FRAGILITÀ OSSEA NELL'ANZIANO:
è colpevole anche il diabete?

AGOSTINO CONSOLI

DMSI - Università d'Annunzio CHIETI

ITALY

58° Congresso Nazionale SIGG

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Il Prof. Agostino Consoli dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

Bristol Mayer Squibb , Astra Zeneca, Boheringer Ingelhaim , Eli Lilly, Merck Sharp & Dhome , Novartis, Novo-Nordisk, Sanofi-Aventis, Sigma-Tau, Takeda.
(Speaker)

Astra Zeneca, Bristol Mayer Squibb, Boheringer Ingelhaim, Eli Lilly, Janssen Farmaceutici,
Merck Sharp & Dhome, Novo-Nordisk.
(Advisory Board)

Novo-Nordisk
(Consultant)

Eli Lilly, Novo-Nordisk
Research Grant

Skeletal Fracture:
the problem size

- More than 250,000 fracture/year in USA
- 25% risk mortality in the following year
- Increased overall risk of death
- Heightned risk for future fractures
- Loss of independence, financial hardship

Dowson-Hughes et al., Osteoporosis Int 2008
Looker et al., Osteoporosis Int 2010
Leibson et al, J Am Geriatr Soc 2002

Relative risk of any fracture (OR with 95% CI) for T1 and T2 diabetes in the population of Denmark in the year 2000

case-control study by conditional logistic regression (124,655 fractures and 373,962 age- and ex matched control subjects)

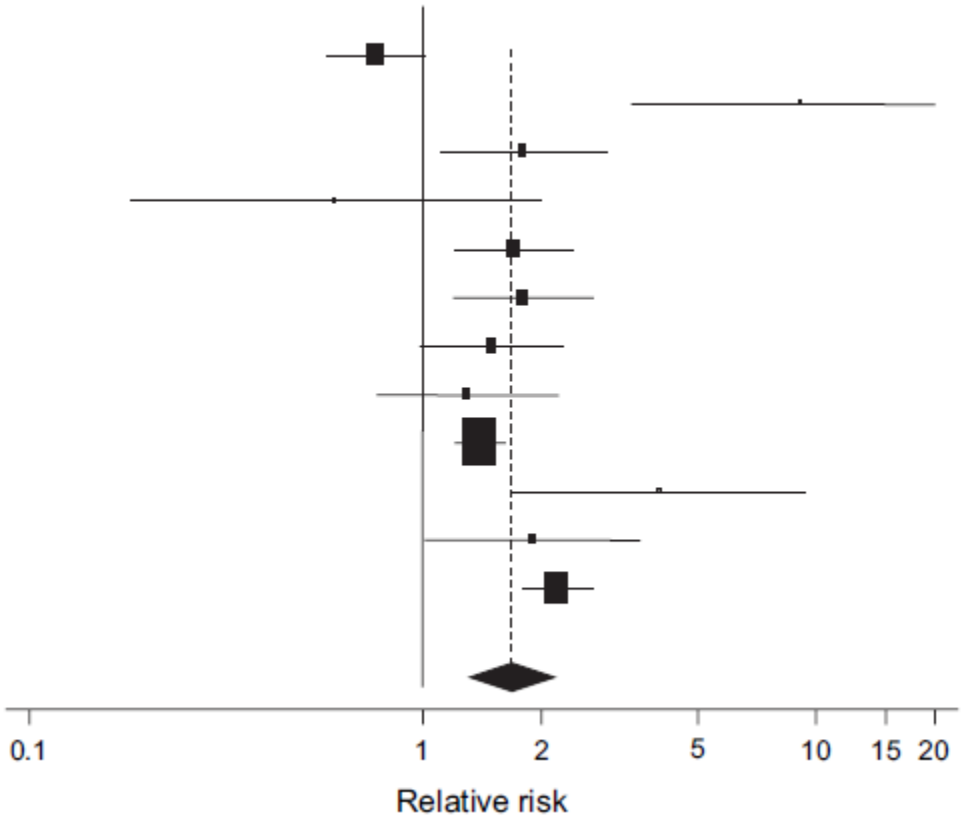
Variable	Crude			Multiply-adjusted[a]		
	OR	Lower 95% CI	Upper 95% CI	OR	Lower 95% CI	Upper 95% CI
Type 1 diabetes vs no diabetes	1.93	1.82	2.05	1.30	1.16	1.46
Type 2 diabetes vs no diabetes	1.55	1.48	1.61	1.19	1.11	1.27

Vestergaard et al, Diabetologia 2007

Association between type 2 diabetes mellitus and risk of hip fracture in case-control and cohort studies

Study	RR (95% CI)
Heath et al., 1980 (15)	0.8 (0.6, 1.02)
Meyer et al., 1993 (25)	9.2 (3.4, 24.9)
Forsen et al., 1999 (14)	1.8 (1.1, 2.9)
Ivers et al., 2001 (8)	0.6 (0.2, 2.2)
Nicodemus and Folsom, 2001 (9)	1.7 (1.2, 2.4)
Schwartz et al., 2001 (12)	1.8 (1.2, 2.7)
Ottenbacher et al., 2002 (23)	1.5 (1.0, 2.3)
de Liefde et al., 2005 (29)	1.3 (0.8, 2.3)
Vestergaard et al., 2005 (20)	1.4 (1.2, 1.6)
Holmberg et al., 2006 (30)	4.0 (1.7, 9.4)
Ahmed et al., 2006 (28)	1.9 (1.02, 3.5)
Janghorbani et al., 2006 (21)	2.2 (1.8, 2.7)
All studies	1.7 (1.3, 2.2)

Test for heterogeneity:
$Q = 58.1; p < 0.001$



Janghorbani et al. Am J Epidemiol 2007

BMD in Diabetes

- The majority of studies in **T1DM** showed a ***moderately decreased*** BMD at the forearm, while BMD measured at the femur or lombar spine was either decreased or not different from controls
- Measurements of bone mineral density at the vertebrae or femoral neck using dual photoabsorptiometry or dual-X-ray-absorptiometry did in most studies show either ***no significant difference*** between subjects with **T2DM** and controls or ***increased values*** in the former.

Leidig-Bruckner and Ziegler, Exp Clin Endocrinol Diabetes 2001

Why do T2DM subjects fracture more ?

BONE QUALITY RELATED CAUSES

- More rapid bone loss
- Decreased cortical density
- Difference in bone geometry
- Microdamage with low bone turn-over
- AGE accumulation

PATIENT RELATED CAUSES

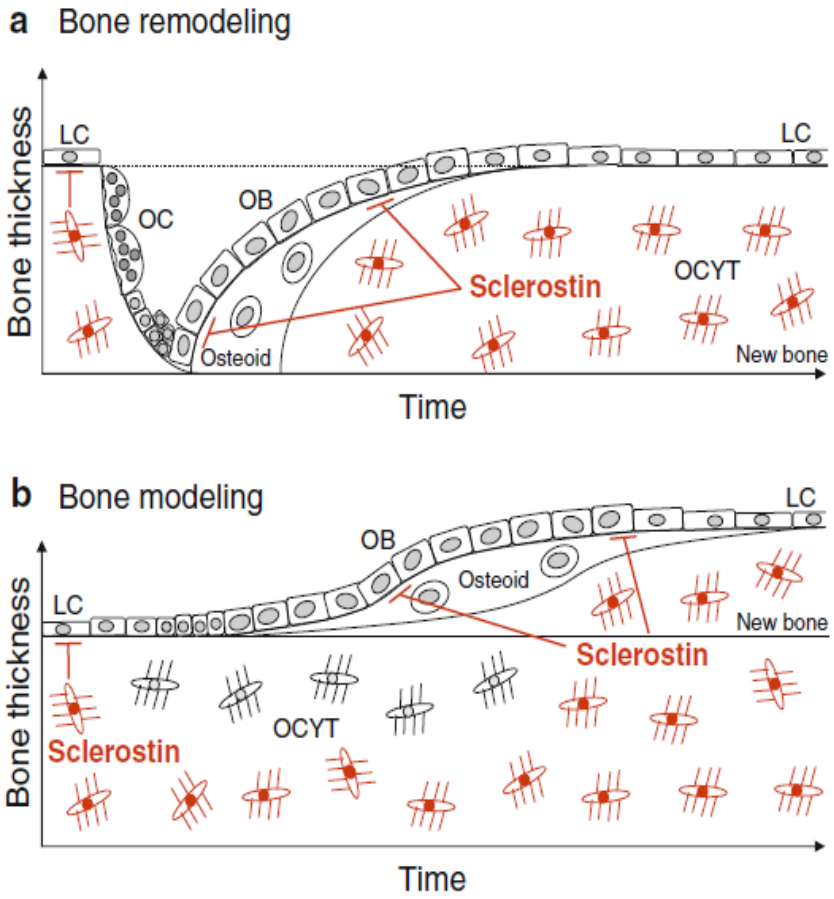
Vision-Related

- Diabetic retinopathy
- Advanced cataracts (visual field deficits)
- Laser therapy for retinopathy (peripheral and night vision decreases)
- Hypoglycemia

