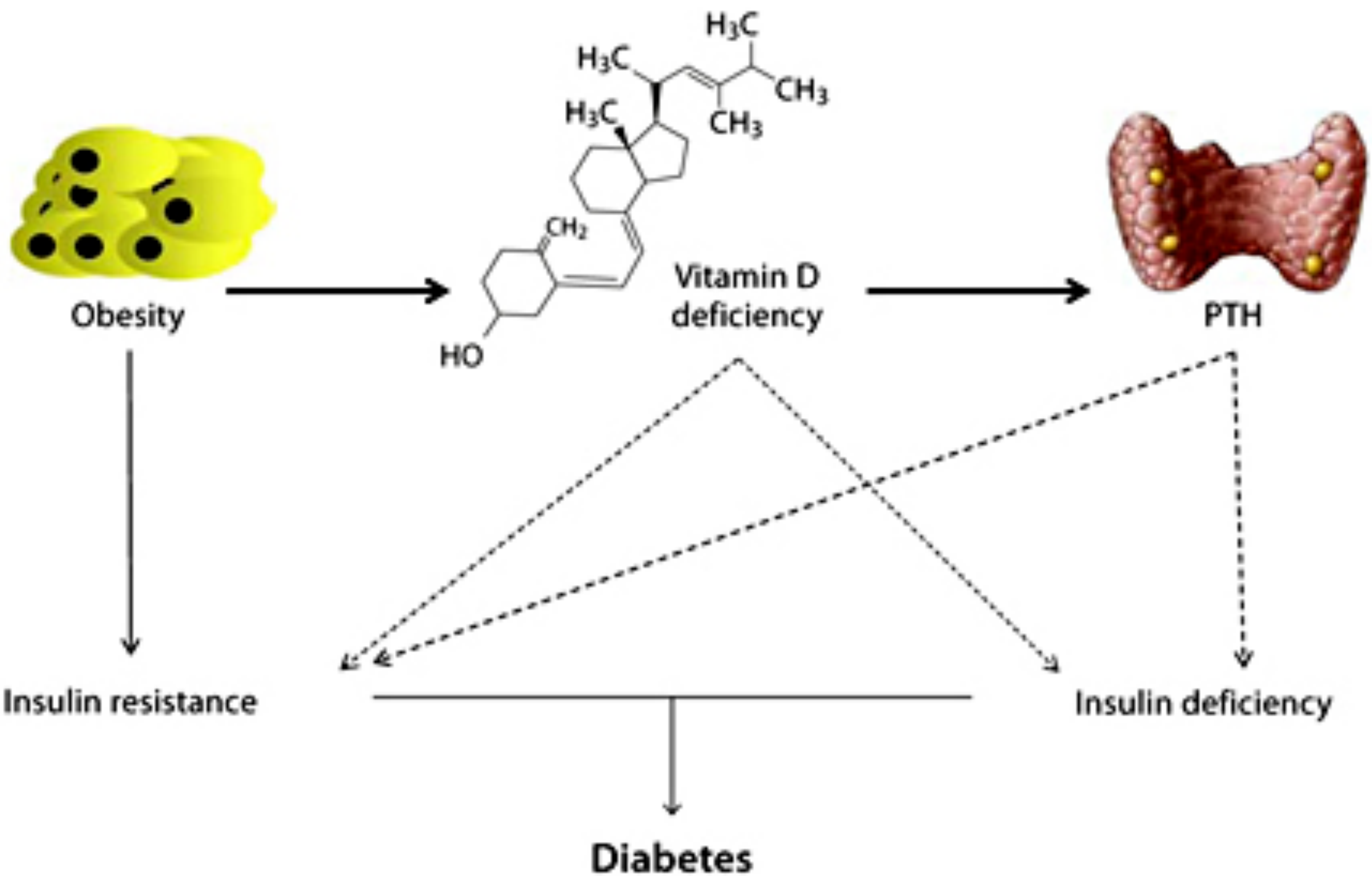
Plasma 25-Hydroxyvitamin D and Progression to Diabetes in Patients at Risk for Diabetes

An ancillary analysis in the Diabetes Prevention Program

Higher plasma 25-hydroxyvitamin D, assessed repeatedly, was associated with lower risk of incident diabetes in high-risk patients, after adjusting for lifestyle interventions (dietary changes, increased physical activity, and weight loss) known to decrease diabetes risk.

