Bone fragility as a new complication of diabetes

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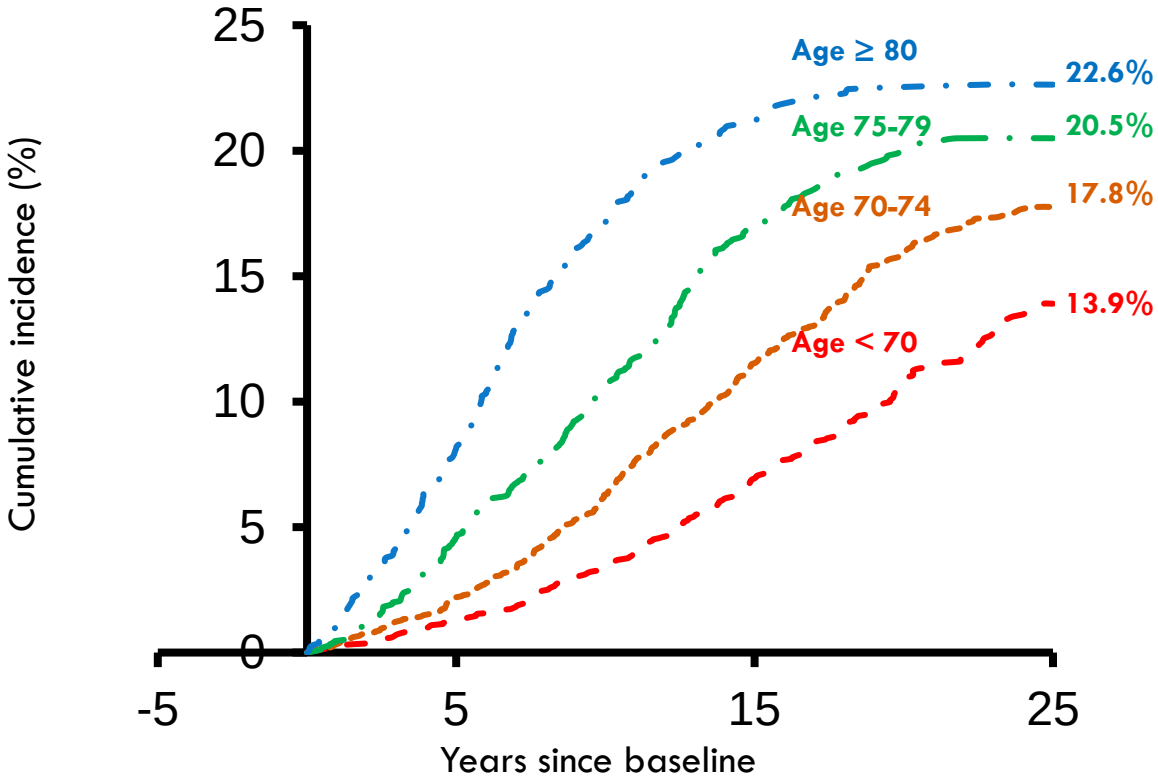
UNIVERSITA' CAMPUS BIO-MEDICO
DI ROMA

COI

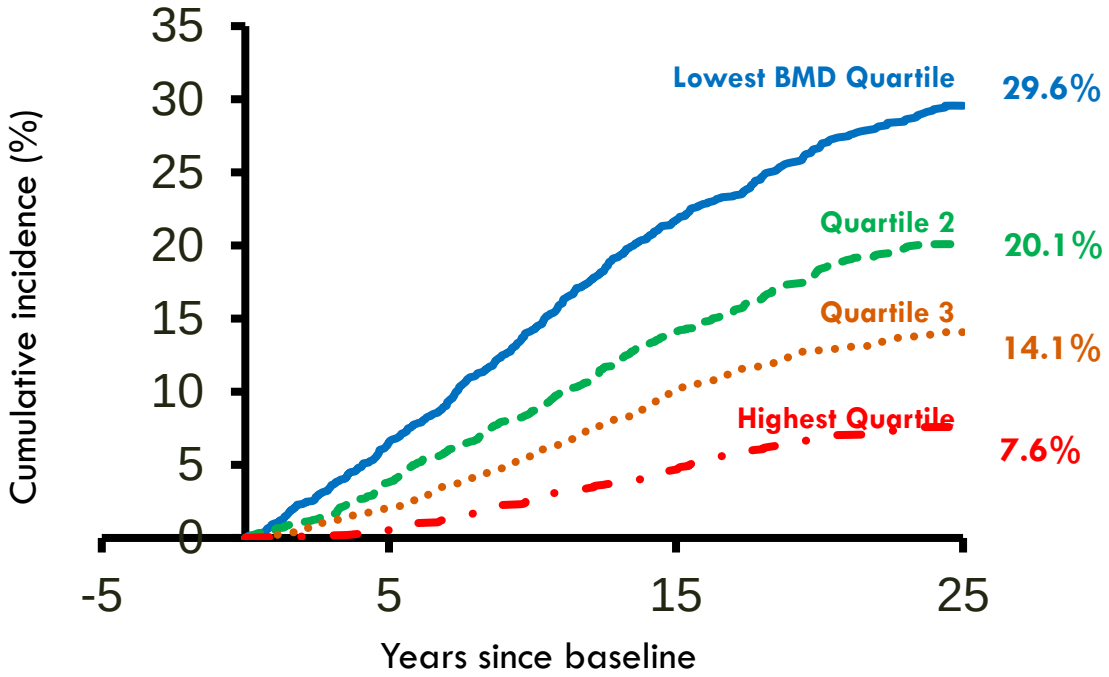
- Eli Lilly
- Novo Nordisk

Hip Fracture Incidence increases with Age



Napoli et al, J Bone Miner Res ,2018

Hip Fracture Incidence increases with lower bone mineral density (BMD)

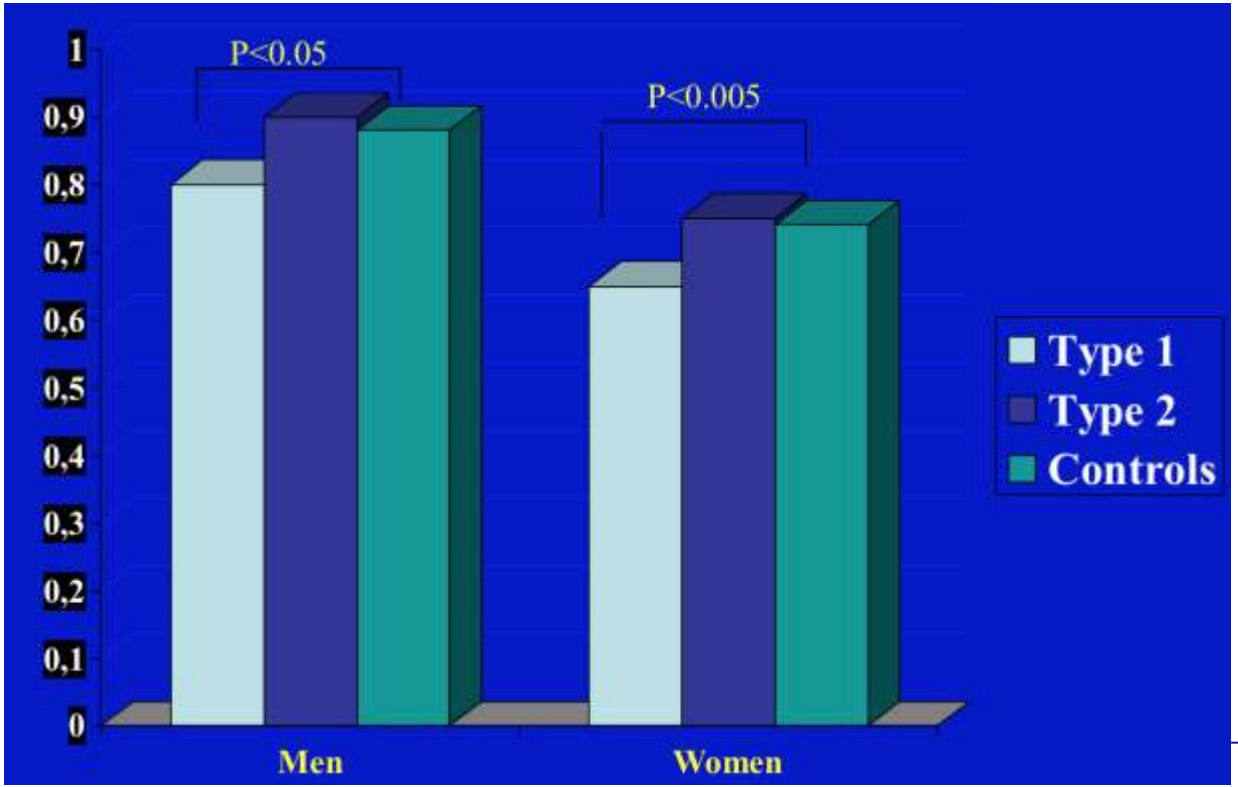


Napoli et al, J Bone Miner Res ,2018

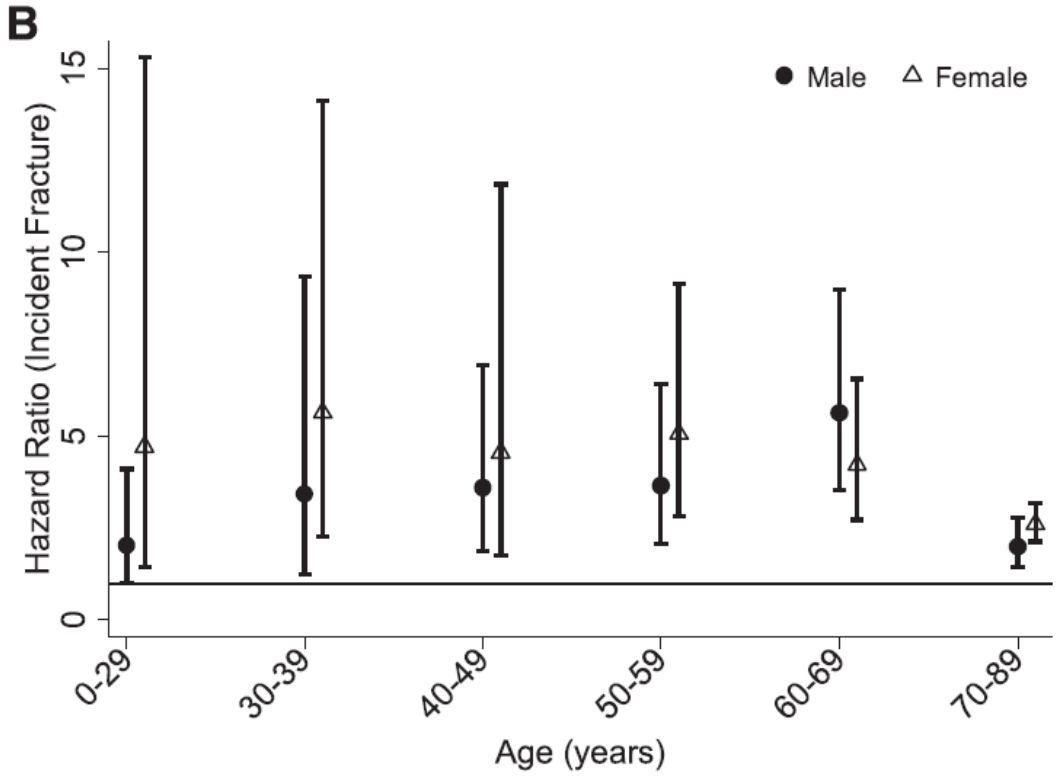
Diabetes: a different story

WHAT WE KNOW

Bone Mineral Density (BMD) at the hip in subjects with T1D, T2D and without diabetes

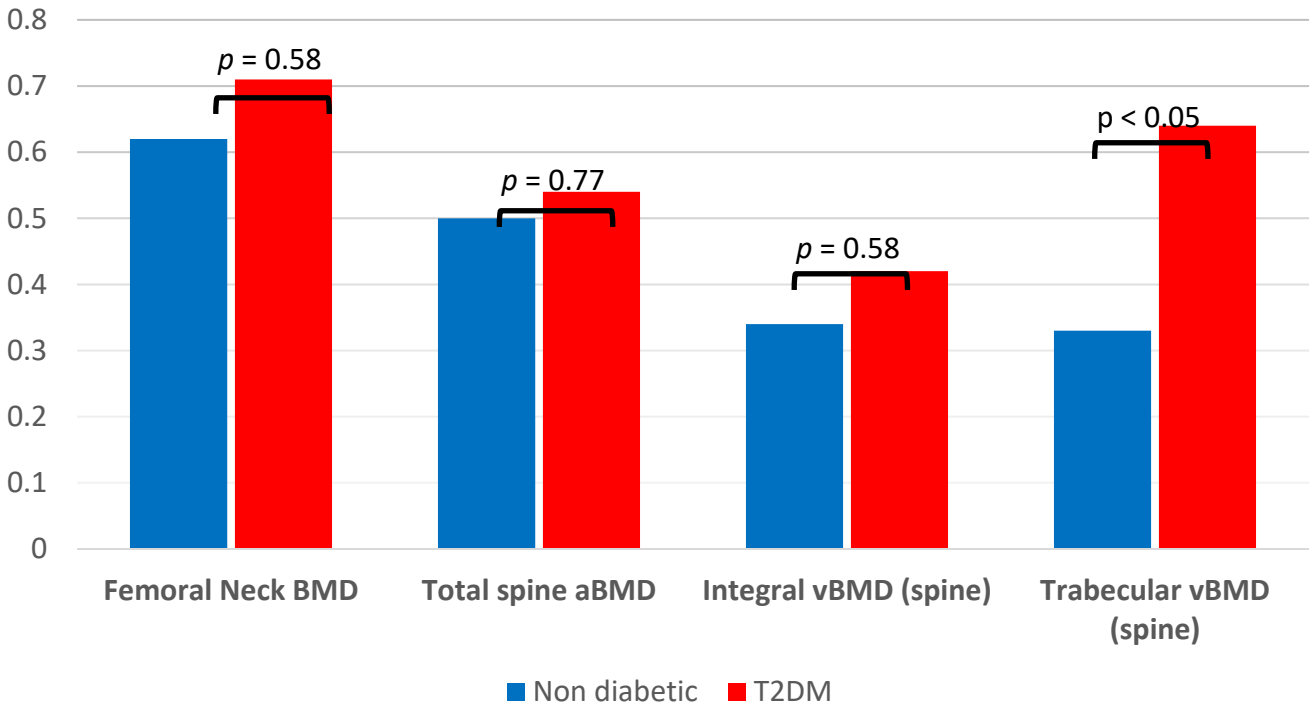


Association between T1DM and risk of hip fracture



Weber, Diabetes Care 2015

Association of BMD at Baseline With Incident Vertebral Fractures in Men With or Without T2DM