Gait/Balance-Related

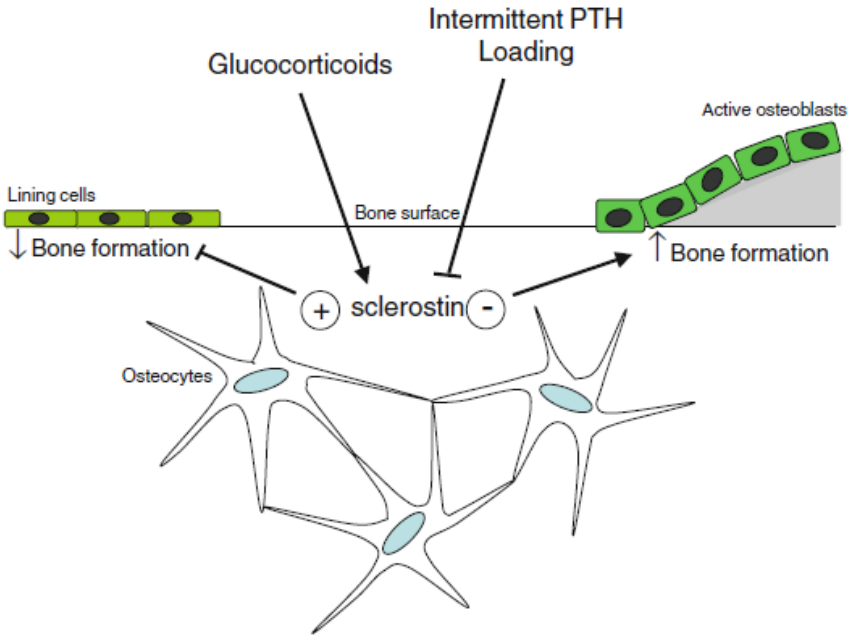
- Peripheral neuropathy
- Foot ulcers
- Polyuria and nocturia, urgent and frequent trips to the restroom, especially at night
- Decreased reflexes