Pittas AG et al, Diabetes Care, 35: 565-573, 2012

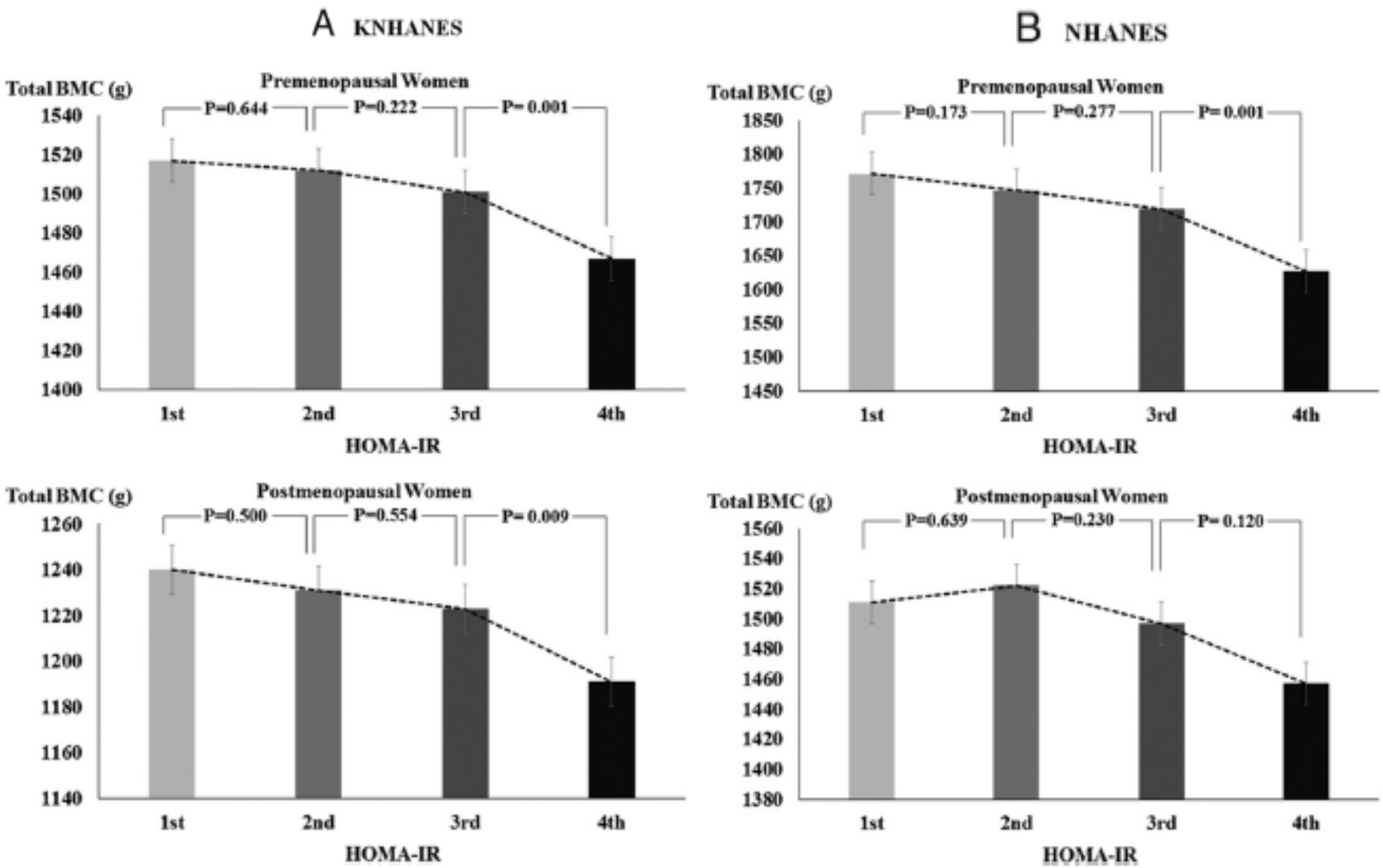
Vitamin D Deficiency: A New Risk Factor for Type 2 Diabetes?