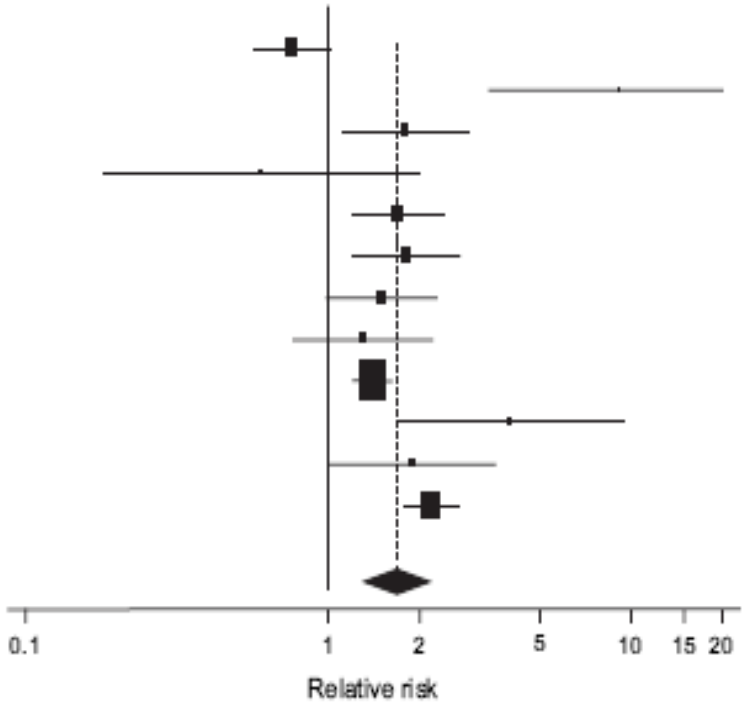


Napoli N. et al., J Bone Miner Res, 2018

Association between type 2 diabetes mellitus and risk of hip fracture

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:
$Q = 58.1$; $p < 0.001$

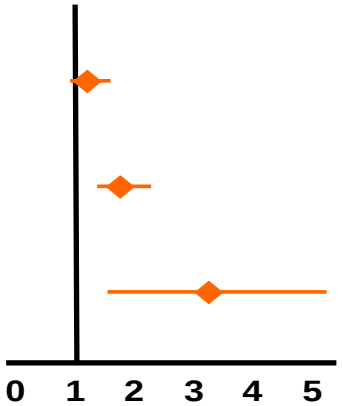


ORIGINAL ARTICLE
Endocrine Care

Risk Factors for Subtrochanteric and Diaphyseal Fractures: The Study of Osteoporotic Fractures

Nicola Napoli, Ann V. Schwartz, Lisa Palermo, Jenny J. Jin, Rosanna Wustrack, Jane A. Cauley, Kristine E. Ensrud, Michael Kelly, and Dennis M. Black

Hip fracture location	No. fx	HR (95% CI)
Femoral neck	768	1.20 (0.90, 1.58)
Intertrochanteric	642	1.76 (1.37, 2.27)
Subtrochanteric/ diaph.	45	3.25 (1.55, 6.82)



Older women (N=9704) in the Study of Osteoporotic Fractures

Adjusted models

Napoli et al. J Clin Endocrinol Metab, 2013

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Full Length Article

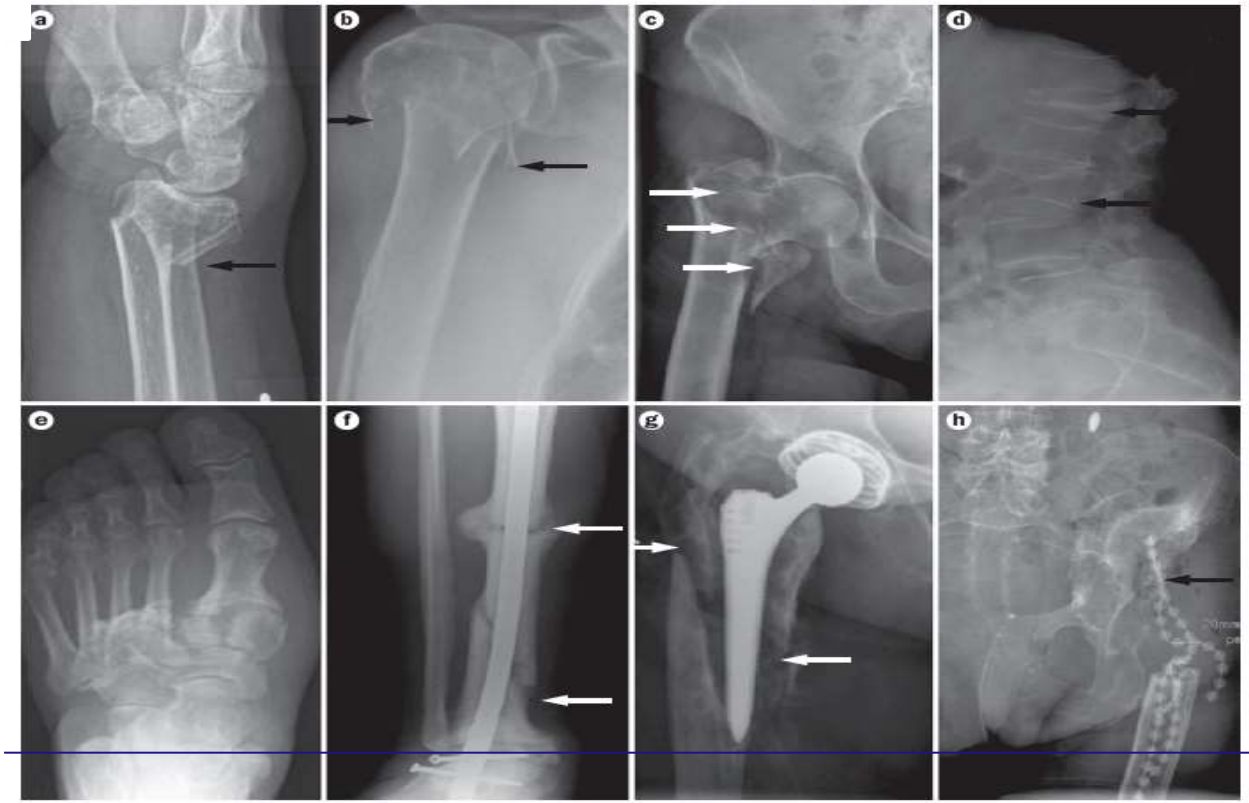
Increased prevalence of self-reported fractures in Asian Indians with diabetes: Results from the ICMR-INDIAB population based cross-sectional study

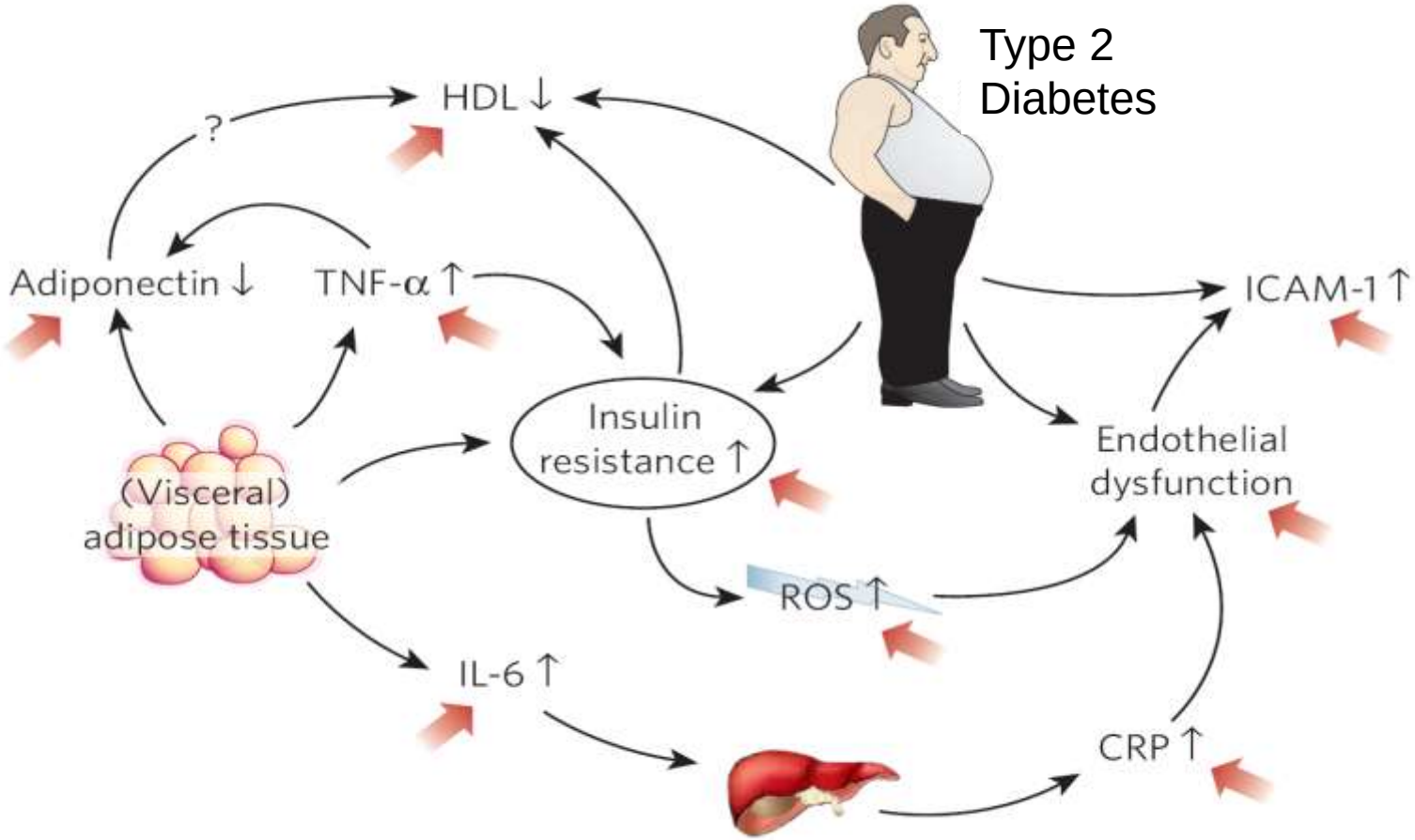
Parjeet Kaur[a,*], Ranjit Mohan Anjana[b], Nikhil Tandon[c], Manish Kumar Singh[d], Viswanathan Mohan[b], Ambrish Mithal[a]

	Total population		Females		Males	
	No Diabetes $N = 50,245$	Diabetes $N = 3848$	No Diabetes $N = 27,848$	Diabetes $N = 1909$	No diabetes $N = 22,397$	Diabetes $N = 1939$
Age (years) Mean (SD)	40.6 (14.3) (range: 20–105)	51.8(13.04)* (range: 20–95)	39.7(13.9)	51.0(13.1)*	41.6(14.8)	52.6(12.8)*
Fractures	1256 (2.5%)	154 (4.0%)*	501 (1.8%)	66 (3.5%)*	761 (3.4%)	87 (4.5%)*
Obesity(BMI > 25 kg/m²)	17,736 (35.3%)	2432 (63.2%)*	10,053 (36.1%)	1260 (66.0%)*	7704 (34.4%)	1173 (60.5%)*
Waist circumference women > 80 cm	6883 (13.7%)	1604 (41.7%)*	3815 (13.7%)	796 (41.7%)*		
Waist circumference men > 90 cm	10,953 (21.8%)	2008 (52.2%)*			4053 (18.1%)	942 (48.6%)*
Alcohol consumption	7938 (15.8%)	550 (14.3%)*	986 (3.5%)	33 (1.7%)*	6965 (31.1%)	518 (26.7%)*
Smoking	8642 (17.2%)	638 (16.6%)	1225 (4.4%)	64 (3.4%)*	7413 (33.1%)	576 (29.7%)*
Urban population	14,169 (28.2%)	1758 (45.7%)*	8062 (29%)	862 (45.2%)*	6105 (27.3%)	895 (46.2%)*
Physically active	23,715 (47.2%)	1450 (37.7%)*	10,888 (39.1%)	578 (30.3%)*	12,811 (57.2%)	874 (45.1%)*

* $p < 0.05$ vs. no diabetes

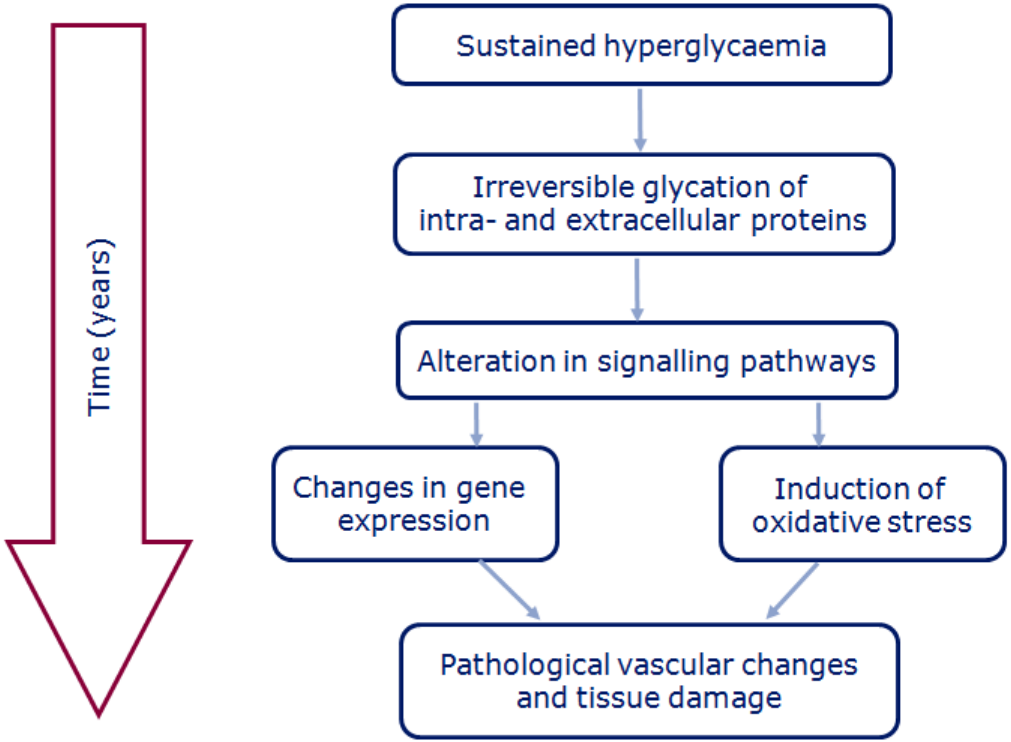
Why a sweet bone is more brittle?