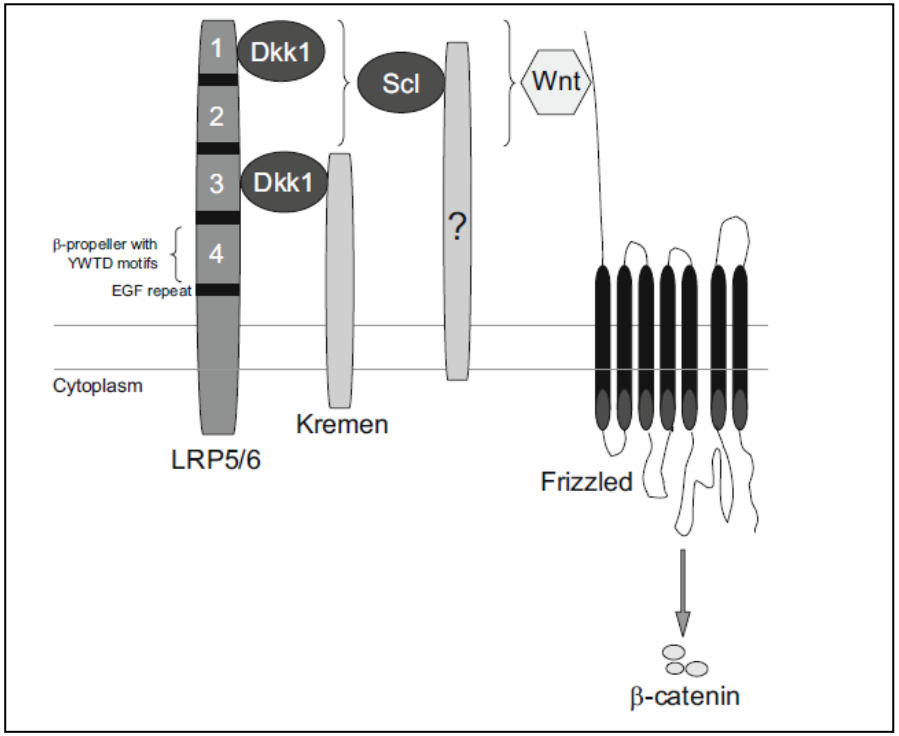
Sclerostin mechanism of action



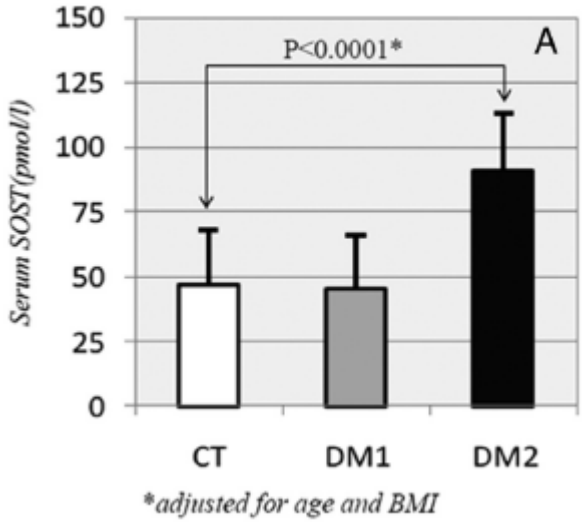
Moester et al., Calcif Tissue Int 2010

Sclerostin and regulation of bone formation

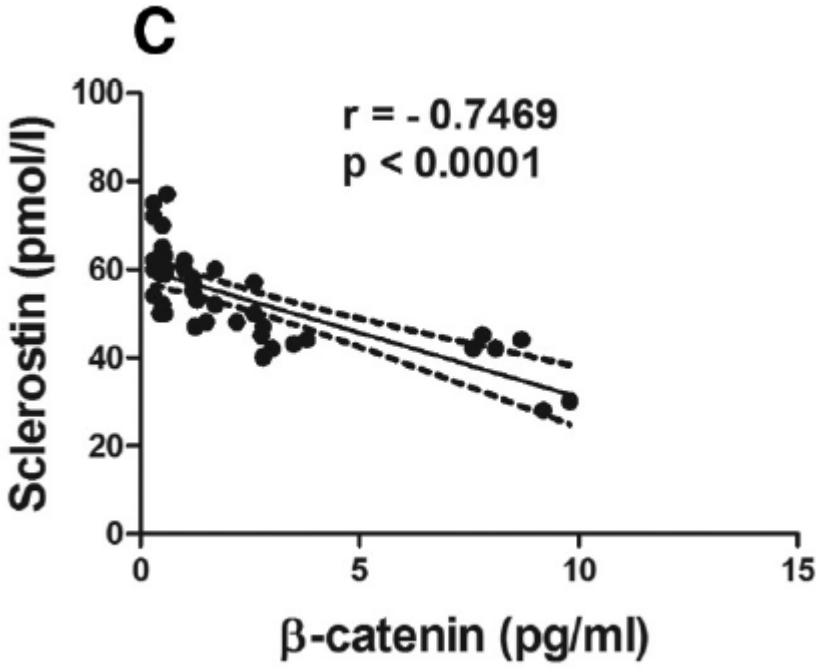




Sclerostin levels in diabetic subjects: relationships with β-catenin levels

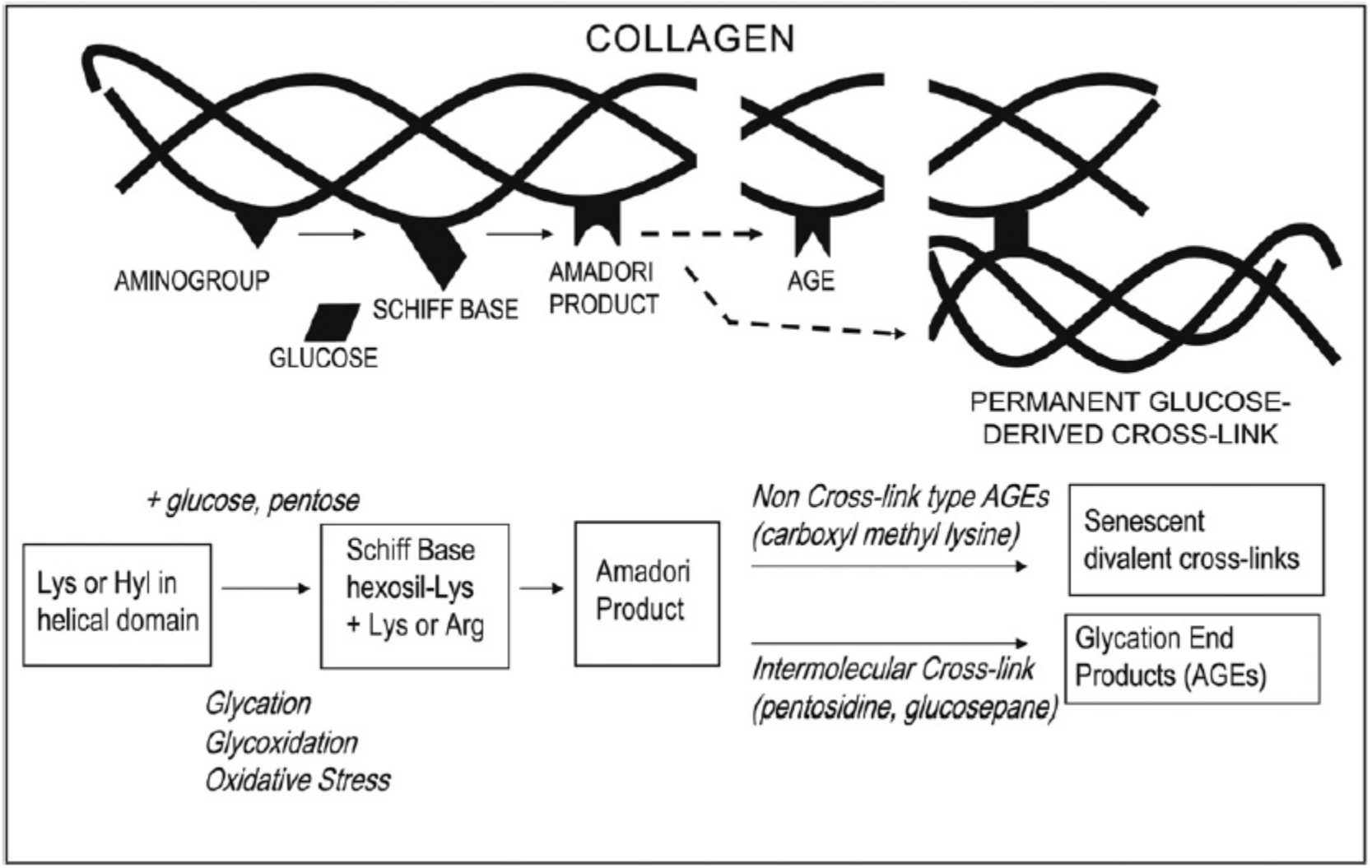


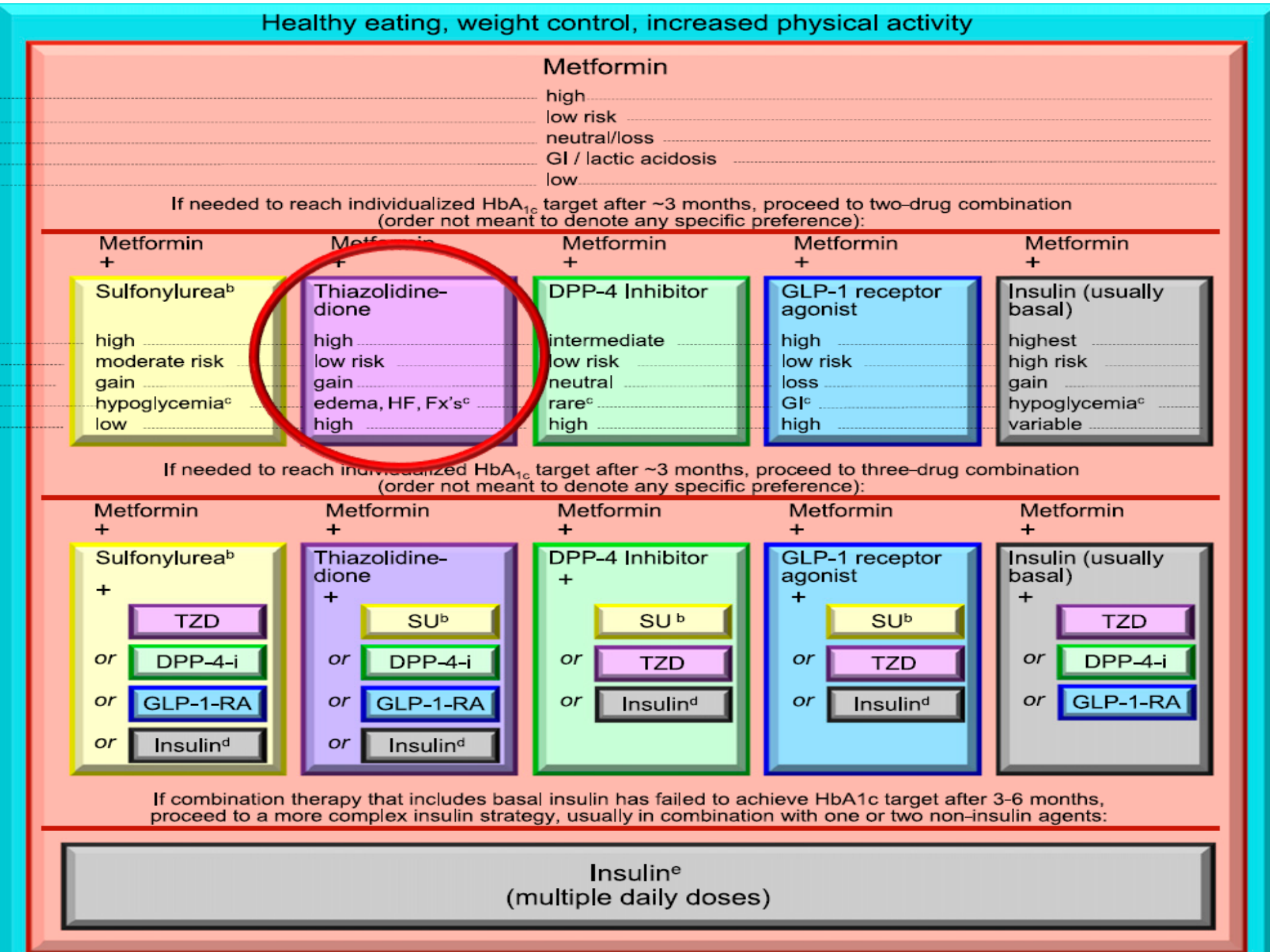
Gennari et al., J Clin Endocrinol Metab 2012



Gaudio et al., J Clin Endocrinol Metab 2012

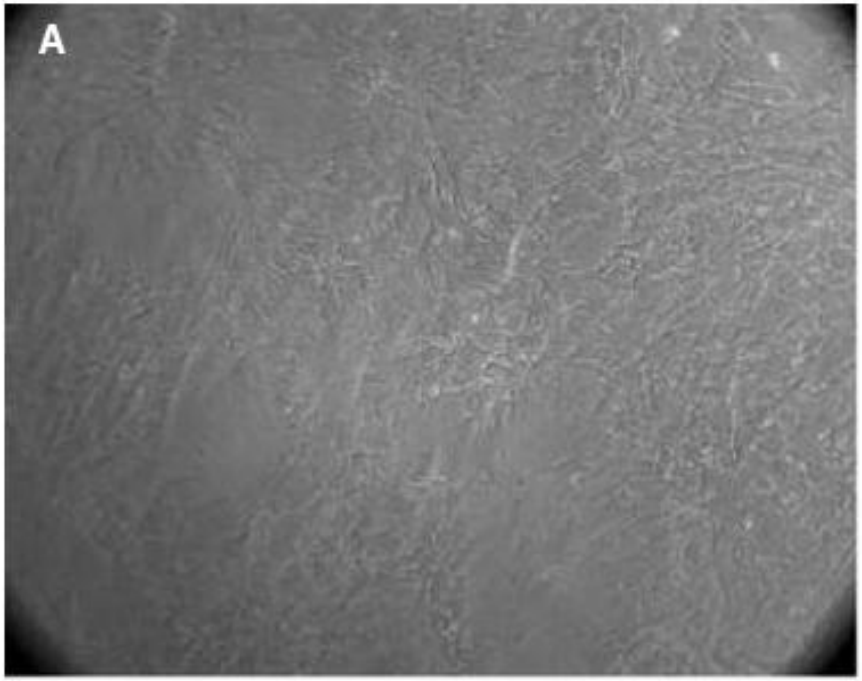
AGEs formation affects bone quality

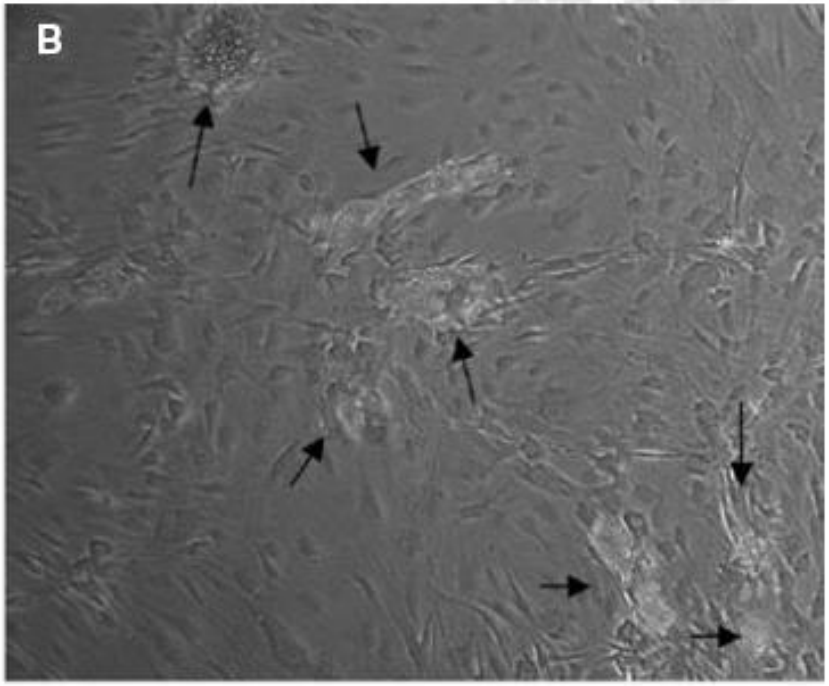



Healthy eating, weight control, increased physical activity
Metformin
high
low risk
neutral/loss
GI / lactic acidosis
low
If needed to reach individualized HbA1c target after ~3 months, proceed to two-drug combination (order not meant to denote any specific preference):
Metformin + Sulfonylurea[b]
high
moderate risk
gain
hypoglycemia[c]
low
Metformin + Thiazolidine-dione
high
low risk
gain
edema, HF, Fx's[c]
high
Metformin + DPP-4 Inhibitor
intermediate
low risk
neutral
rare[c]
high
Metformin + GLP-1 receptor agonist
high
low risk
loss
GI[c]
high
Metformin + Insulin (usually basal)
highest
high risk
gain
hypoglycemia[c]
variable
If needed to reach individualized HbA1c target after ~3 months, proceed to three-drug combination (order not meant to denote any specific preference):
Metformin + Sulfonylurea[b] + TZD or DPP-4-i or GLP-1-RA or Insulin[d]
Metformin + Thiazolidine-dione + SU[b] or DPP-4-i or GLP-1-RA or Insulin[d]
Metformin + DPP-4 Inhibitor + SU[b] or TZD or Insulin[d]
Metformin + GLP-1 receptor agonist + SU[b] or TZD or Insulin[d]
Metformin + Insulin (usually basal) + TZD or DPP-4-i or GLP-1-RA
If combination therapy that includes basal insulin has failed to achieve HbA1c target after 3-6 months, proceed to a more complex insulin strategy, usually in combination with one or two non-insulin agents:
Insulin[e] (multiple daily doses)