Mezza et al, Annals Nutr Metab, 61: 337-348, 2012

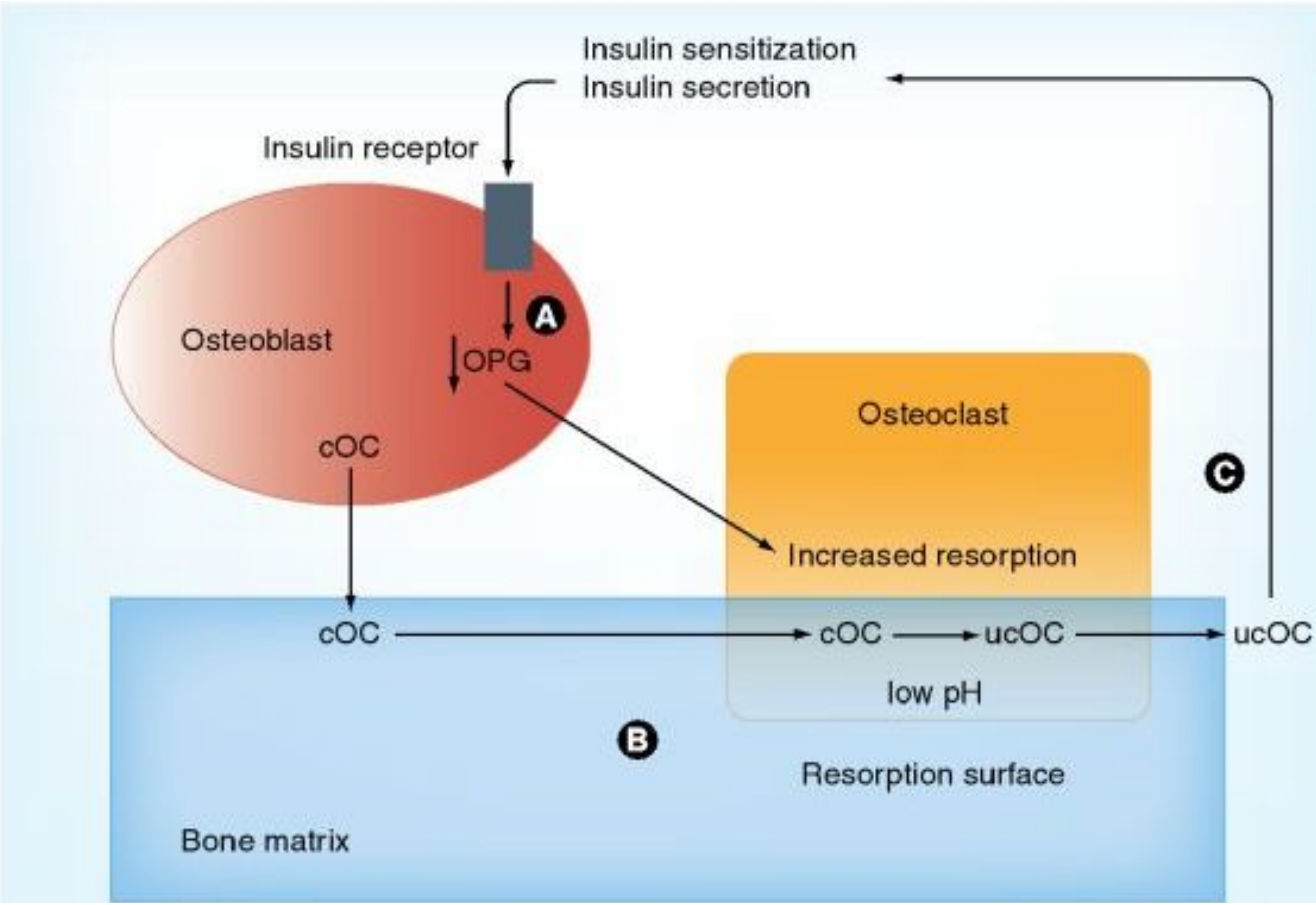
Insulin Is Inversely Associated With Bone Mass, Especially in the Insulin-Resistant Population: The Korea and US National Health and Nutrition Examination Surveys