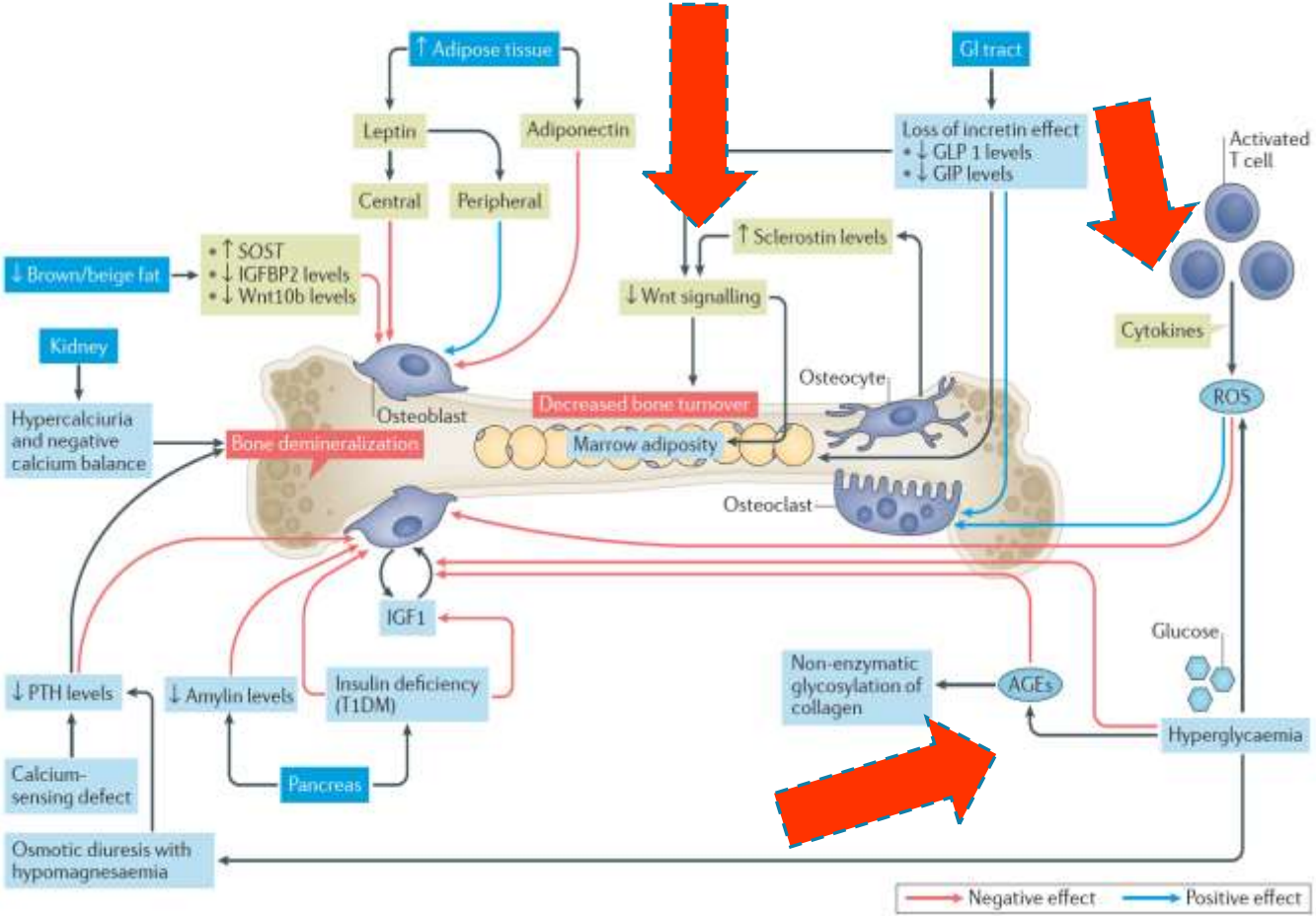




NATURE|Vol 444|14 December 2006|doi:10.1038/nature05487

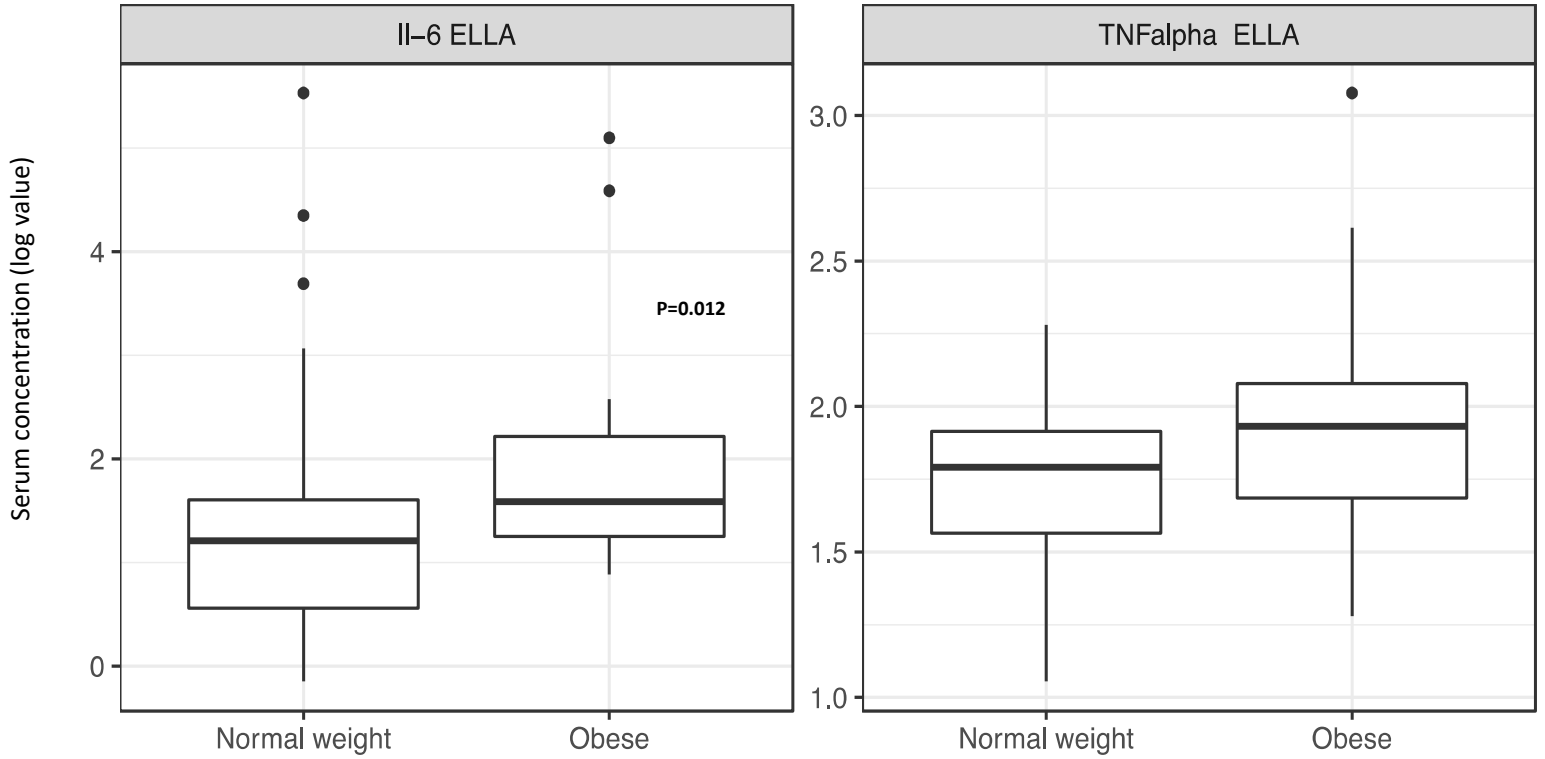
Type 2 diabetes progression: vascular changes and tissue damage




↑ Adipose tissue
Leptin
Adiponectin
Central
Peripheral
↓ Brown/beige fat
• ↑ SOST
• ↓ IGFBP2 levels
• ↓ Wnt10b levels
Kidney
Hypercalciuria and negative calcium balance
Bone demineralization
Osteoblast
Osteocyte
Decreased bone turnover
Marrow adiposity
Osteoclast
↓ Wnt signalling
↑ Sclerostin levels
GI tract
Loss of incretin effect
• ↓ GLP 1 levels
• ↓ GIP levels
Activated T cell
Cytokines
ROS
IGF1
↓ PTH levels
↓ Amylin levels
Insulin deficiency (T1DM)
Pancreas
Calcium-sensing defect
Osmotic diuresis with hypomagnesaemia
Non-enzymatic glycosylation of collagen
AGEs
Glucose
Hyperglycaemia
Negative effect
Positive effect

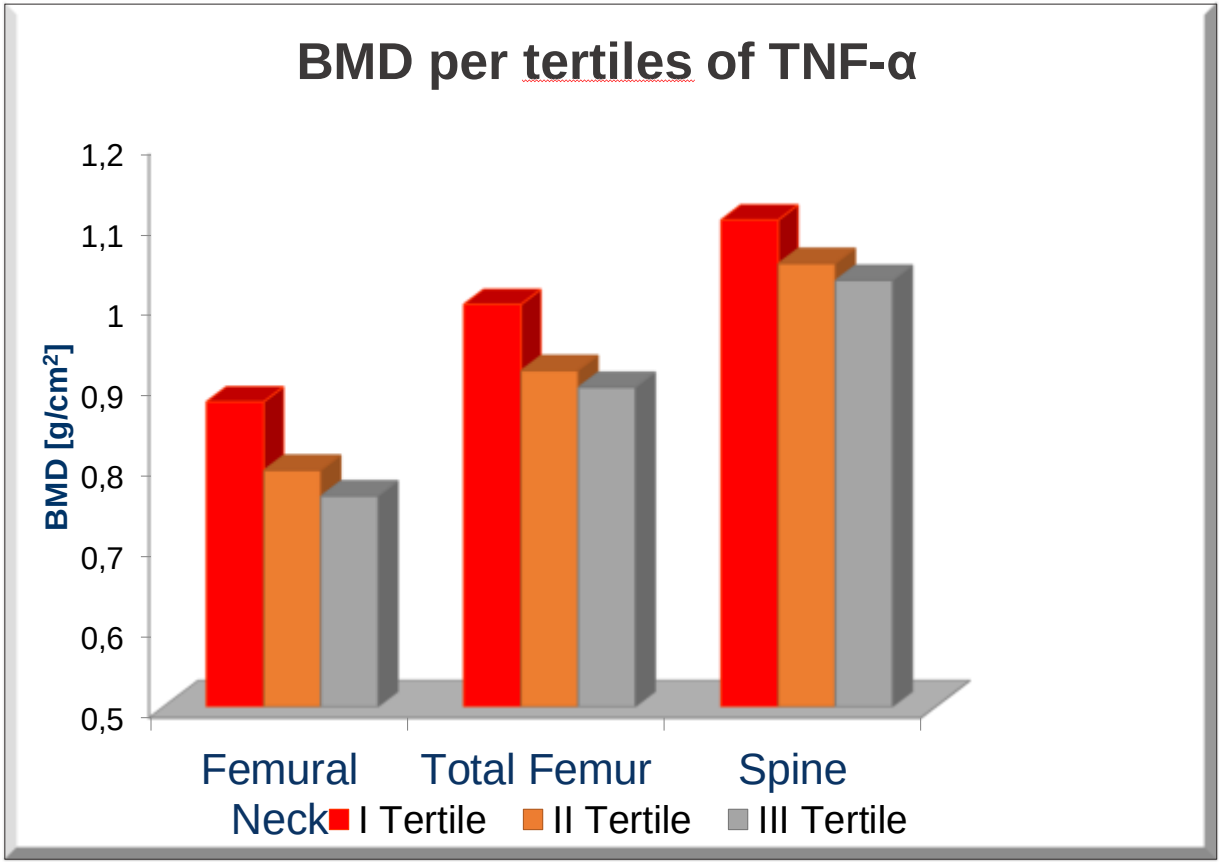
Role of inflammation

Serum cytokines are increased in the T2D-obese



Napoli, unpublished

Inflammation is associated to bone loss



Napoli, unpublished

Increased adiposity is associated to lower BMD

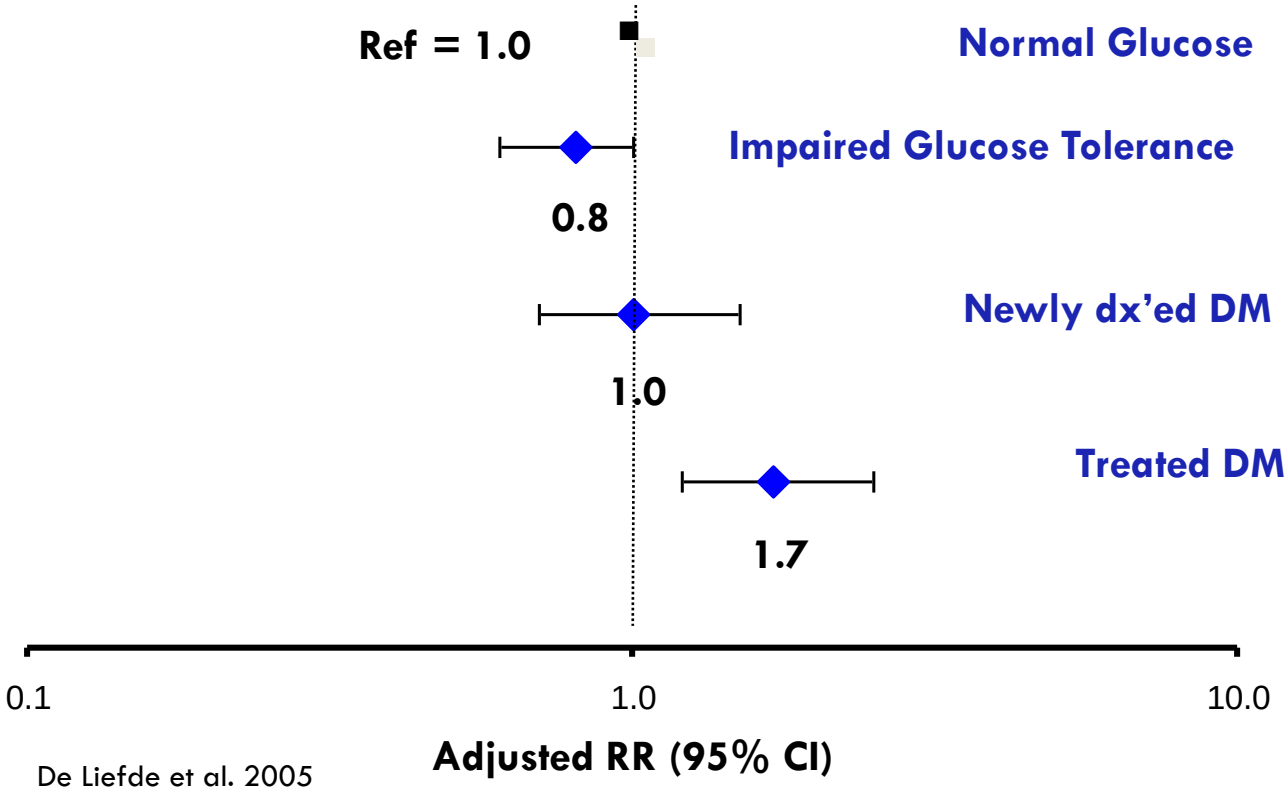
Clinical Variable	Females (n = 92)			
	First Tertile (n = 30)	Second Tertile (n = 31)	Third Tertile (n = 31)	*P* Value
Age, y	69.6 ± 3.0	69.8 ± 3.5	69.3 ± 4.7	.94
Median (IQR)[a]	69.6 (67.0, 71.5)	68.0 (67.0, 73.0)	68.0 (66.0, 72.0)	
Weight, kg	101.0 ± 11.7	90.0 ± 13.0	102.7 ± 15.6	<.001
Height, cm	172.5 ± 10.5	162.4 ± 6.6	160.6 ± 7.1	<.001
BMI, kg/m^2	34.0 ± 3.3	35.8 ± 4.4	39.0 ± 5.8[b,c]	<.001
PPT	29.4 ± 1.5	28.3 ± 3.4	26.2 ± 3.9[b,c]	.001
BMD				
Spine	1.190 ± 0.16	1.060 ± 0.14	1.063 ± 0.12	<.001
Total femur	1.049 ± 0.14	0.939 ± 0.11	0.947 ± 0.14	<0.001
hs-CRP, mg/L	1.5 (1.0, 2.0)	4.1 (2.3, 5.8)	5.5 (3.5, 7.5)[a]	.002

Aguirre, Napoli et al, JCEM 2014

Is diabetic bone different?
Or, what is the evidence that diabetes, especially with longer duration, affects bone