Rosiglitazone stimulates adipogenesis and decreases osteoblastogenesis in human mesenchymal stem cells

S. Benvenuti*[1], I. Cellai*[1], P. Luciani[1], C. Deledda[1], S. Baglioni[1], C. Giuliani[1], R. Saccardi[2], B. Mazzanti[2], S. Dal Pozzo[2], E. Mannucci[3], A. Peri[1], and M. Serio[1]





J. Endocrinol. Invest. 30: RC26-RC30, 2007
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MOLECULAR PHARMACOLOGY, 50:1087–1094 (1996).

Peroxisome Proliferator-Activated Receptor-γ Activation by Thiazolidinediones Induces Adipogenesis in Bone Marrow Stromal Cells

JEFFREY M. GIMBLE, CLAUDIUS E. ROBINSON, XIYING WU, KATHERINE A. KELLY, BRENDA R. RODRIGUEZ, STEVEN A. KLIEWER, JURGEN M. LEHMANN, and DAVID C. MORRIS

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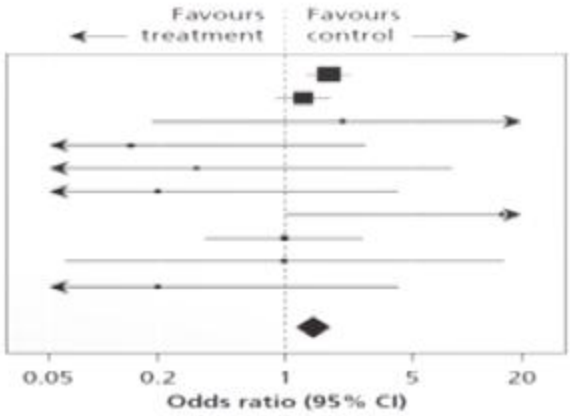
Activation of peroxisome proliferator-activated receptor-γ (PPARγ) induces cell death through MAPK-dependent mechanism in osteoblastic cells

Sung Hun Kim [a], Chong Il Yoo [a,c], Hui Taek Kim [a,c], Ji Yeon Park [b], Chae Hwa Kwon [b], Yong Keun Kim [b,c,d,*]

Risk of fractures in TZDs treated individuals

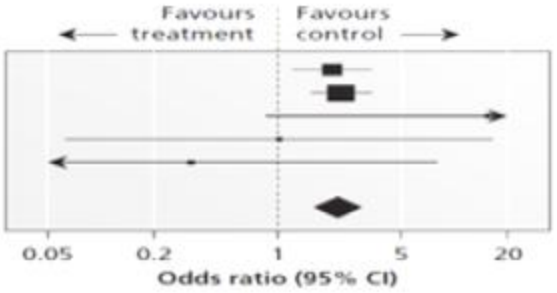
A. Fractures overall

Study	No. of fractures: Thiazolidinedione	No. of fractures: Control	Odds ratio (95% CI)
Kahn et al.[23]	92/1456	108/2895	1.74 (1.31–2.32)
Dormandy et al.[24]	74/2605	60/2633	1.25 (0.89–1.77)
AVM100264 trial[25]	2/294	1/301	2.05 (0.19–22.78)
GSK49653 334 trial[27]	0/277	3/278	0.14 (0.01–2.76)
GSK49653 351 trial[28]	0/30	1/30	0.32 (0.01–8.24)
Jain et al.[29]	0/251	2/251	0.20 (0.01–4.15)
Nissen et al.[30]	8/270	0/273	17.71 (1.02–308.42)
DeFronzo et al.[31]	8/303	8/299	0.99 (0.37–2.66)
Seufert et al. (a)[32]	1/317	1/313	0.99 (0.06–15.85)
Seufert et al. (b)[32]	0/319	2/320	0.20 (0.01–4.17)
Overall (95% CI)	**185/6122**	**186/7593**	**1.45 (1.18–1.79)**



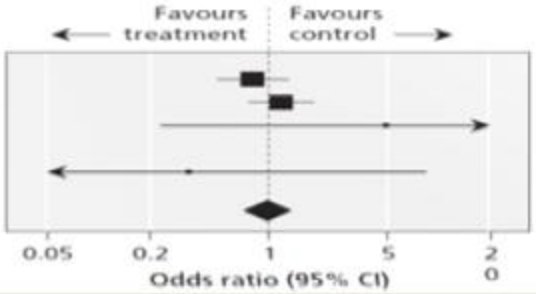
B. Fractures in women

Study	No. of fractures: Thiazolidinedione	No. of fractures: Control	Odds ratio (95% CI)
Dormandy et al.[24]	44/870	23/905	2.04 (1.22–3.41)
Kahn et al.[23]	60/645	51/1195	2.30 (1.56–3.39)
Nissen et al.[30]	6/84	0/93	15.48 (0.86–279.18)
Seufert et al. (a)[32]	1/156	1/159	1.02 (0.06–16.44)
Seufert et al. (b)[32]	0/148	1/145	0.32 (0.01–8.03)
Overall	**111/1903**	**76/2497**	**2.23 (1.65–3.01)**

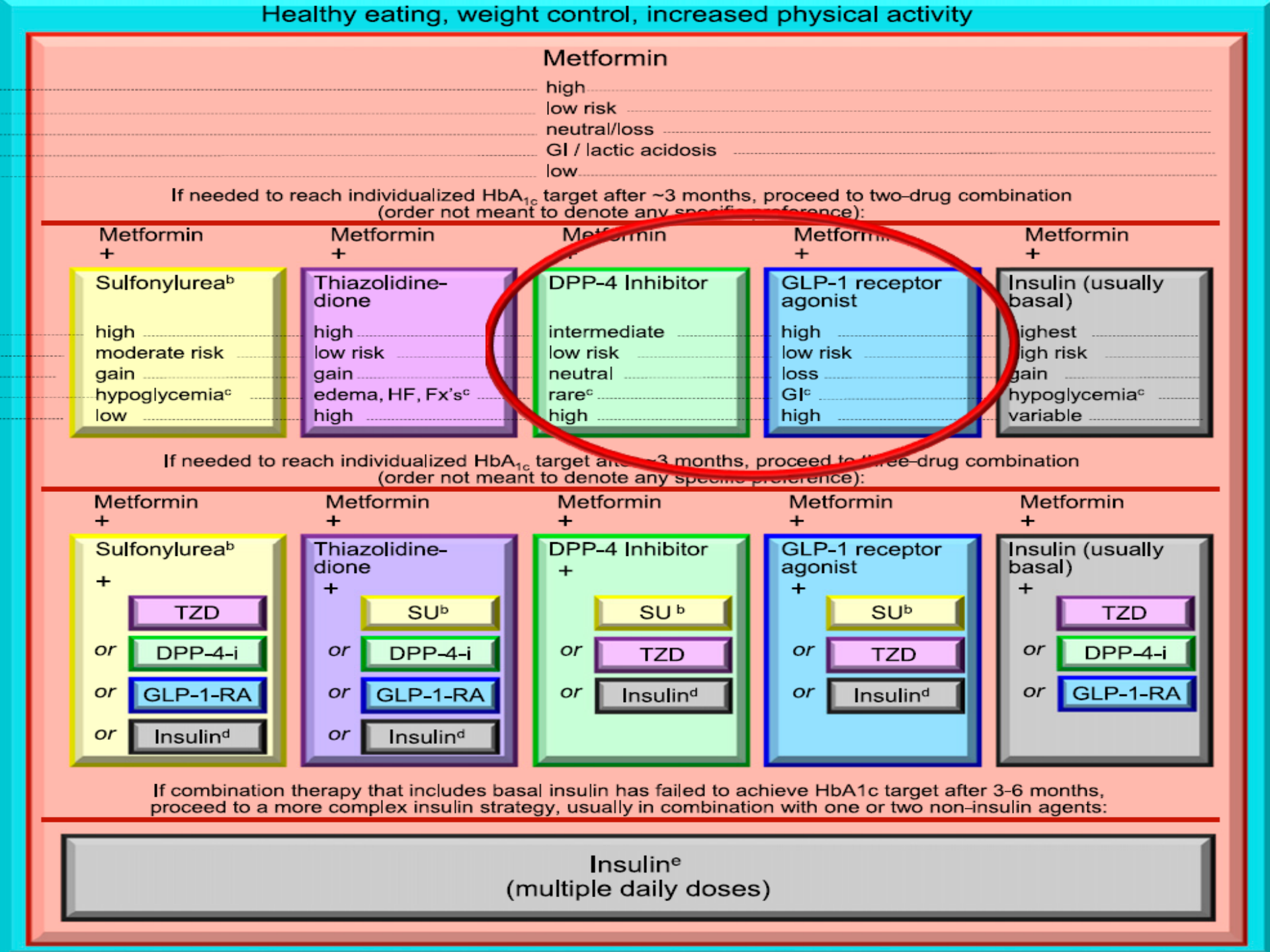


C. Fractures in men

Study	No. of fractures: Thiazolidinedione	No. of fractures: Control	Odds ratio (95% CI)
Dormandy et al.[24]	30/1735	37/1728	0.80 (0.49–1.31)
Kahn et al.[23]	32/811	57/1700	1.18 (0.76–1.84)
Nissen et al.[30]	2/186	0/180	4.89 (0.23–102.60)
Seufert et al. (a)[32]	0/161	0/154	Not estimable
Seufert et al. (b)[32]	0/171	1/175	0.34 (0.01–8.38)
Overall	**64/3064**	**95/3937**	**1.00 (0.73–1.39)**