Indipendentemente da età, massa grassa ed etnia

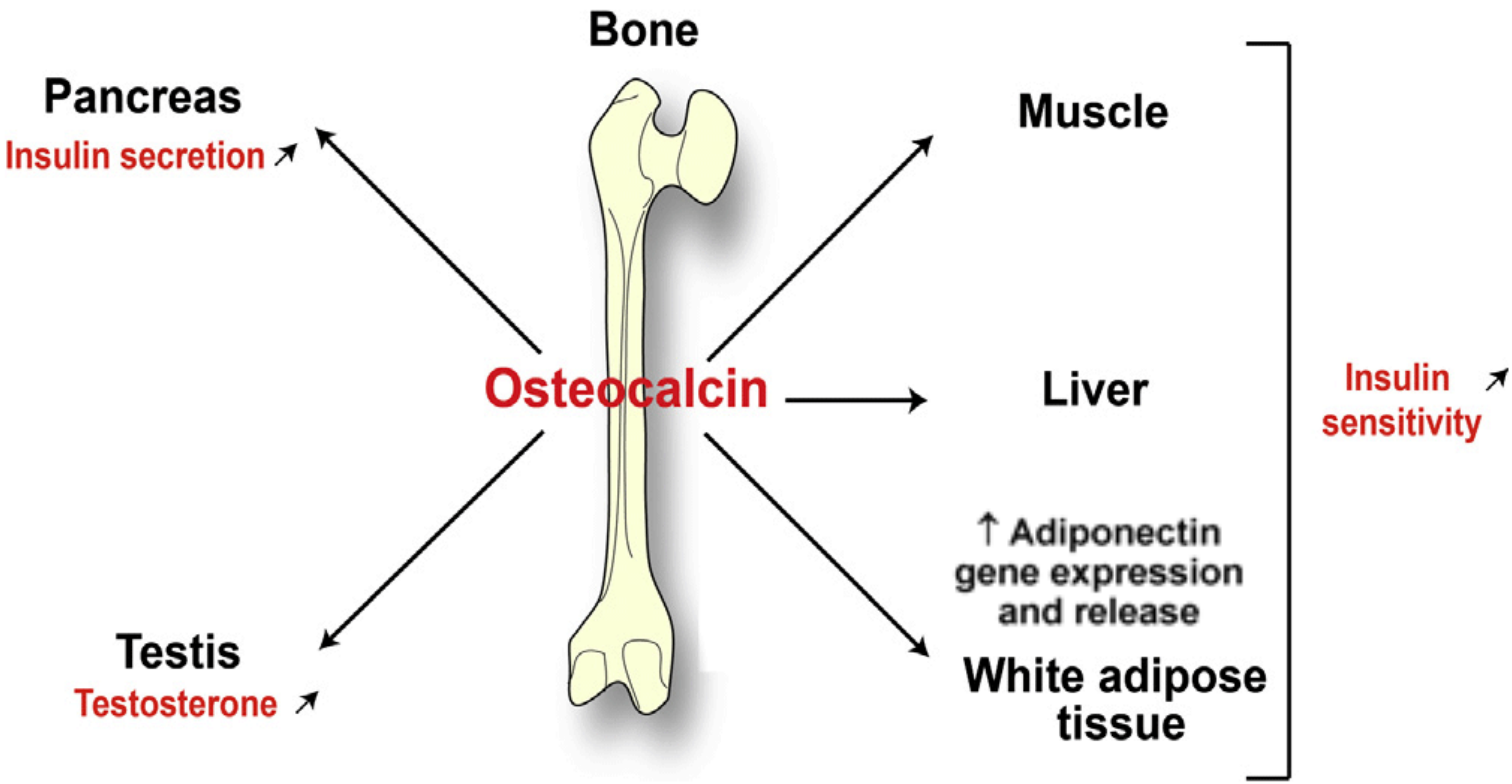


Choi YJ et al, J Clin Endocrinol Metab, 99: 1433-1441, 2014

EFFETTO DELL'INSULINA SULL'OSSO



Serum Osteocalcin Is Associated With Measures of Insulin Resistance, Adipokine Levels, and the Presence of Metabolic Syndrome



Saleem et al, ATVB, 30: 1474-8, 2010

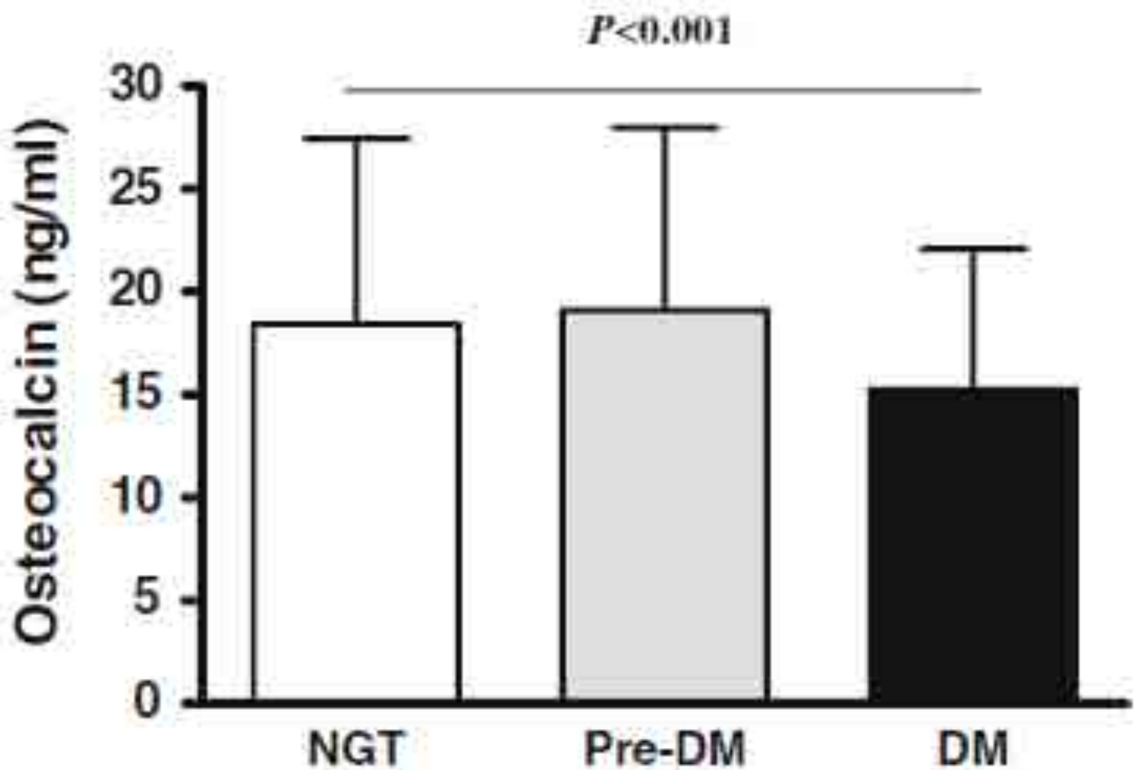
The role of osteocalcin in the endocrine cross-talk between bone remodelling and energy metabolism

In humans, serum osteocalcin levels are inversely correlated with multiple variables of type 2 diabetes such as glucose intolerance and insulin resistance.

Subcutaneous infusion of recombinant osteocalcin improves glucose tolerance and insulin resistance in mouse models of hyperphagia and diet-induced obesity.