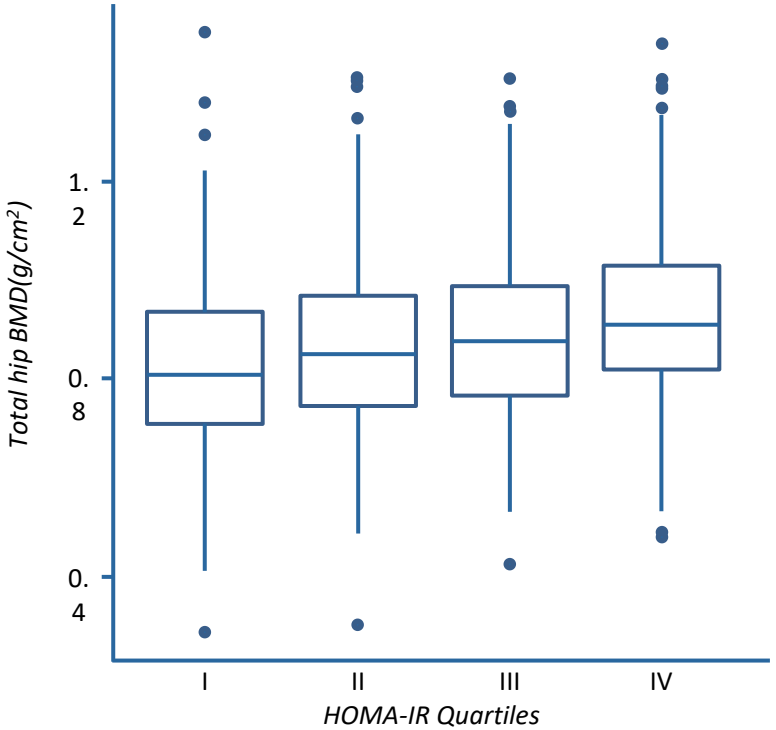
- Disease progression
- Disease duration
- Glycaemic control
- Complications and falls

Impaired Glucose Tolerance (Pre-Diabetes) and Non-Spine Fracture Risk - Rotterdam Study



De Liefde et al. 2005

Total hip bone mineral density is increased by quartiles of HOMA-IR index

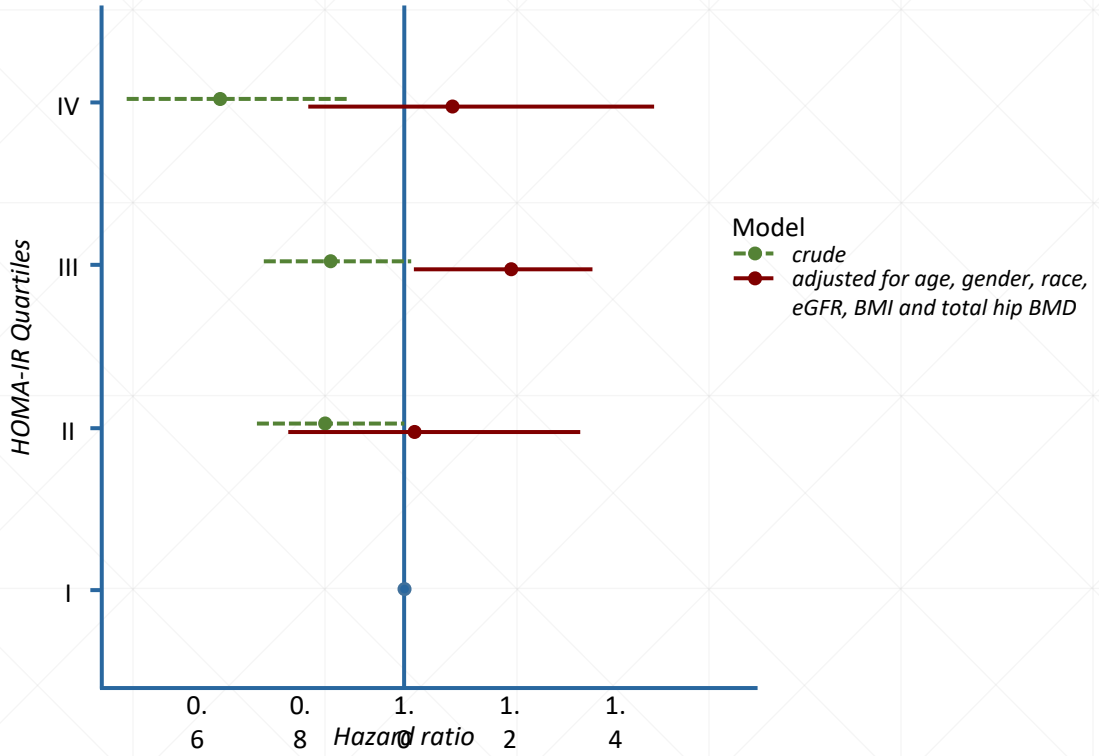


n = 2398
Mean age 73.6±2.9
53.1% women
37.5% black
Median follow-up for fracture: 11.9 yrs

ANOVA P < 0.001

Napoli N and Conte C, JCEM 2019

Non-spine fractures are increased according to quartiles of HOMA-IR index

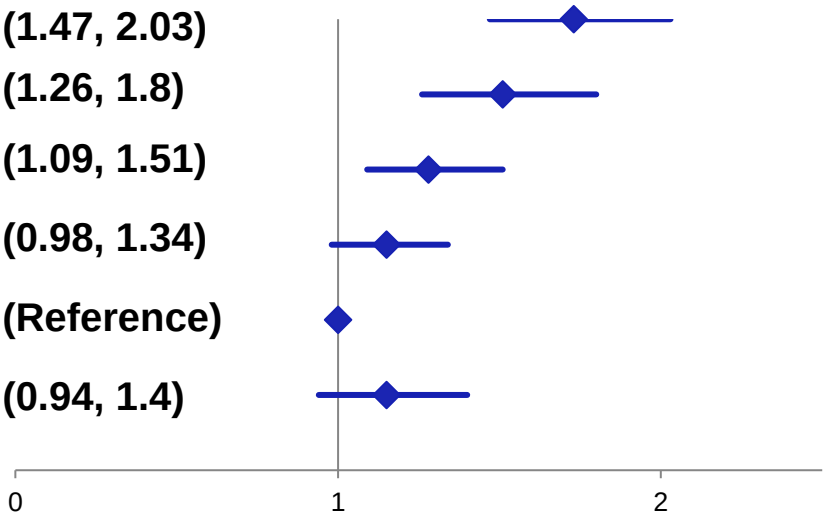


Napoli N and Conte C, JCEM 2019

Poor glycemic control increases hip fracture risk

Taiwan Diabetes Cohort Study. N= 20,025. 65+ y.o.

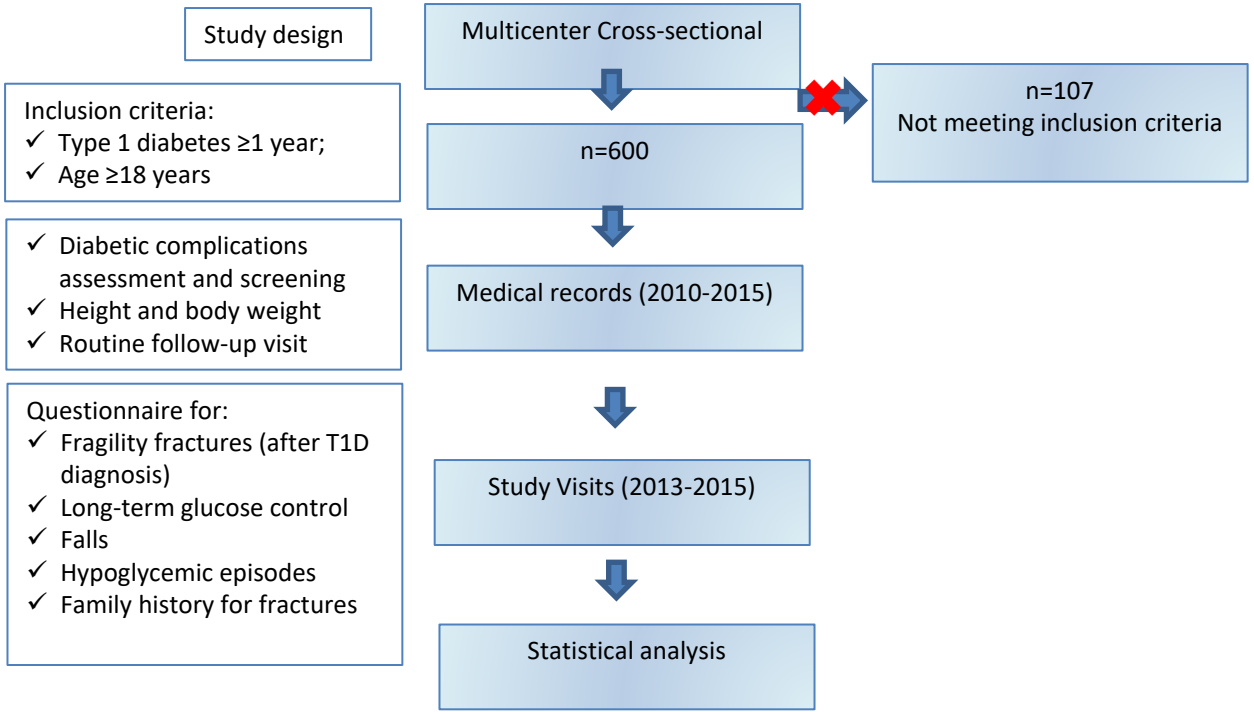
A1C	HR (95% CI)
≥10	1.73 (1.47, 2.03)
9 – 10	1.51 (1.26, 1.8)
8 – 9	1.28 (1.09, 1.51)
7 – 8	1.15 (0.98, 1.34)
6 – 7	1.00 (Reference)
≤6	1.15 (0.94, 1.4)



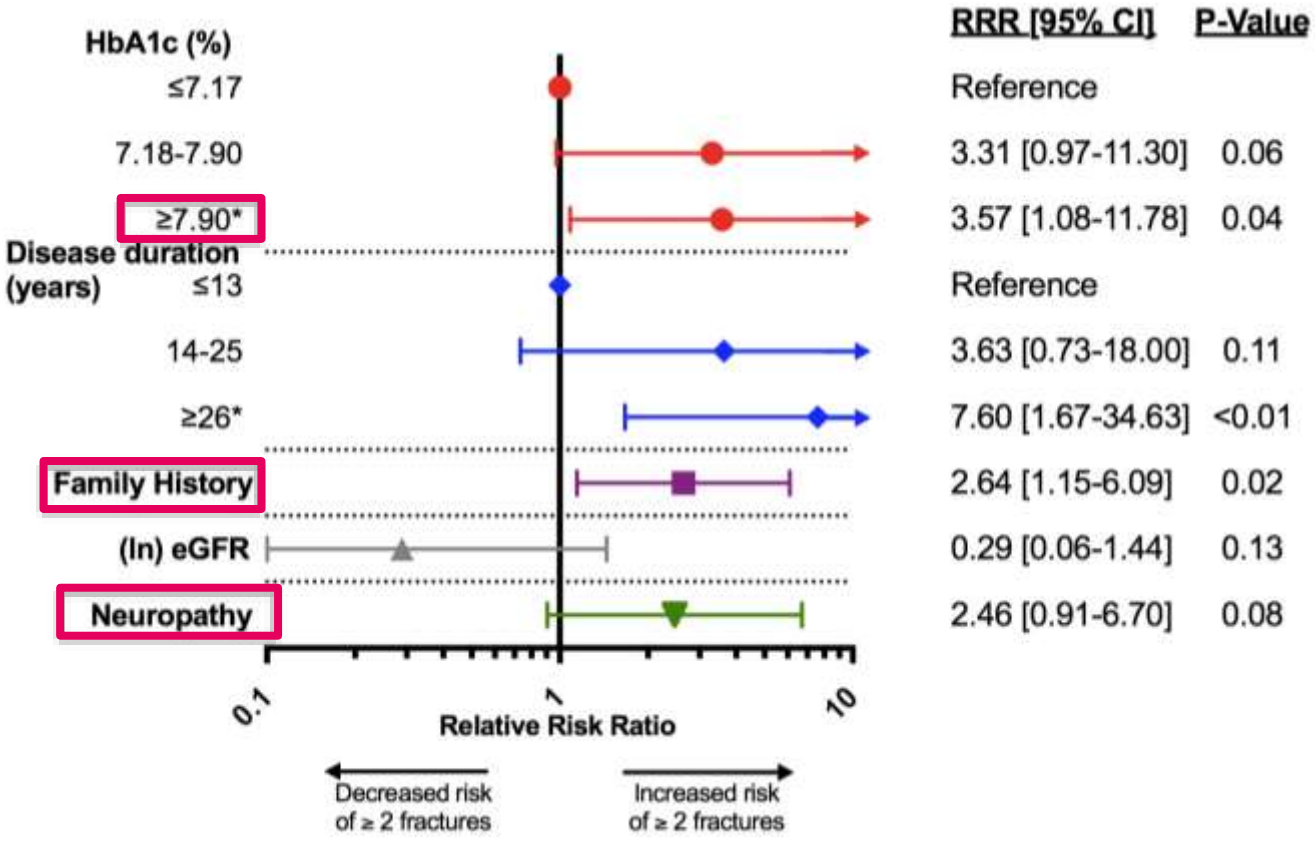
1514 hip fracture cases

Li et al *J Bone Miner Res* 2015

To determine clinical risk factors for any and multiple fragility fractures in type 1 diabetes