Loke et al., CMAJ 2009; 180:32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Metformin + DPP-4 Inhibitor
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neutral
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Metformin + GLP-1 receptor agonist
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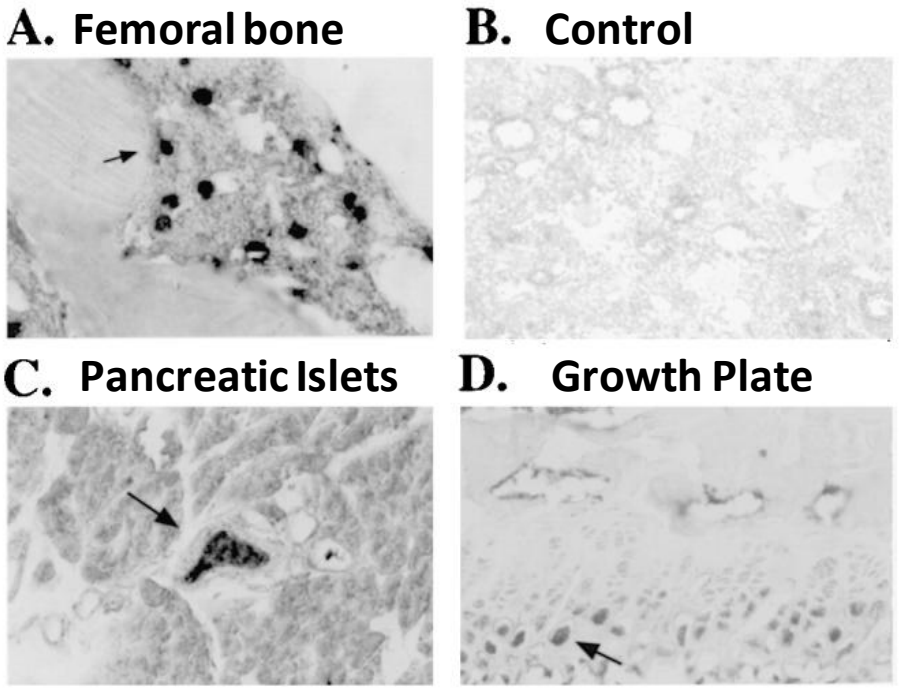
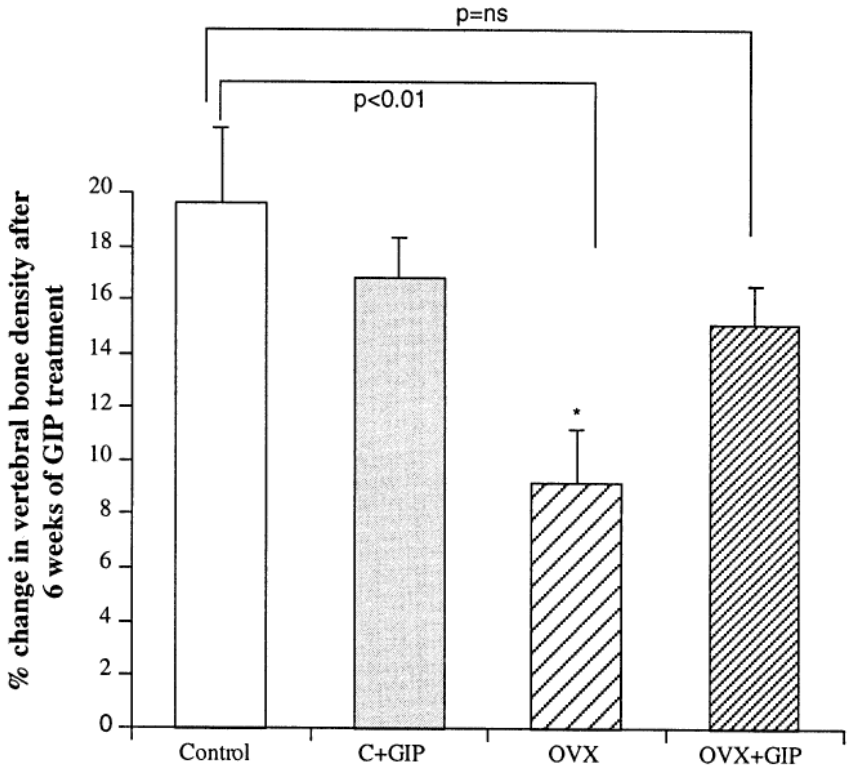
Insulin[e] (multiple daily doses)

Effects of incretin hormones on bone metabolism: GIP



GIP-Rx mRNA (in situ hybridization)