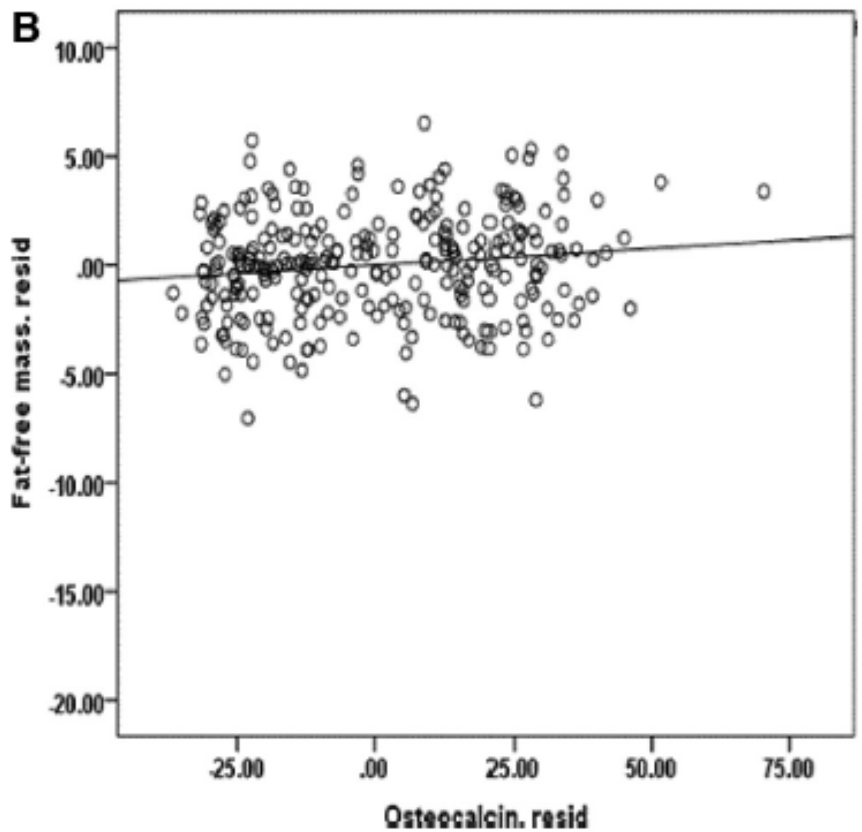
Ducy P, Diabetologia, 54: 1291-1297, 2011

Circulating osteocalcin level is associated with improved glucose tolerance, insulin secretion and sensitivity independent of the plasma adiponectin level



Hwang YC et al, Osteoprosis International, 2011

An Independent Positive Relationship Between the Serum Total Osteocalcin Level and Fat-Free Mass in Healthy Premenopausal Women