Leanza, Maddaloni, Napoli Bone 2019

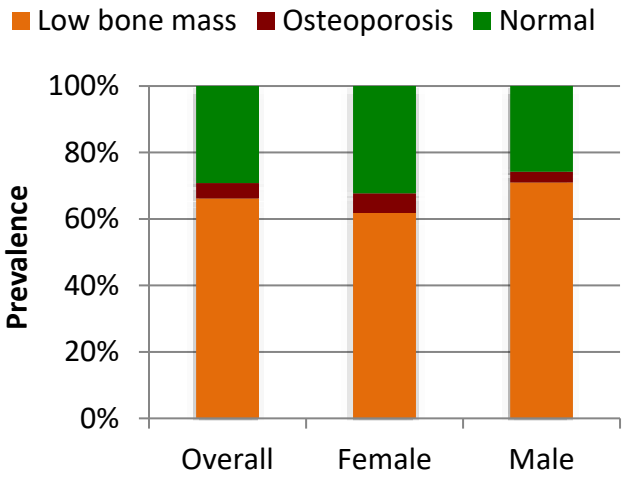


Leanza, Maddaloni, Napoli Bone 2019

Bone health in subjects with T1D for ≥50 years

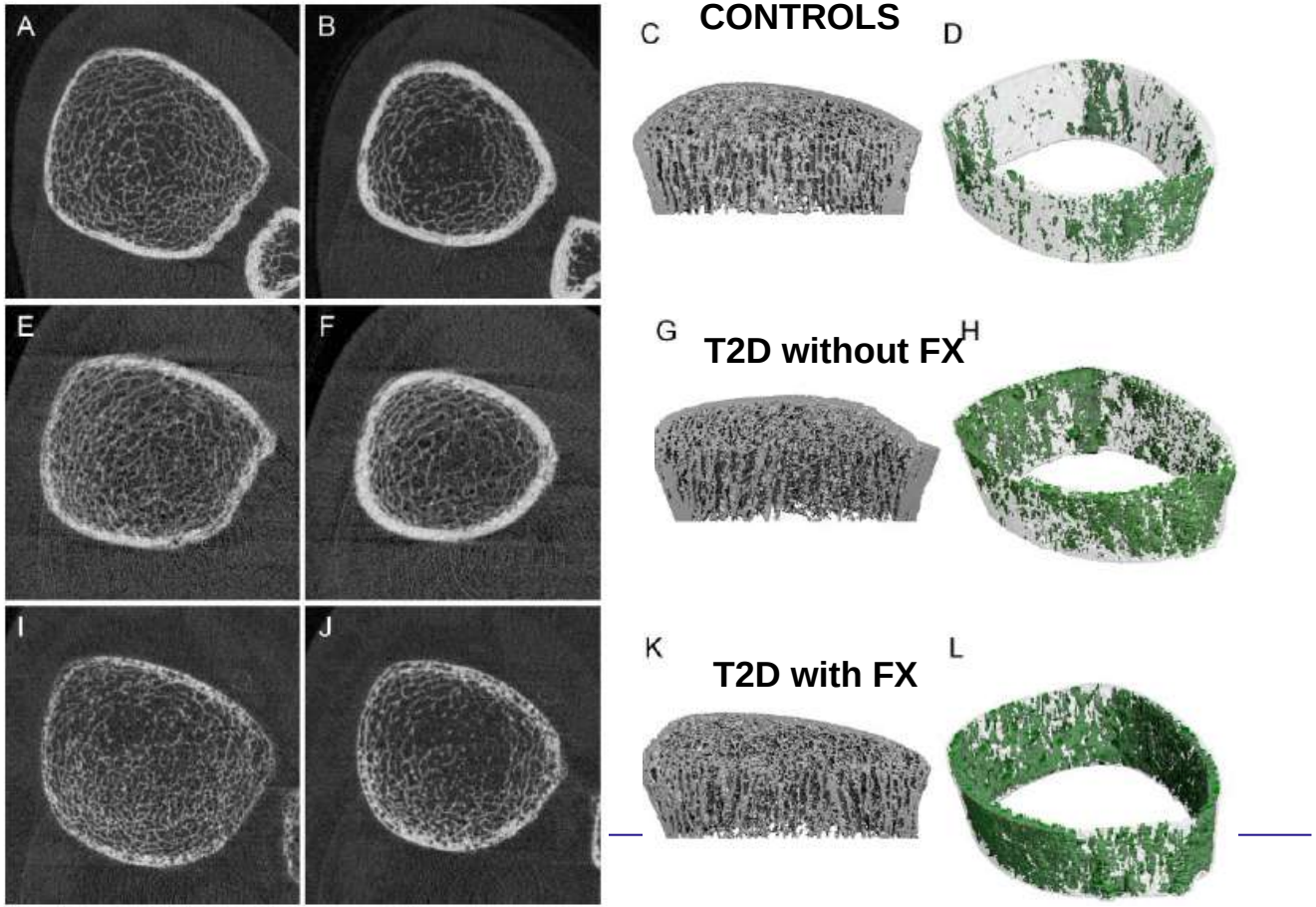
✓**40% free from CV complications** despite long-term T1D[1,2]

✓**Only 1.2%** of the 985 Medalists had history of non-vertebral fragility fractures[3]

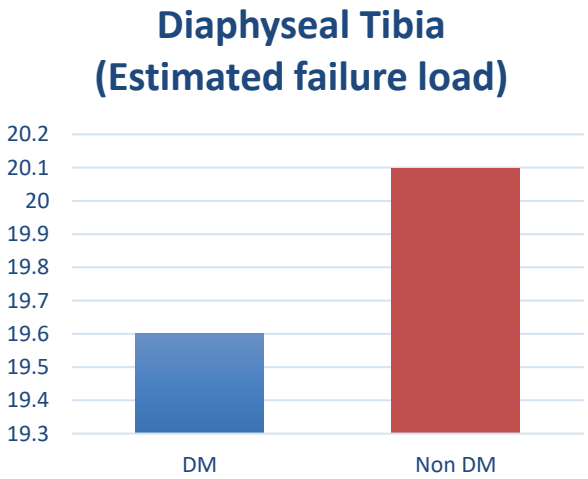


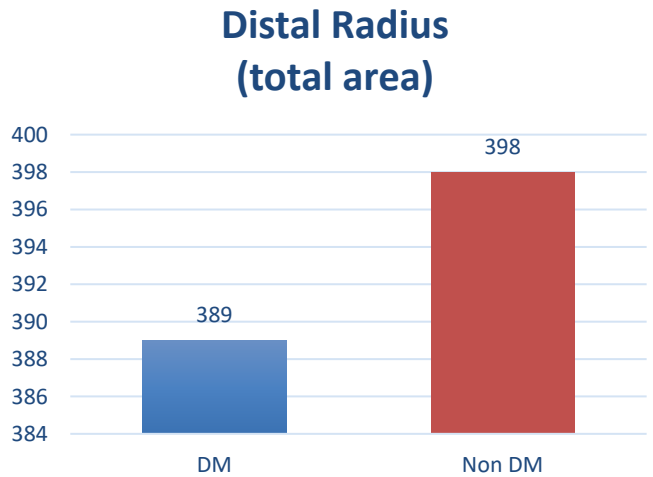
[1]*Keenan HA, et al., Diabetes 2007,*
[2]*Sun et al. Diabetes Care 2011;* [3]*Maddaloni E. et al., Acta Diabetol 2017*

Alterations in bone microarchitecture



Micro-architecture is impaired in T2D

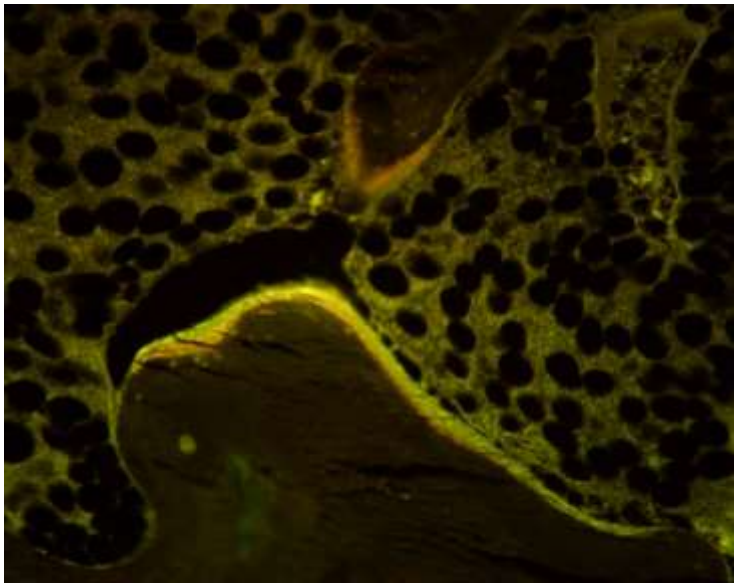


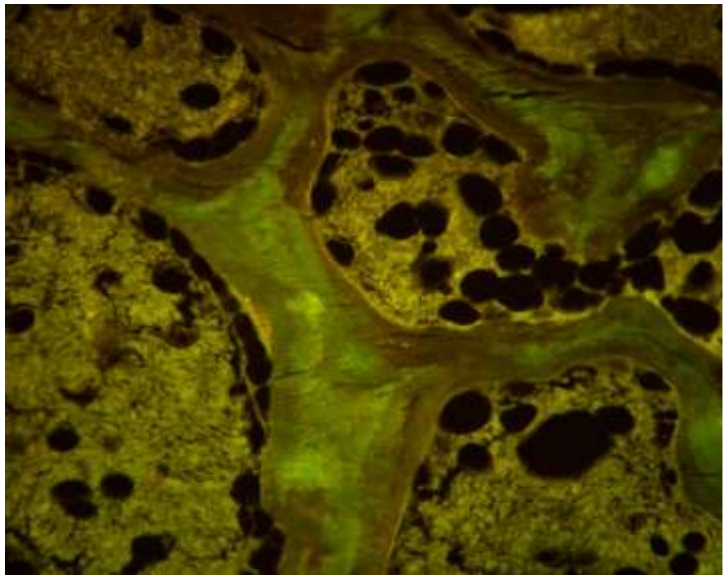


Napoli, Schwartz, ASBMR 2019

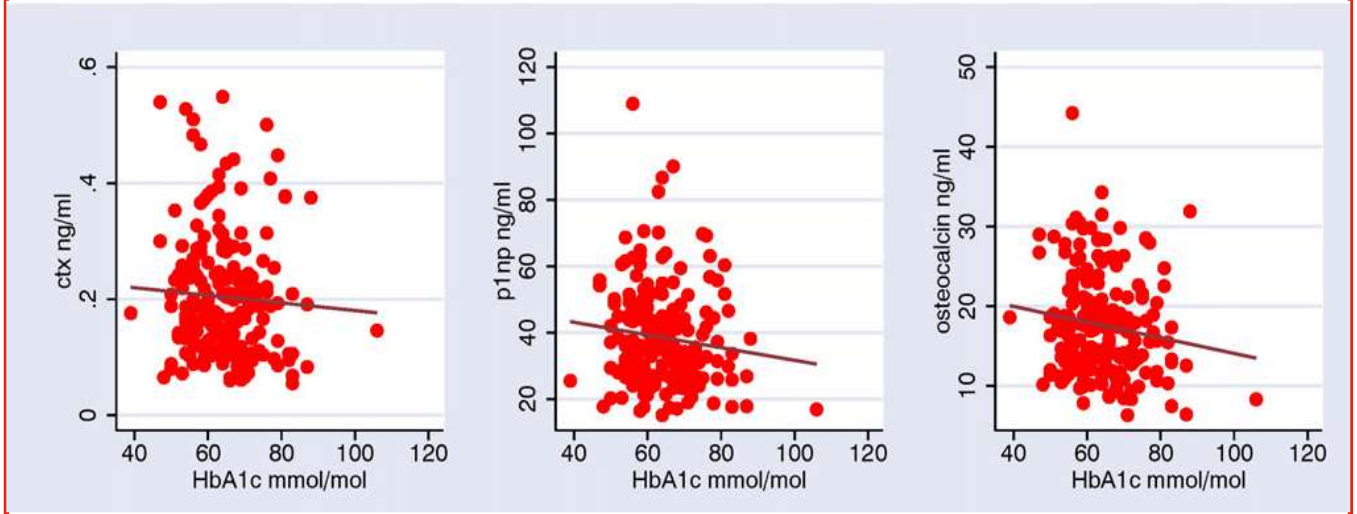
Wnt pathway

Bone Formation, by dynamic bone histomorphometry, is low in T2DM





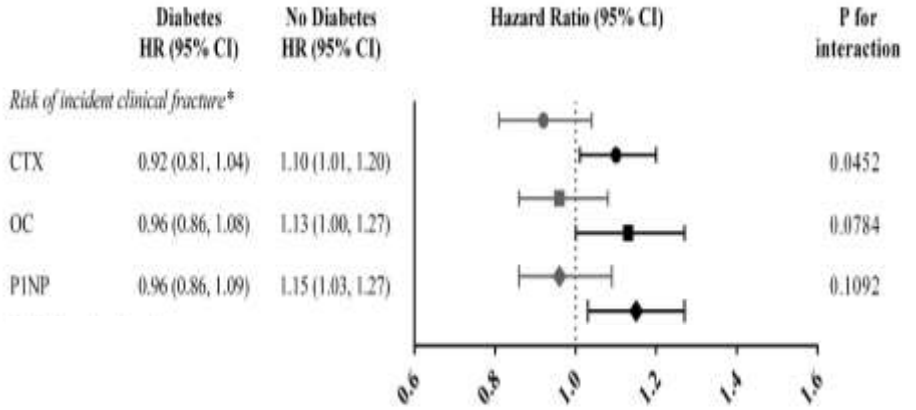
Low Bone Turnover in Diabetics



Vestergaard,oi 2014 and Bone 2016

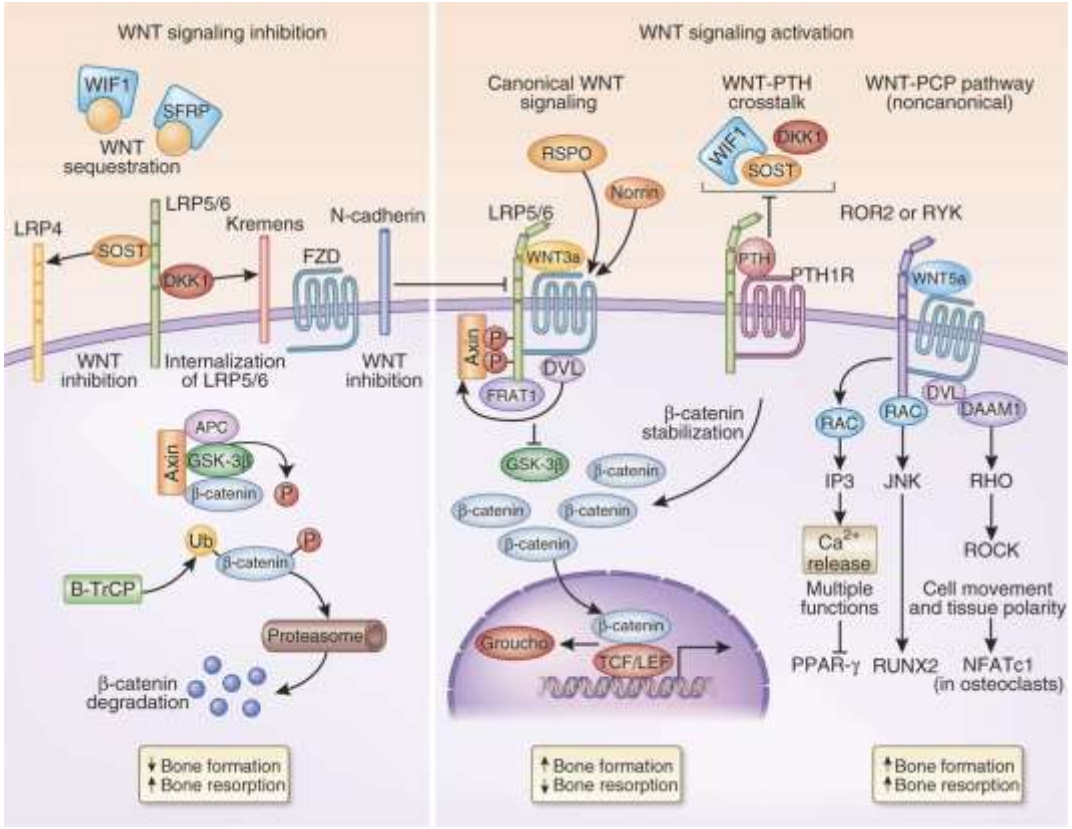
Low Bone turnover in T2DM

	Normoglycemia N =167	Pre-diabetes N = 172	Diabetes N = 169	P for trend
Bone turnover marker				
CTX, ng/ml	0.49 (0.45, 0.53)	0.48 (0.45, 0.52)	0.43 (0.40, 0.47)	0.0404
OC, ng/ml	8.3 (7.7, 8.8)	8.1 (7.6, 8.7)	7.0 (6.5, 7.4)	0.0007
P1NP, ng/ml	44.1 (41.1, 47.4)	41.2 (38.5, 44.2)	40.3 (37.6, 43.2)	0.0850