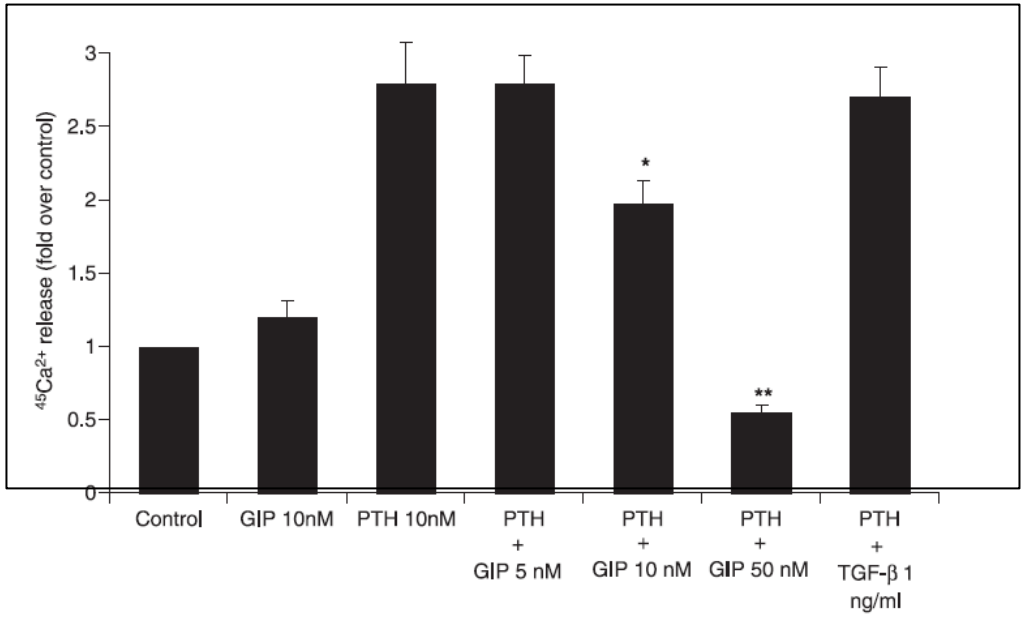


Effect of GIP treatment in OVX rats

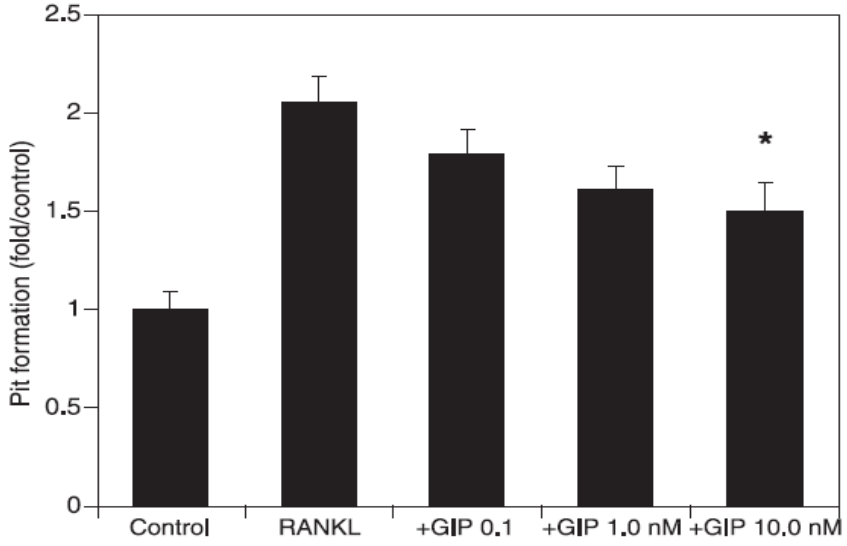
Bollag et al., Mol Cell Endocrinol 2001

Effects of incretin hormones on bone metabolism: GIP

Fetal bone-resorbing assay



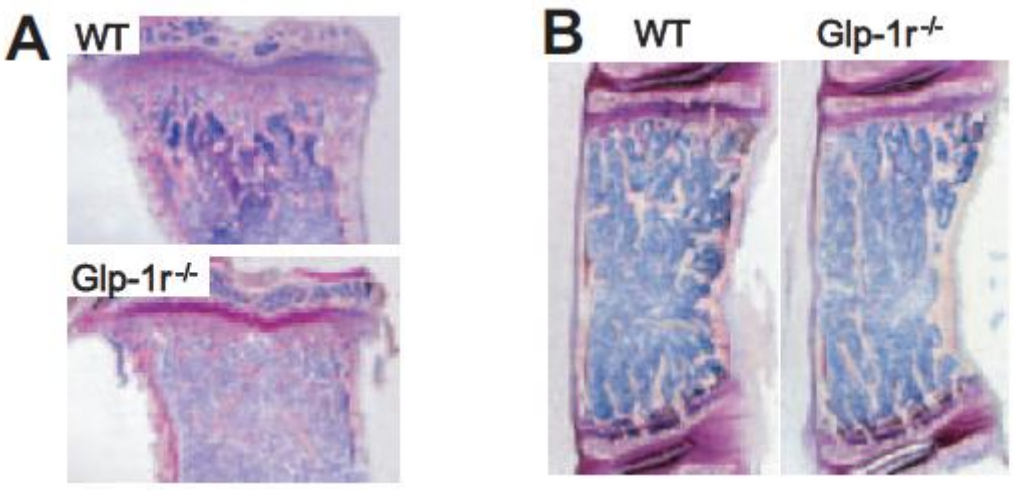
RANKL stimulated murine osteoclast-like cells