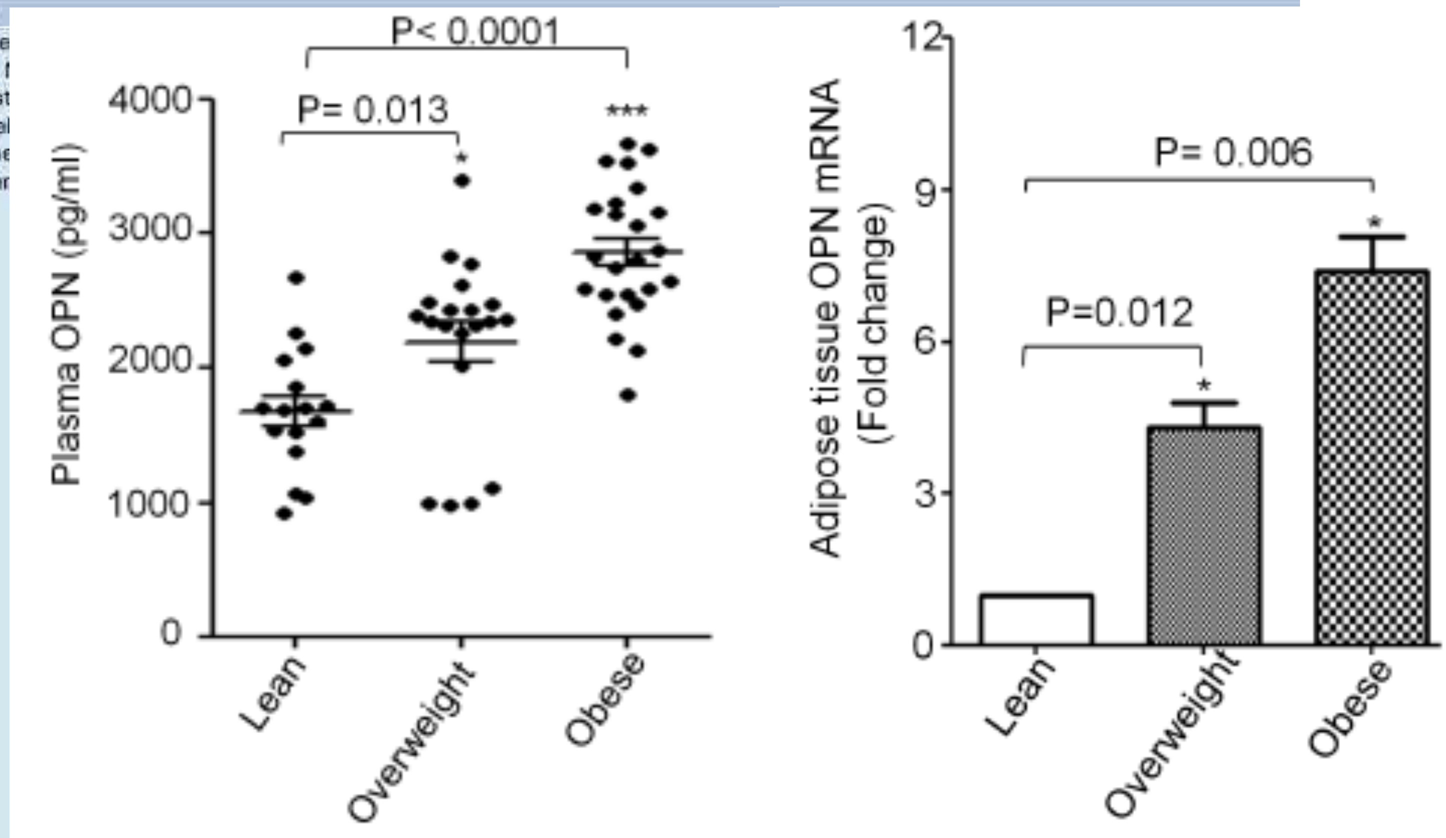


Liu J, J Clin Endocrinol Metab, 98: 2146-2152, 2013

ADIPONECTIN

Secreting cells	Modulators of secretion	Target cell	Cellular mechanism	Biological effect
Adiponectin				
Adipocyte	**Stimulators** Weight loss; uc-osteocalcin **Inhibitors** TNF-α; IL-6; resistin; insulin; glucocorticoids	Hepatocytes, adipocytes, muscle	↑ AMPK activation → ↑ mitochondrial fatty acid β oxidation ↑ Insulin signaling ↓ SREBP-1c expression → ↓ *de novo* lipogenesis ↓ Apoptosis ↓ Proinflammatory cytokine secretion	↓ Steatosis ↓ Hepatic, muscle and adipose tissue insulin resistance ↓ Hepatic, necroinflammation
		HSCs	↑ Apoptosis ↓ Activity and collagen deposition	↓ Fibrogenesis
		Osteoblasts	↑ Proliferation, differentiation, and activity ↑ RANKL secretion ↓ Osteoprotegerin secretion	↑ Bone deposition
		Osteoclasts	↓ APPL1-mediated Akt1 activity → ↓ RANKL-induced osteoclastogenesis ↑ osteoclast apoptosis ↓ Survival/proliferation of osteoclast precursor cells	↓ Bone resorption