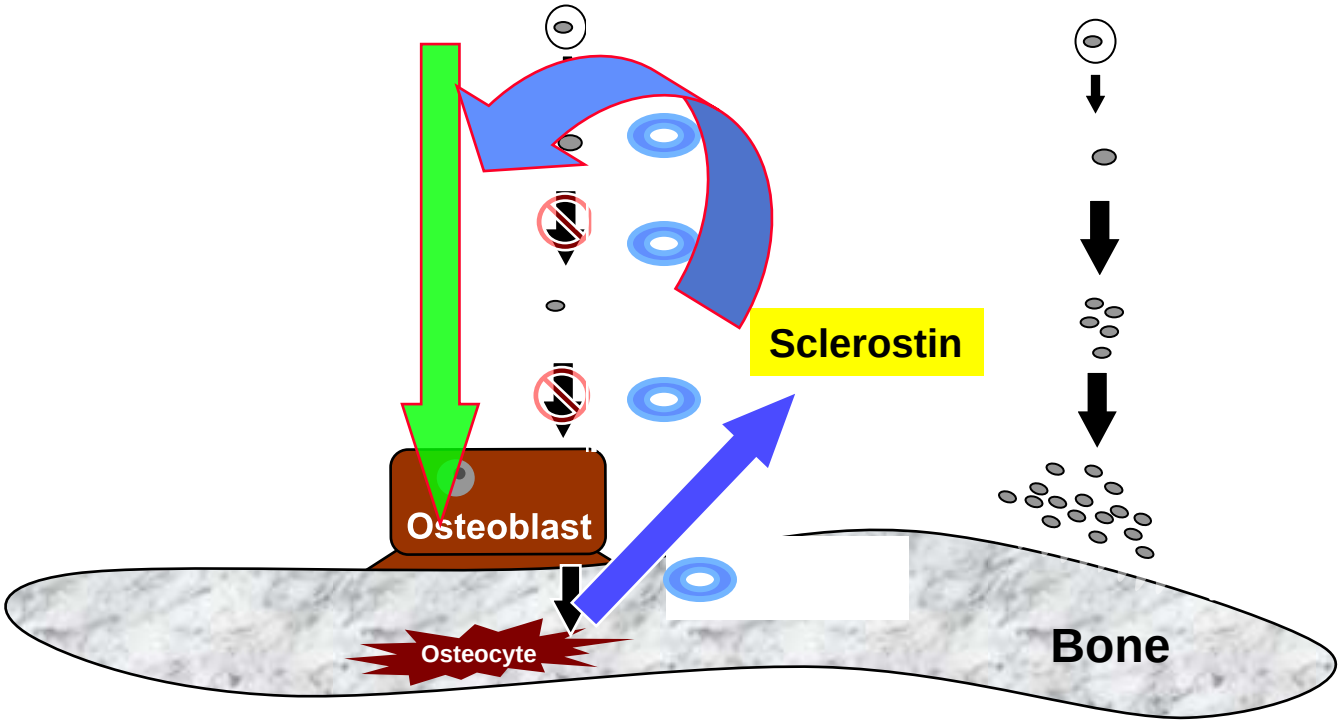


WNT PATHWAY

- During the past decade, secreted signaling molecules of the Wnt family have been widely investigated and found to play a central role in in the regulation of bone mass.
- Recent published data reveal that Wnt signaling pathway is activated during postnatal bone regenerative events
- Dysregulation of this pathway greatly inhibits bone formation and healing process.

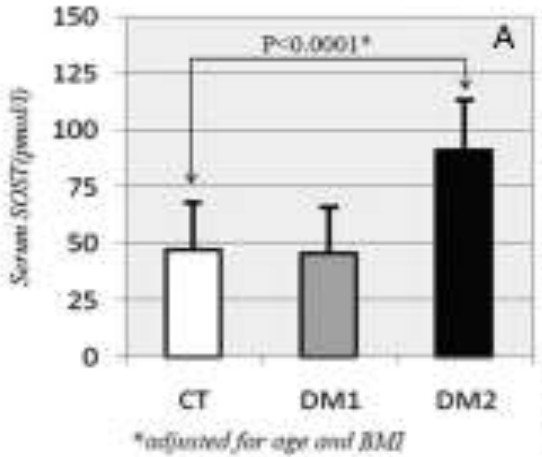


More evidence for reduced bone formation in T2DM: abnormalities in Sclerostin

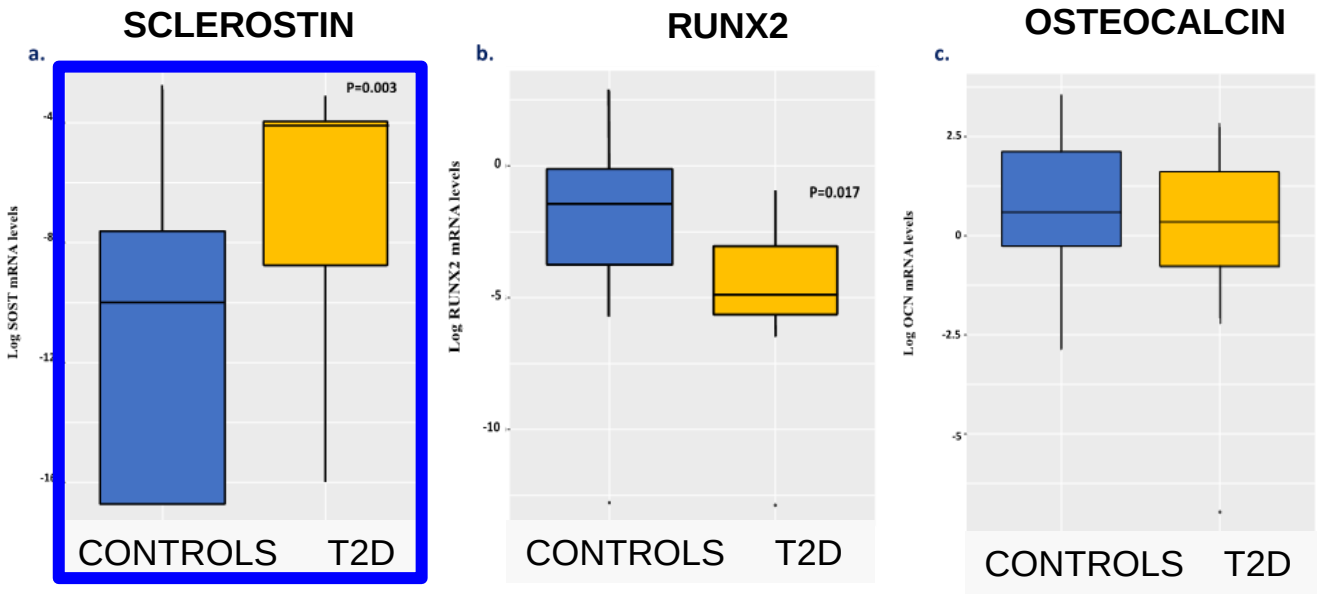


Circulating Sclerostin Levels and Bone Turnover in Type 1 and Type 2 Diabetes

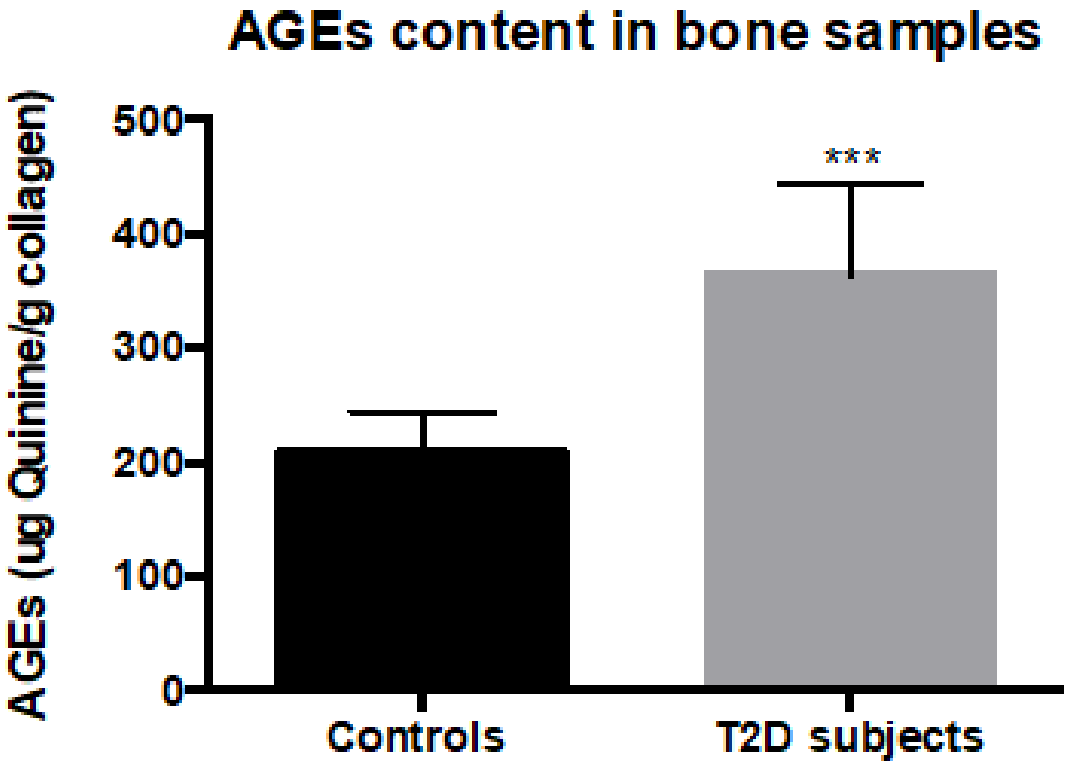
Luigi Gennari, Daniela Merlotti, Roberto Valenti, Elena Ceccarelli, Martina Ruvio, Maria G. Pietrini, Cosimo Capodarca, Maria Beatrice Franci, Maria Stella Campagna, Anna Calabrò, Dorica Cataldo, Konstantinos Stolakis, Francesco Dotta, and Ranuccio Nuti



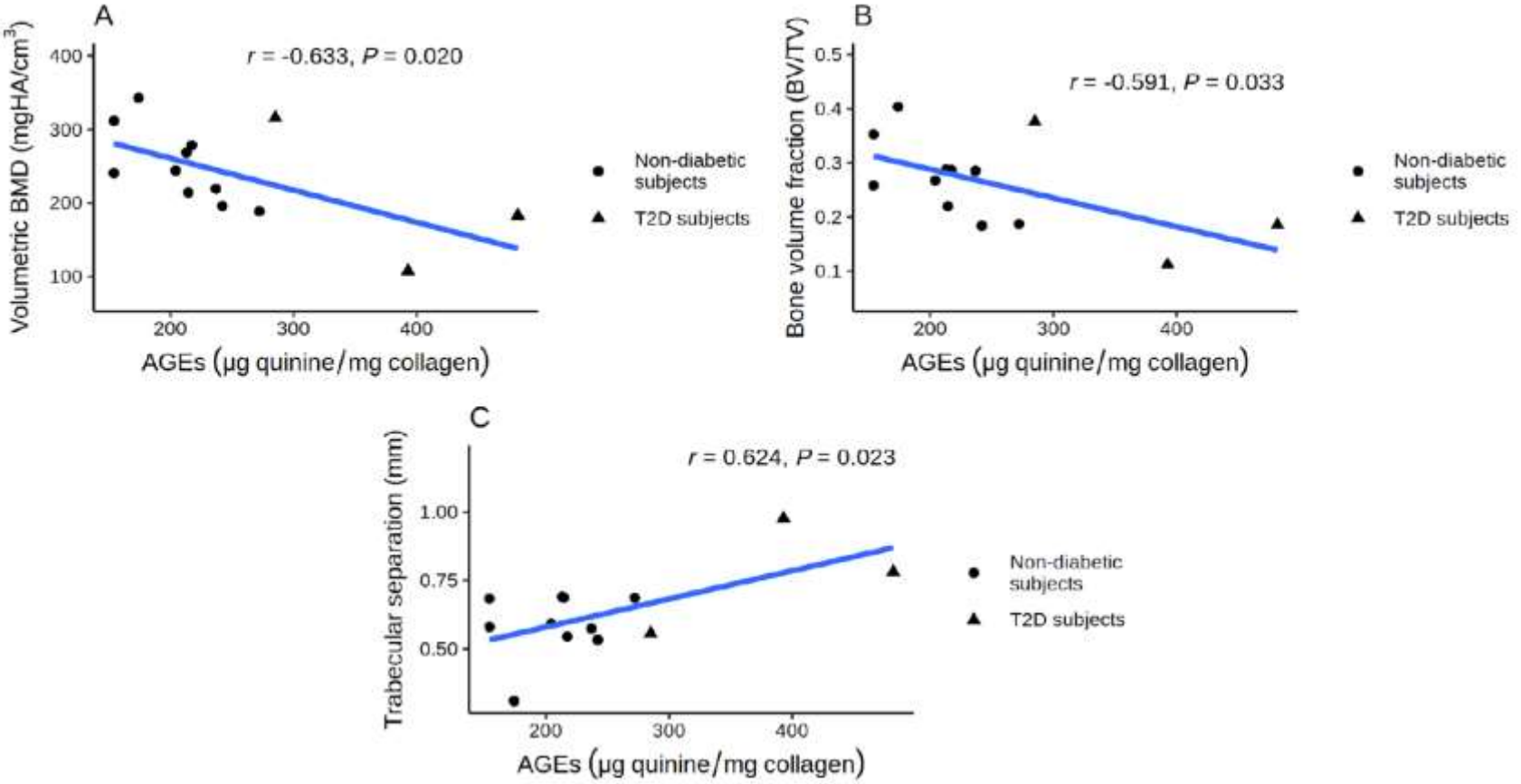
Bone formation is downregulated in bone in T2DM