Zhong et al., AJP- Endocrinol Metab 2007

Effects of incretin hormones on bone metabolism: GLP-1

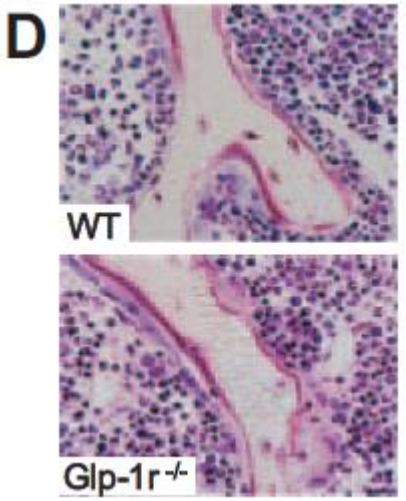
Bone histomorphometry



tibia

lumbar spine

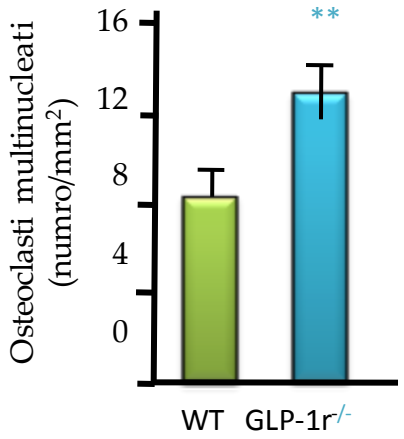
Multinuclear osteoclasts



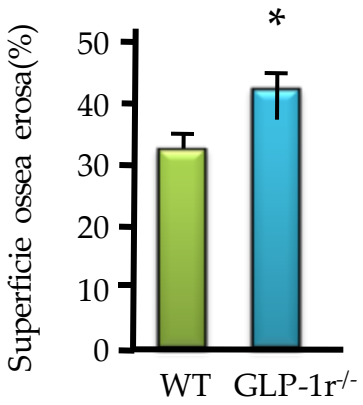
Yamada et al., Endocrinology 2008

Bone alterations in GLP-1-Rx Ko mice

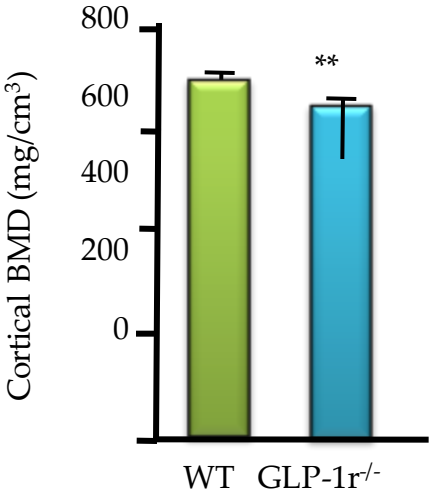
Osteoclasti multinucleati nella tibia



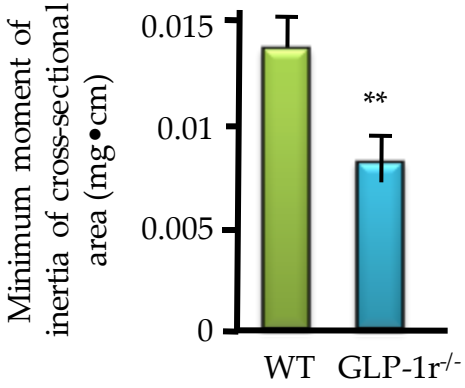
Erosioni superficie ossea

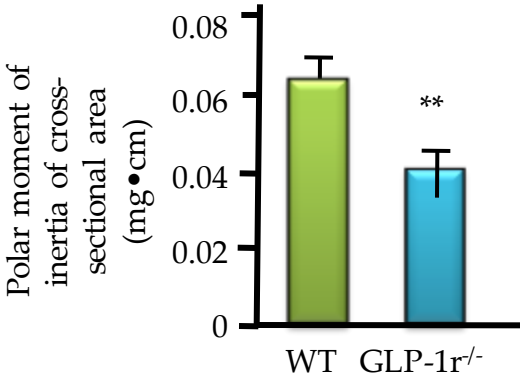


Densità minerale ossea



Indici di rigidità ossea

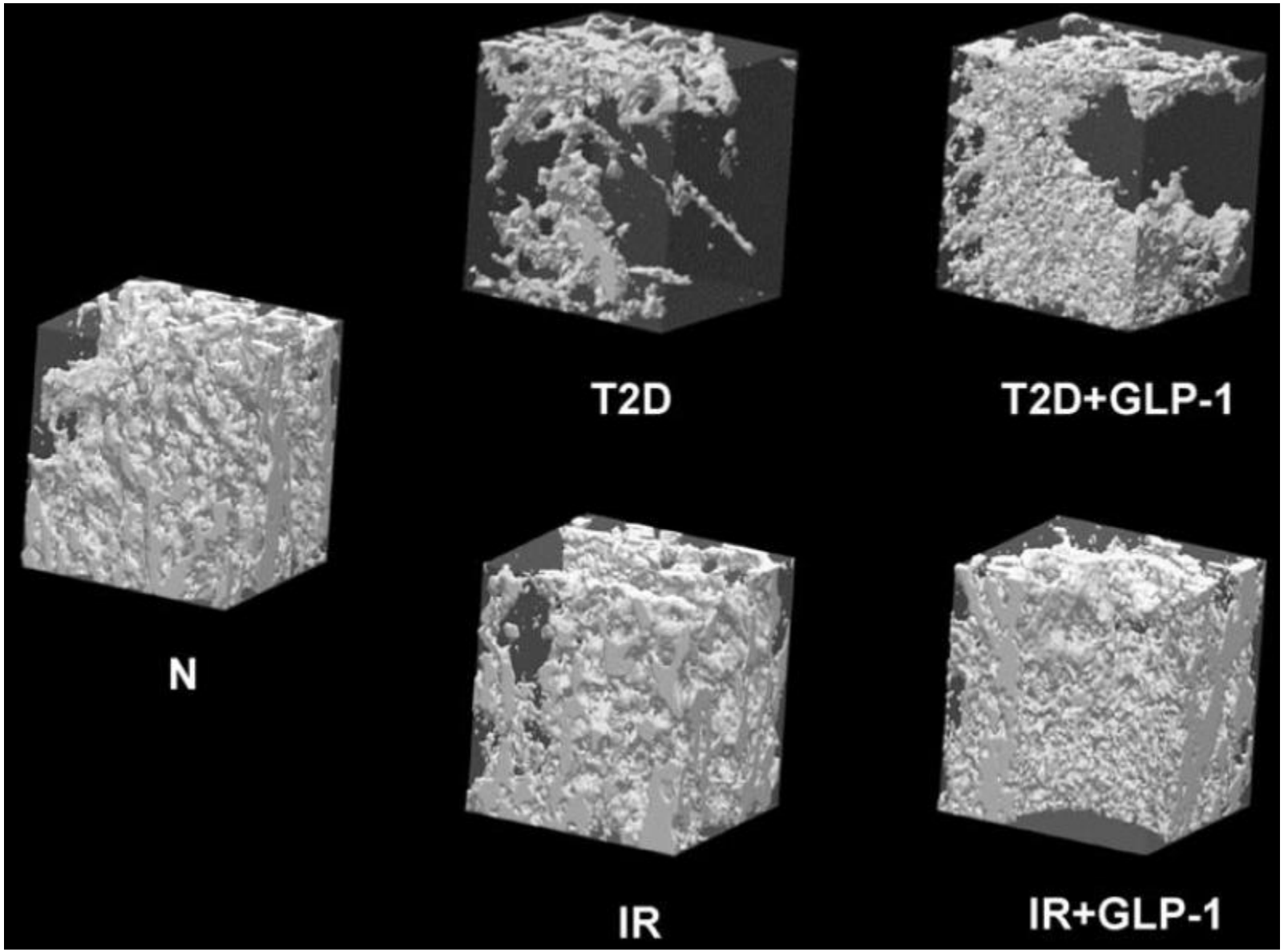




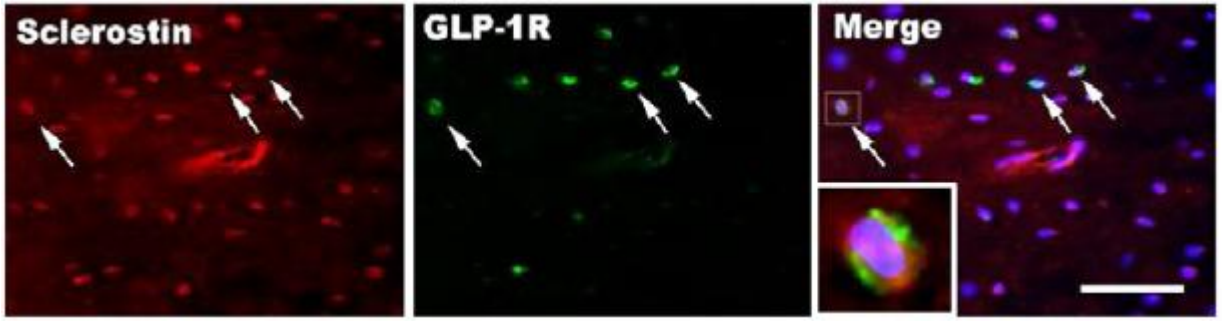
Yamada et al, Endocrinology 2008

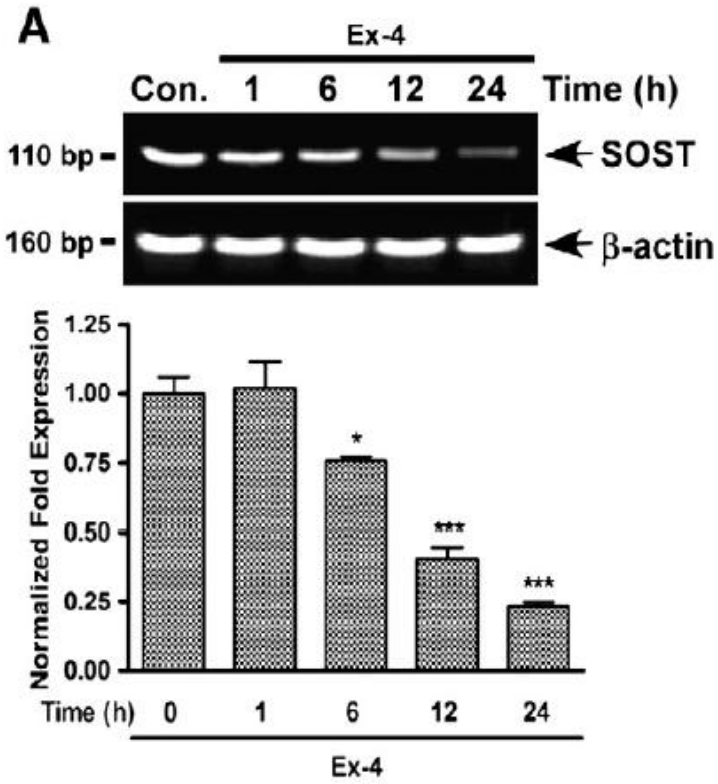
Defective trabecular structure in the bones of T2DM or IR animal model: Effects of GLP-1

Nuche-berenguer 2009



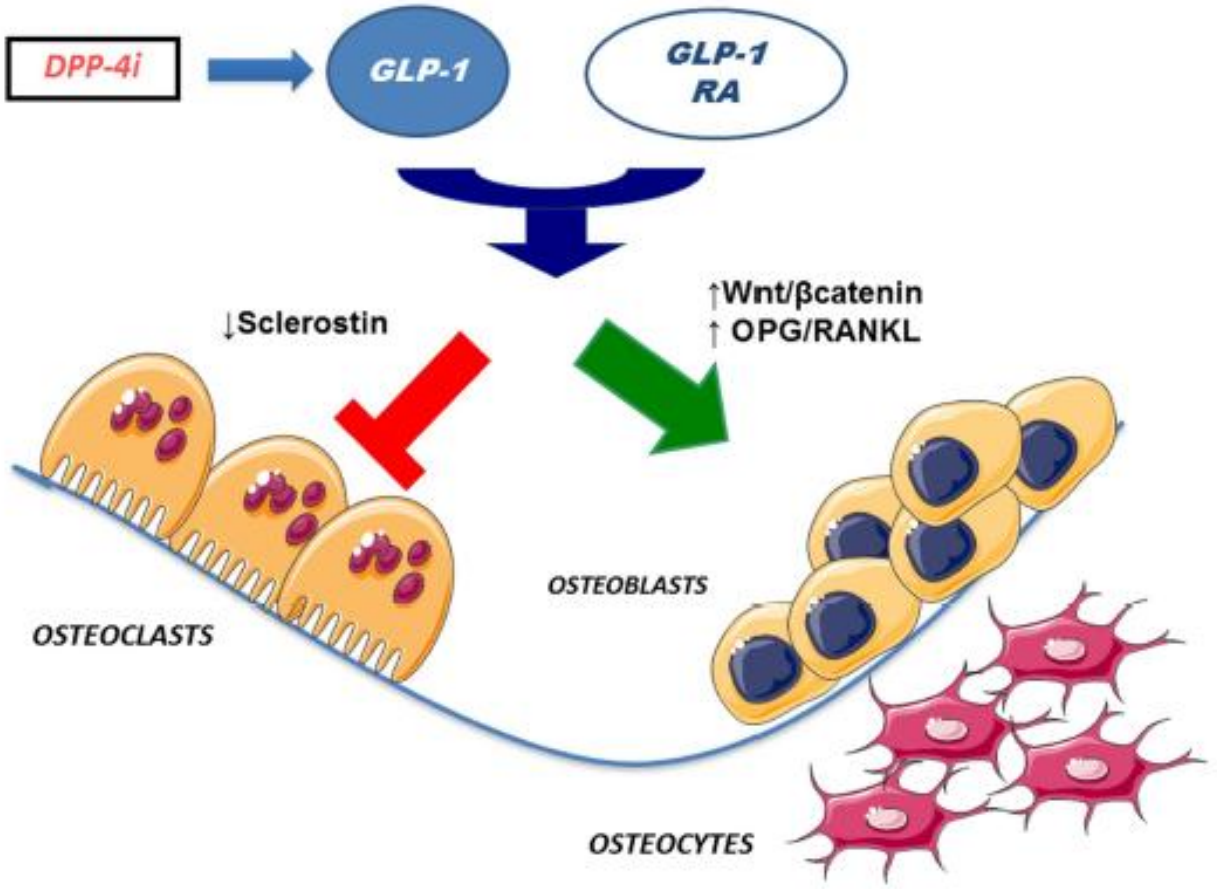
1) Sclerostin and GLP-1 receptor co-localize in the same cell
2) Exendin-4 exposure decreases sclerostin expression in osteocytes





Kim et al., Life Sciences 2013

Putative mechanisms of GLP-1 Rx agonists and DPP-4 inhib. effects on bone



Ceccarelli et al., Frontiers in Endocrinology 2013

Macro and Microscopic bones quality changes in HFD fed mice treated by placebo, pioglitazone or sitagliptin