OSTEOPONTIN



Secreting cells	Modulators of secretion	Target cell	Cellular mechanism	Biological effect
Osteopontin				
Activated T he… macrophage, N… cell, osteoclast… endothelial cel… hepatocyte, he… stellate cell, ar… adipocyte				
			↑ IL-6 secretion ↔ NF-κB pathway(unaffected)	resistance
		HCC	↑ PI3K/Akt and HIF-1 pathway activation→↑ NF-κB pathway activation	Prosurvival, antiapoptosis, and proliferation
			↑ MMP-2/-7/-9 and Upa expression→↑ ECM degradation	↑ Tumor invasion and metastasis
			↑ VEGF expression→↑ angiogenesis	
		Bone marrow multipotent stromal cells (BMSCs)	OPN mediates high-fat diet-induced differentiation of BMSCs towards adipocyte and away from osteoblast cell line	↓ Bone deposition
		Osteoclasts	↑ Surface CD44 expression→↑ motility ↑ Attachment of osteoclast to bone matrix via the αvβ3 integrin receptor in the sealing zone of resorptive pit	↑ Bone resorption

TNF-α

Secreting cells	Modulators of secretion	Target cell	Cellular mechanism	Biological effect
TNF-α				
Adipocyte, macrophage, Kupffer cell, and hepatocyte	**Stimulators** Oxidative stress **Inhibitors** Adiponectin	Adipocytes	↓ Secretion of leptin and adiponectin ↓ GLUT-4 expression ↓ LPL activity ↑ Hormone-sensitive lipase → ↑ lipolysis ↑ JNK-1 activation → phosphorylation of IRS-1 → insulin receptor signaling inactivation ↑ IKKβ/NF-κB pathway activation → ↑ apoptosis, proinflammatory cytokine secretion	Insulin resistance Adipose tissue and systemic inflammation
		Hepatocytes	↑ JNK-1 activation → phosphorylation of IRS-1 → ↓ insulin receptor signaling ↑ JNK-1 and NF-κB pathway activation → ↑ apoptosis and proinflammatory cytokine secretion	Insulin resistance Hepatic and systemic inflammation NASH
		Kupffer cells	↑ JNK-1 and NF-κB pathway activation → ↑ apoptosis, proinflammatory cytokine secretion	Insulin resistance Hepatic and systemic inflammation NASH
		Osteoblasts	↑ Ubiquitination of RUNX2 → ↓ RUNX2 expression → ↓ osteoblast differentiation, proliferation, and activation ↓ MAPK pathway activation → ↓ osteoblast differentiation, proliferation, and activation ↓ Expression of alkaline phosphatase, vitamin D receptor, parathyroid hormone receptor ↑ RANKL secretion	↓ Bone formation
		Osteoclasts	↑ TNF-R1-mediated NF-κB stimulation of osteoclast differentiation ↑ RANKL-induced stimulation of osteoclast differentiation ↑ Rapamycin/S6 kinase activation → ↓ apoptosis	↑ Bone resorption

CONCLUSIONI

- La obesità si associa ad una riduzione della deposizione ossea (osteoporosi)

- Tale fenomeno è probabilmente dovuto a 1) maggiore conversione delle cellule mesenchimali staminali del midollo osseo in adipociti piuttosto che in osteoblasti, 2) riduzione dei livelli circolanti della vitamina D ed aumento di quelli del PTH 3) minore sintesi di osteocalcina e maggiore produzione di osteopontina da parte dell'osso, 4) minore sintesi di adiponectina ed una maggiore produzione di TNFa da parte degli adipociti

- La riduzione della vitamina D e della osteocalcina e l'aumento del PTH e della osteopontina possono contribuire alla insulino-resistenza, alla iperinsulinemia ed al rischio di diabete nei pazienti con obesità addominale

- Anche la insulino-resistenza per se favorisce la riduzione dei livelli circolanti di vitamina D ed osteocalcina ed è responsabile di una riduzione della densità ossea

The End