AGEs are doubled in T2D

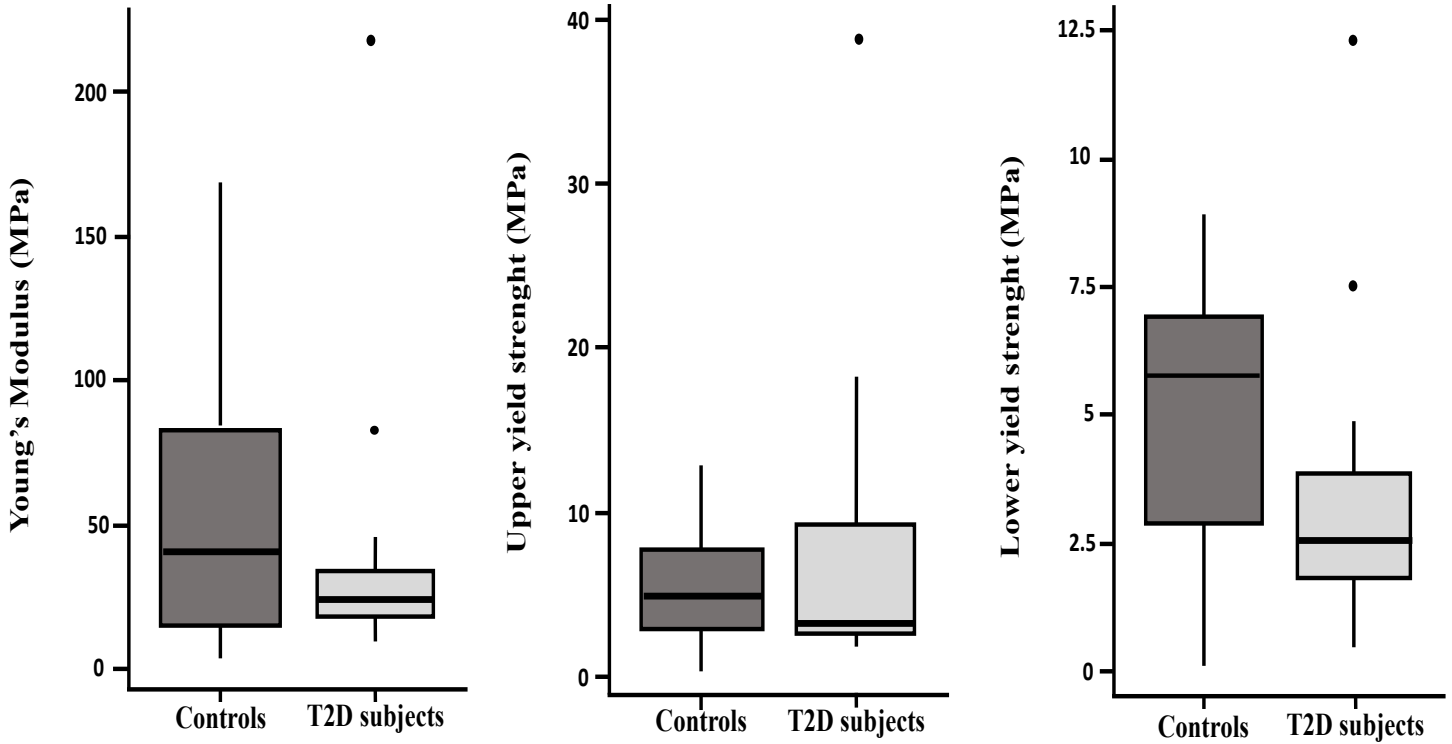


Napoli N, JBMR 2020



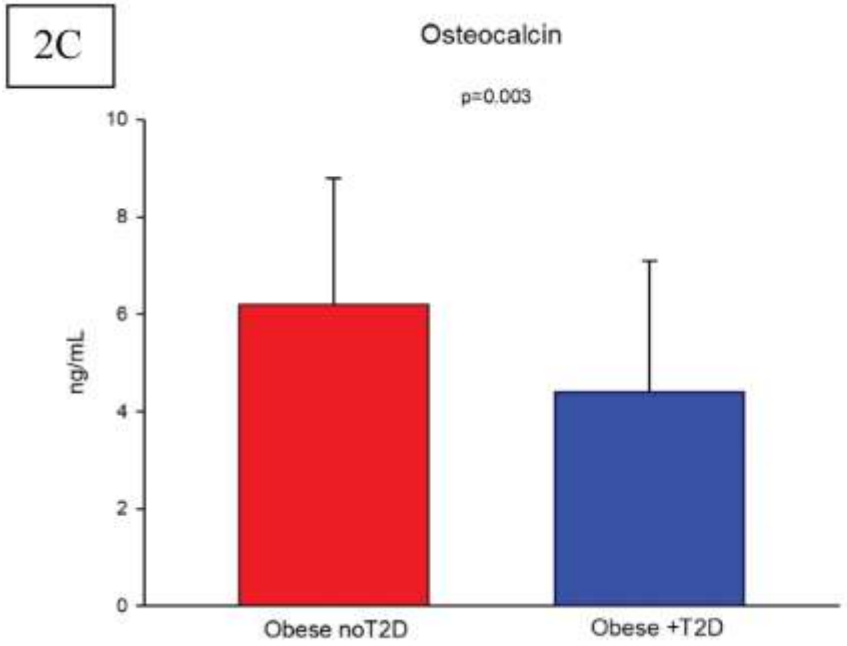
Napoli N, JBMR 2020

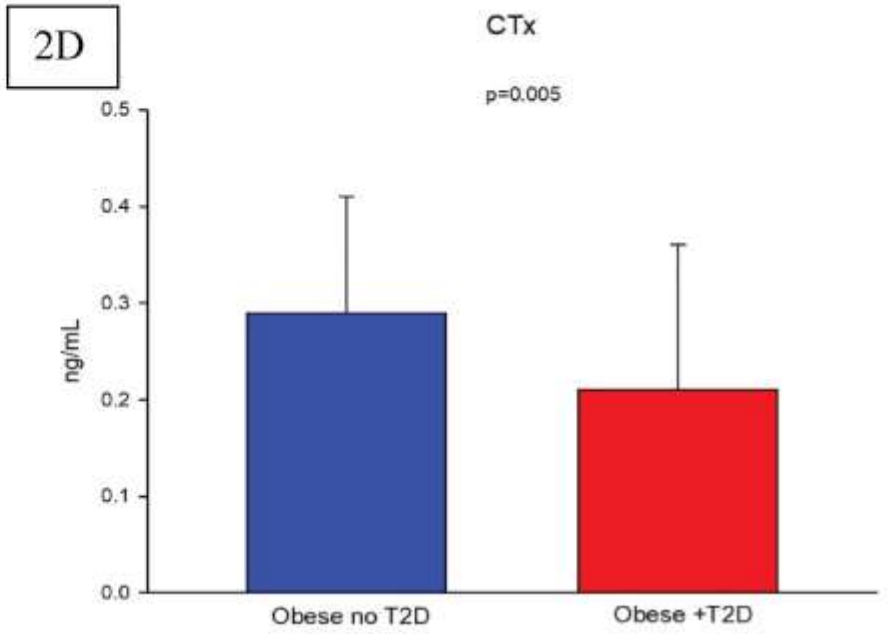
Bone strength is reduced in T2D



Napoli N, unpublished

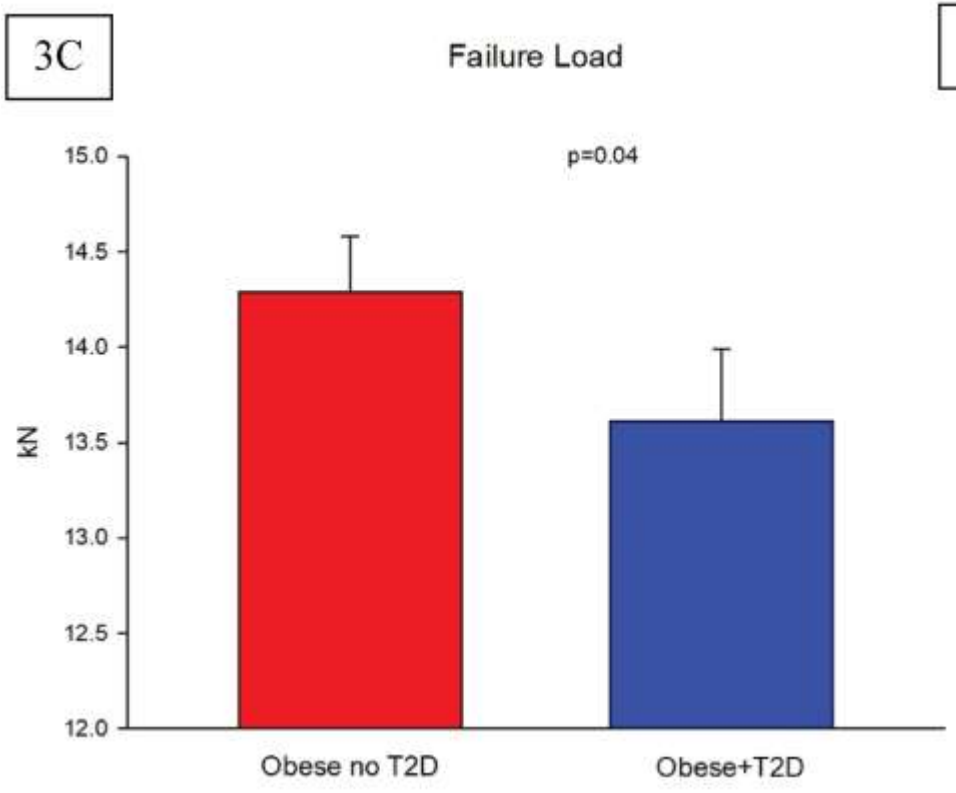
Obese T2D have lower bone turnover vs obese no-T2D

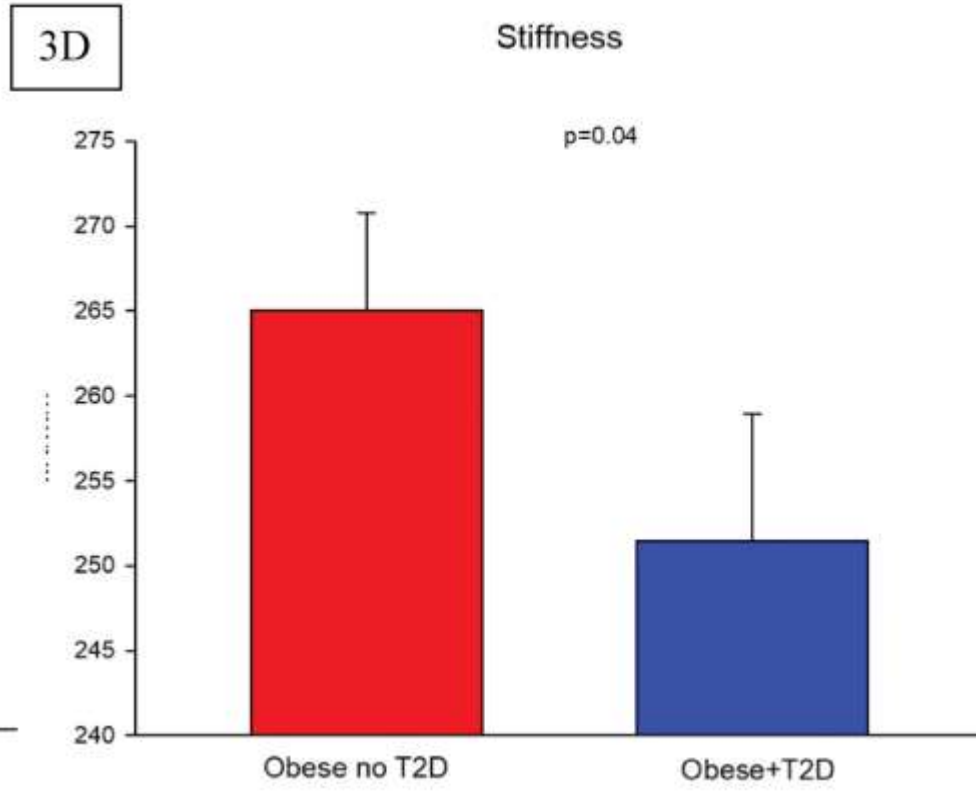




Vigevano, Napoli JCEM 2021

Obese T2D have lower bone strength vs obese no-T2D





Vigevano, Napoli JCEM 2021

Summary

SOST gene expression

RUNX2 gene expression

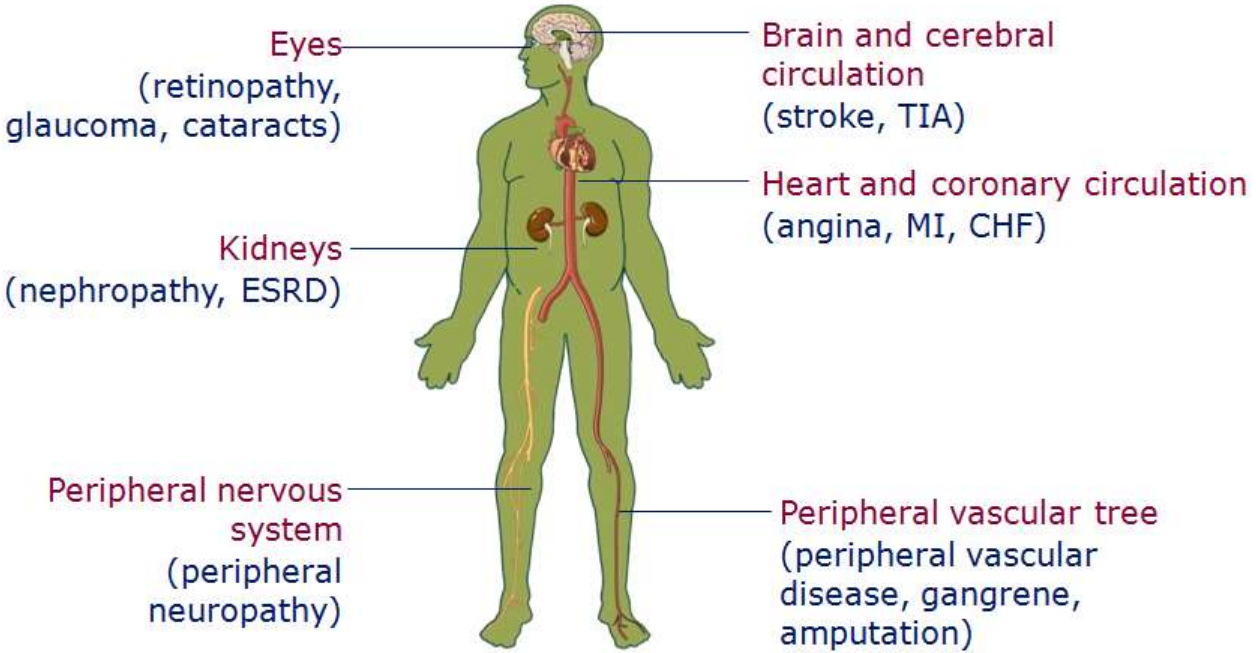
AGEs

Impaired WNT signaling

Low bone formation

Low bone quality and strength

Late stage of the disease



- **Risk of falls in diabetes:** OR 2.25, (CI 1.21–4.15)
  OR 2.76 (1.52–5.01)

CHF, congestive heart failure; ESRD, end-stage renal disease; MI, myocardial infarction; TIA, transient ischaemic attack

Adapted from *Diabetes Atlas* 4th edn. International Diabetes Federation. 2009

Diabetes complications further increased the risk for hip fractures

Risk for hip fracture among women hospitalized at least once for type 1 diabetes. Population-based cohort of 24,605 patients (12,551 men and 12,054 women)

	All hip fractures†			Femoral neck fracture		
	Exp	Obs	SHR (95% CI)	Exp	Obs	SHR (95% CI)
Total	5.2	51	9.8 (7.3–12.9)	3.4	29	8.5 (5.7–12.3)
Ophthalmic complications						
No	3.4	14	4.1 (2.3–6.9)	2.2	9	4.1 (1.9–7.8)
Yes	1.8	37	20.5 (14.5–28.3)	1.2	20	16.8 (10.3–25.9)
Nephropathic complications						
No	4.5	29	6.4 (4.3–9.2)	3.0	17	5.8 (3.4–9.2)
Yes	0.7	22	32.6 (20.4–49.4)	0.4	12	26.9 (13.9–47.1)
Neurologic complications						
No	4.6	26	5.7 (3.7–8.3)	3.0	14	4.7 (2.6–7.8)
Yes	0.6	25	41.6 (26.9–61.4)	0.4	15	37.3 (20.9–61.5)
Cardiovascular complications						
No	4.8	39	8.1 (5.8–11.0)	3.1	22	7.1 (4.4–10.7)
Yes	0.4	12	29.2 (15.1–51.1)	0.2	7	25.3 (10.2–52.2)