Kyle KA et al, *Endocrinology* 2011

DPP4 Inhibition Attenuates Bone Loss in Diabetic Rats

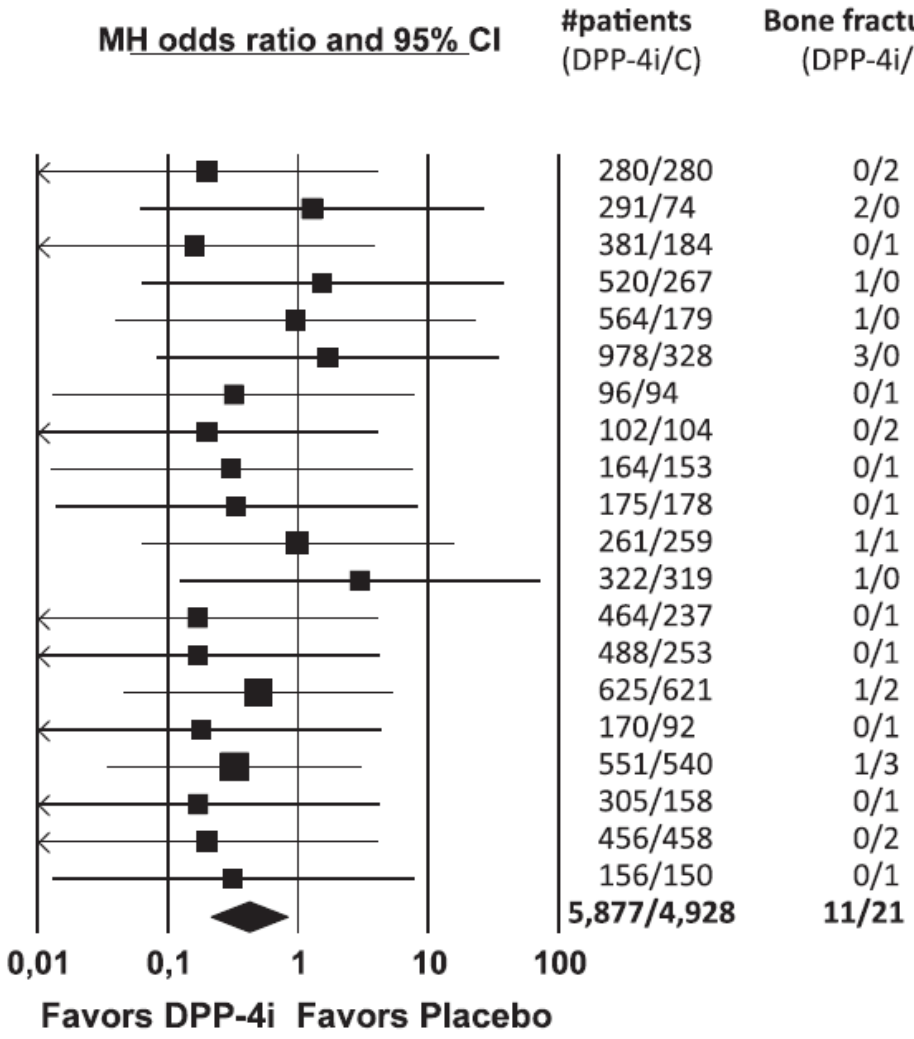
- Trabecular bone volume & bone/tissue volume ratio in the tibia was significantly lower in STZ-treated rats compared to untreated rats, but was normalized through ***Sitagliptin*** treatment (significant at week 9 & 12).
- Trabecular thickness was decreased and trabecular spacing was increased in diabetic rats. ***Sitagliptin*** treatment also in resulted in partial but significant recovery of these trabecular parameters in diabetic rats.
- Although nonsignificant, ***Sitagliptin*** treatment resulted in increased presence of osteoid in diabetics.
- In a three-point bending test performed on femora of rats sacrificed after 12 weeks, applied ultimate load in ***Sitagliptin*** - treated diabetic rats was significantly higher than in non-treated diabetic rats.

Glorie et al., *ASBMR 2013 (Abs)*

Dipeptidyl Peptidase-4 Inhibitors and Bone Fractures

Diabetes Care 34:2474–2476, 2011

A meta-analysis of randomized clinical trials



Monami et al.

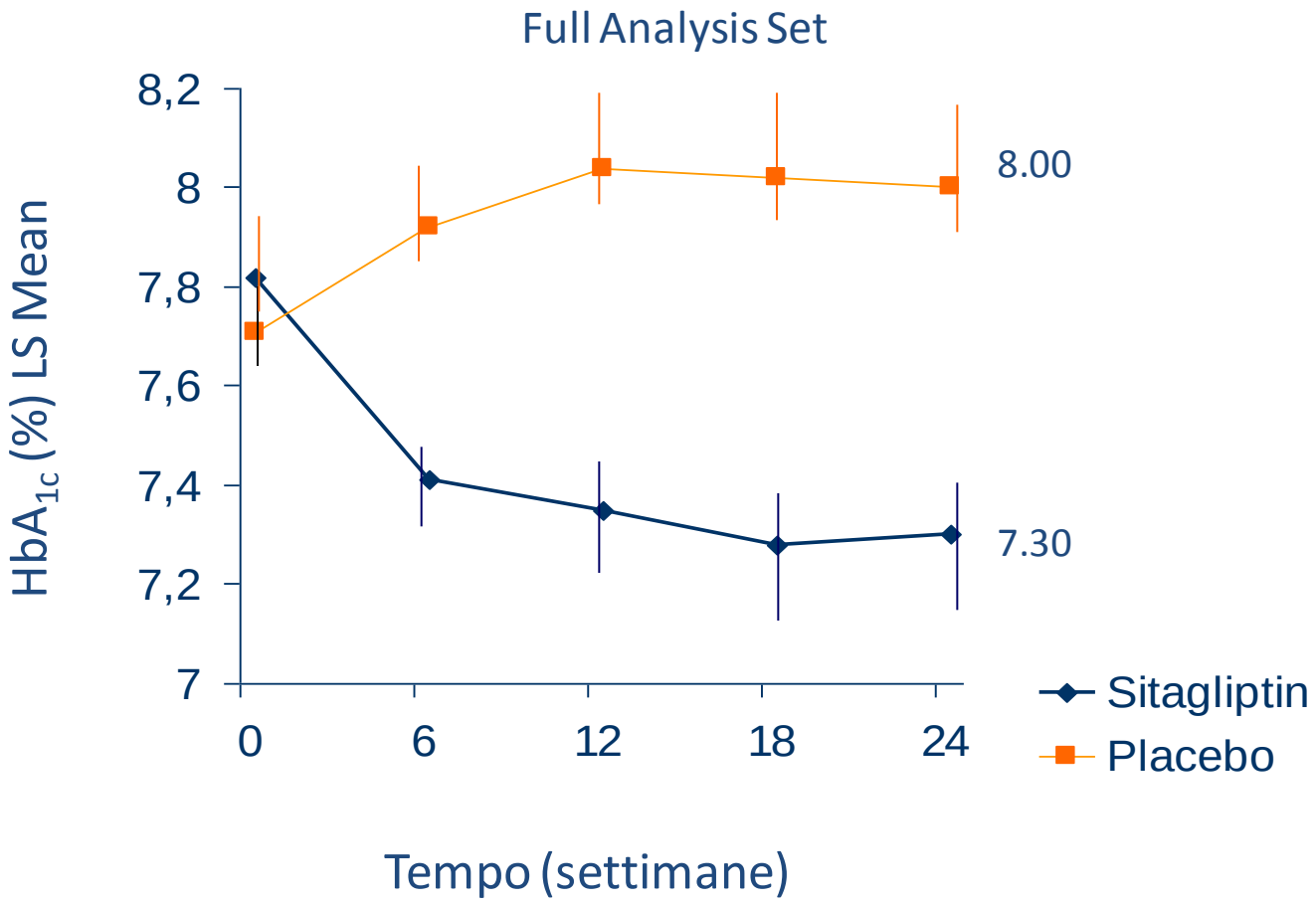
Relationships between hypoglycemia and accidental fall

Population with type 2 diabetes and nature of accident	Number (%)		Hazard ratio (95% CI)	Predicted incidence rate per 10 000 person-years (95% CI)	
	Hypoglycaemia	No hypoglycaemia		Hypoglycaemia	No hypoglycaemia
Age ≥65 years	(n = 2235)	(n = 9414)			
Any accident	133 (6.0)	270 (2.9)	1.46 (1.18, 1.80)*	135.5 (108.0, 162.9)	92.9 (78.9, 106.9)
Accidental fall	99 (4.4)	176 (1.9)	1.52 (1.18, 1.95)*	78.9 (58.3, 99.4)	52.0 (41.4, 62.6)
Motor vehicle accident	4 (0.2)	16 (0.2)	0.79 (0.26, 2.38)	4.7 (0.0, 9.7)	6.0 (2.6, 9.4)
Other accident	33 (1.5)	86 (0.9)	1.23 (0.82, 1.85)	38.0 (23.6, 52.3)	30.8 (23.1, 38.6)

Signorovitch et al., DOM 2013

Sitagliptin efficacy in ealderly patients: Effects on HbA_{1c}

Età media 72 aa , n=216



Barzilai et al Curr Med Res Op 27, 2011; 1049-1058

Sitagliptin:
Safety in ealderly patients

	Sitagliptin 100 mg (N = 102)		Placebo (N = 104)	
	n	(%)	n	(%)
Number (%) of patients:				
With one or more adverse experiences	47	(46.1)	55	(52.9)
With no adverse experience	55	(53.9)	49	(47.1)
With drug-related adverse experiences†	11	(10.8)	9	(8.7)
With serious adverse experiences	7	(6.9)	14	(13.5)
With serious drug-related adverse experiences	0	(0.0)	0	(0.0)
Who died	0	(0.0)	0	(0.0)
Discontinued due to adverse experiences	5	(4.9)	3	(2.9)
Discontinued due to drug-related adverse experiences	1	(1.0)	2	(1.9)
Discontinued due to serious adverse experiences	3	(2.9)	1	(1.0)
Discontinued due to serious drug-related adverse experiences	0	(0.0)	0	(0.0)

† Determined by the investigator to be possibly, probably or definitely drug related.

incidence of hypoglycemia similar to that of placebo

Barzilai et al Curr Med Res Op 27, 2011; 1049-1058

Conclusioni

- I soggetti diabetici di tipo 2 sono più esposti a rischio di frattura
- Meccanismi legati alla malattia possono determinare una aumentata fragilità ossea
- L'aumentato rischio di caduta, ed in particolare quello legato alle ipoglicemie iatrogene, può certamente contribuire all'aumentato rischio di frattura
- Ai fini di ridurre il rischio di frattura, nei soggetti più esposti, è consigliabile scegliere tra le più appropriate terapie anti-diabete quelle che non hanno effetti negativi sull'osso e quelle che non sono legate ad un aumento del rischio di ipoglicemia
- Le terapie basate sulle incretine hanno potenzialmente effetti favorevoli sull'osso e non aumentano il rischio di ipoglicemia
- Iniziali evidenze cliniche suggeriscono che la terapia con DPP-IV inibitori può risultare vantaggiosa nei confronti del rischio di frattura.