Miao et al. Diabetes Care 2005

Treatment

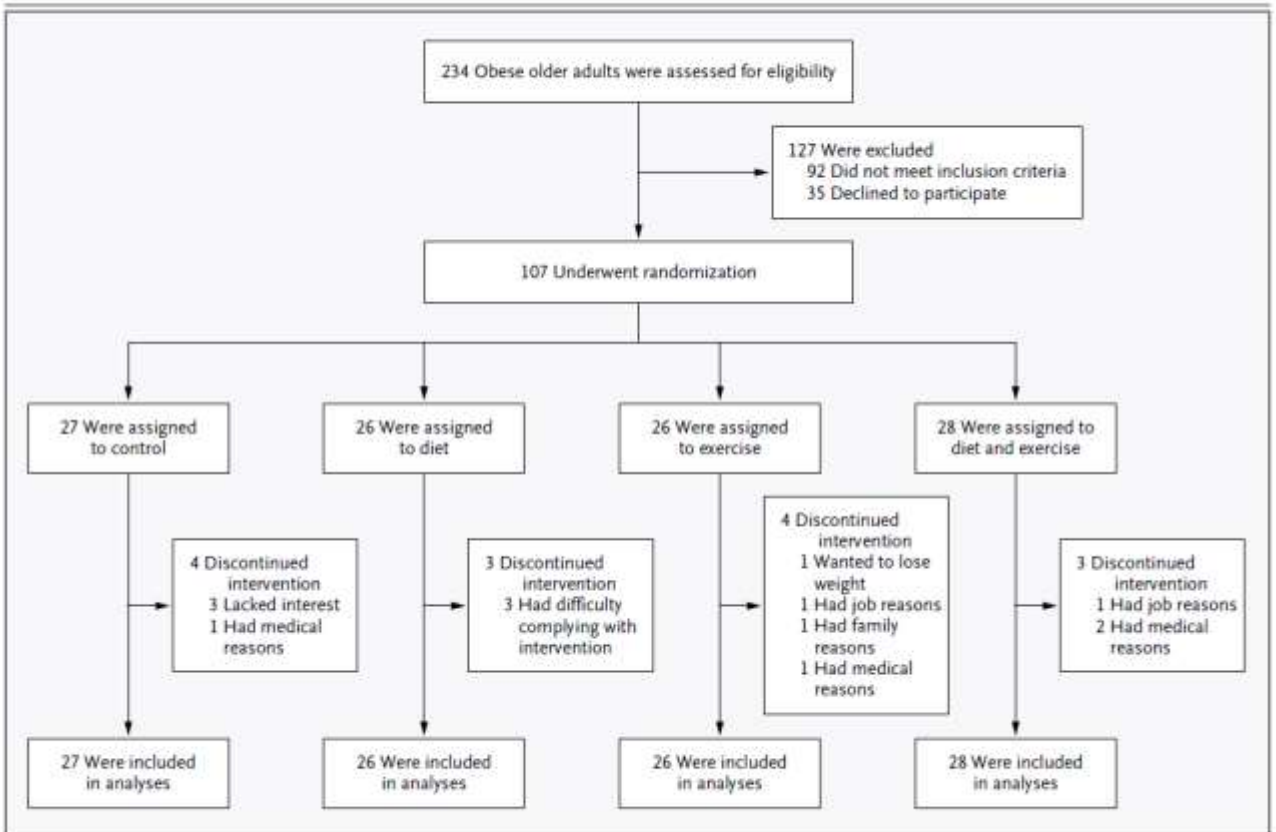
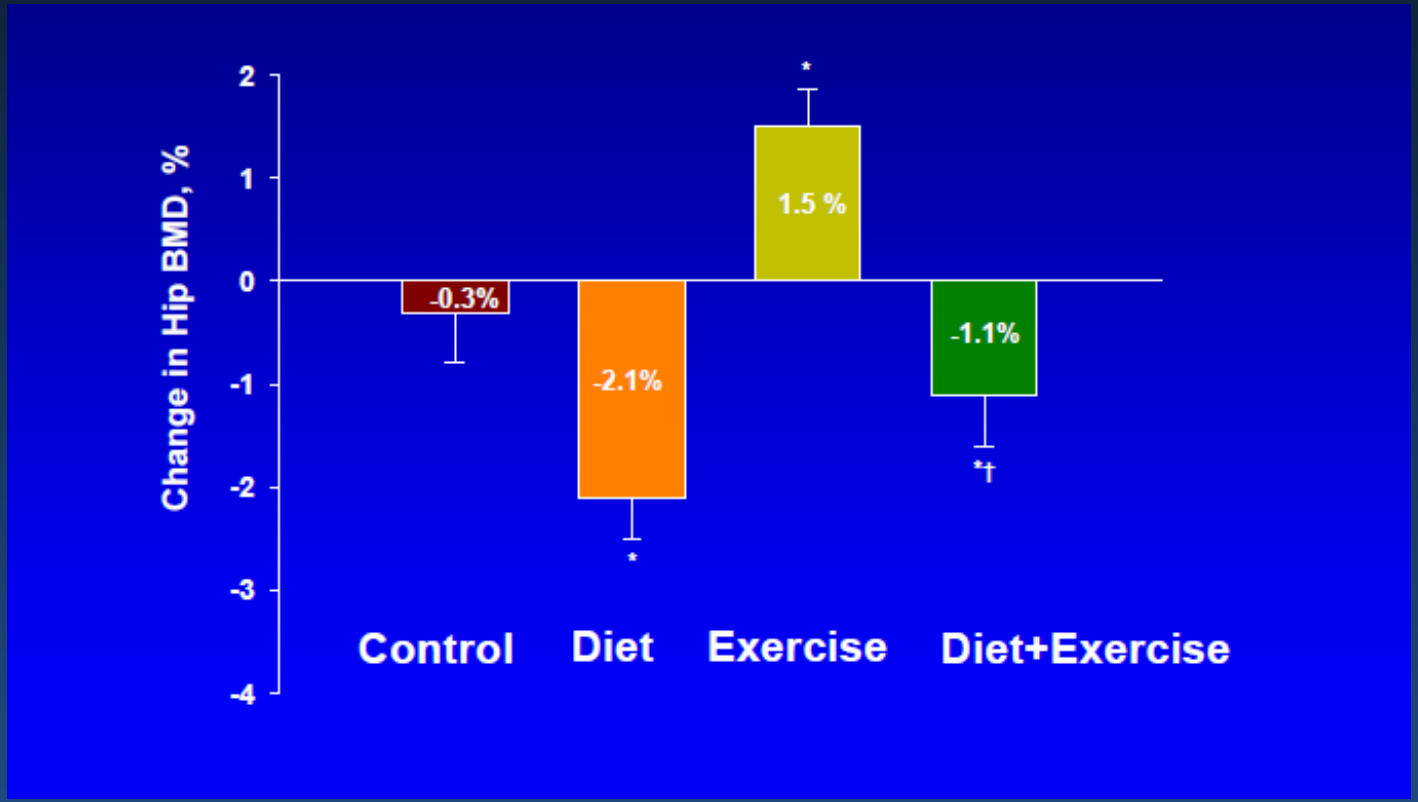


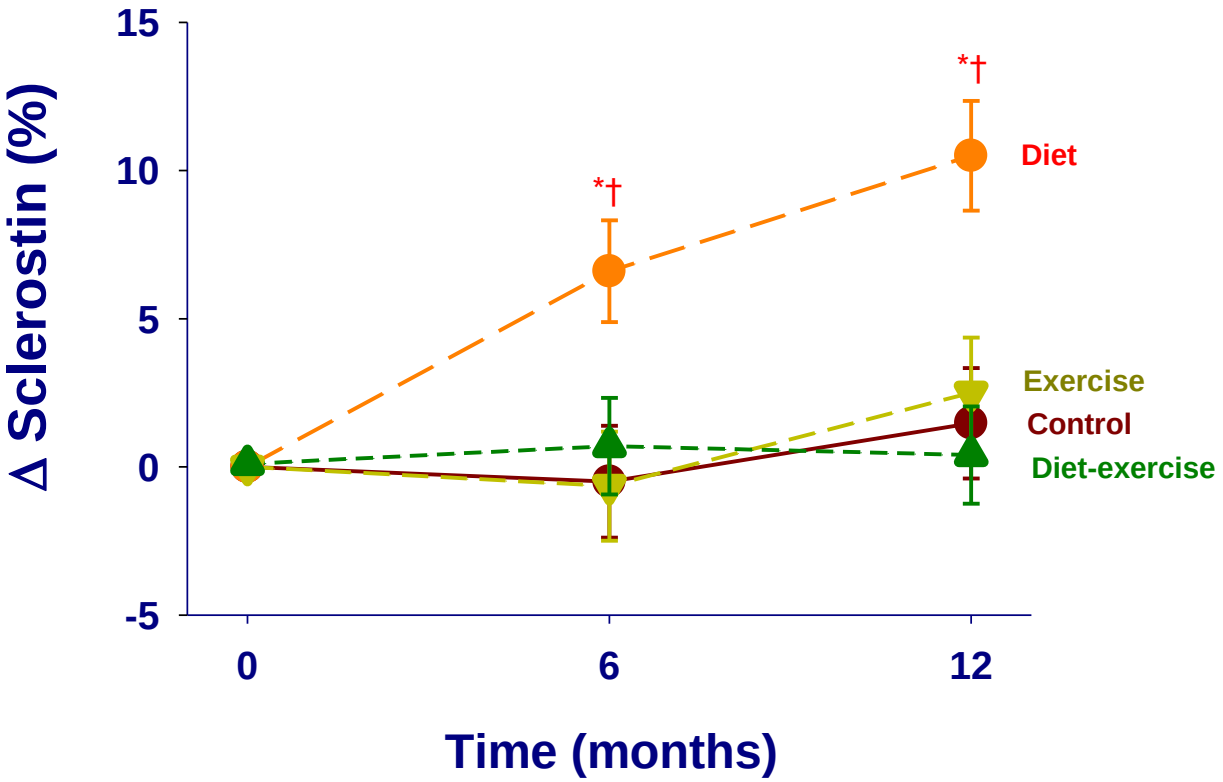
Figure 1. **Screening, Randomization, and Follow-up.**

Villareal--- Napoli et al, NEJM 2011

Changes from baseline in bone mineral density



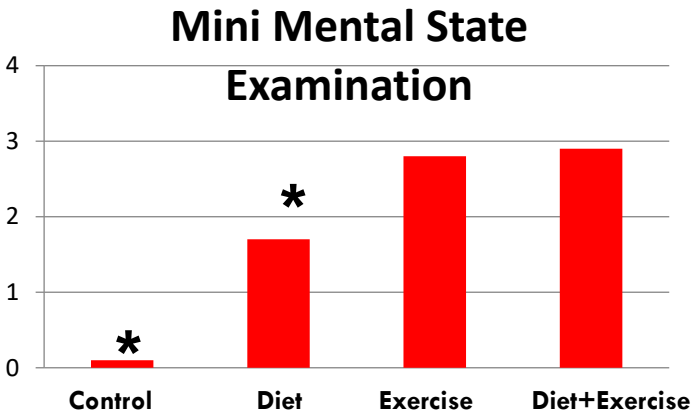
Changes in Sclerostin with lifestyle therapy

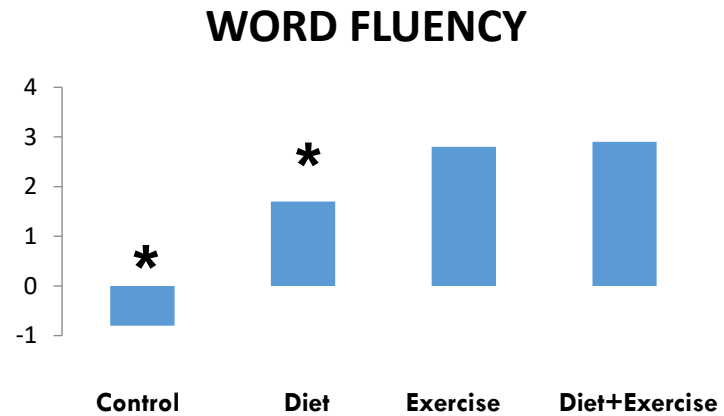


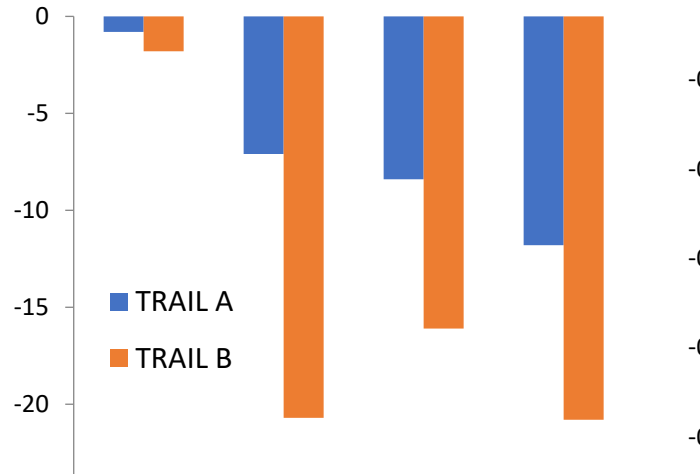
Villareal, Napoli et al, JBMR 2012

* p<0.005 vs. diet + exercise

% Change from baseline for both cognition and mood

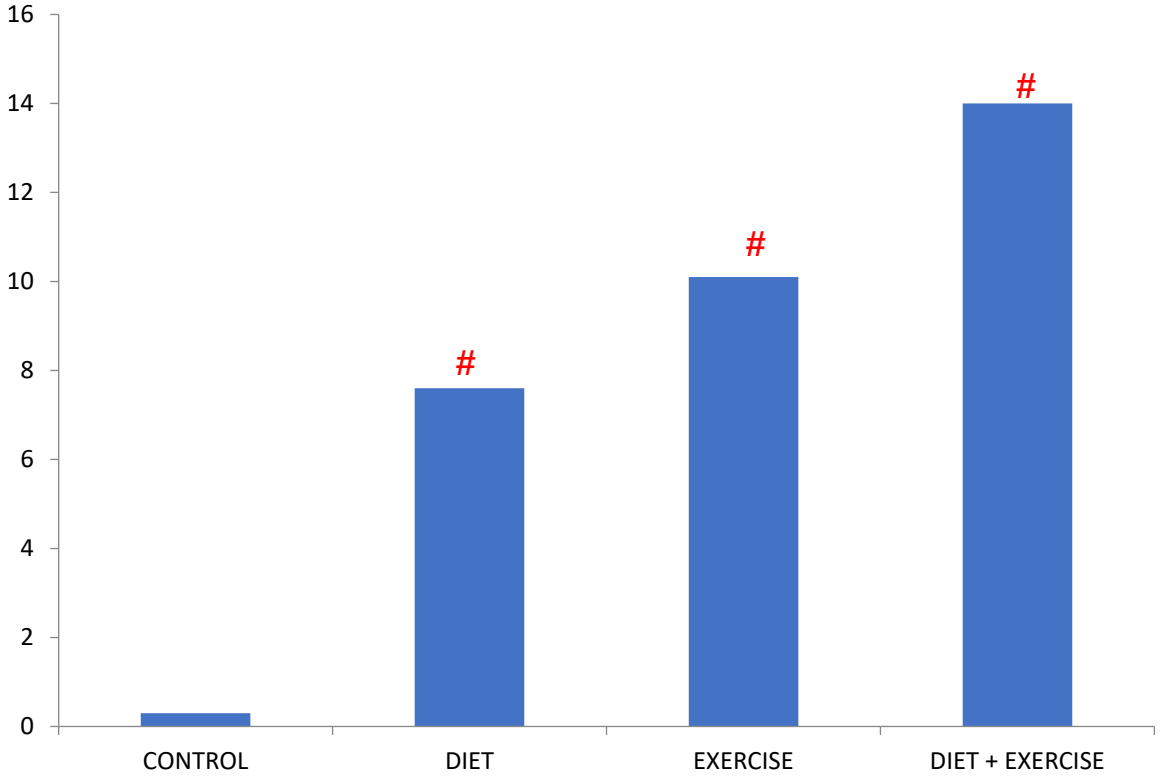






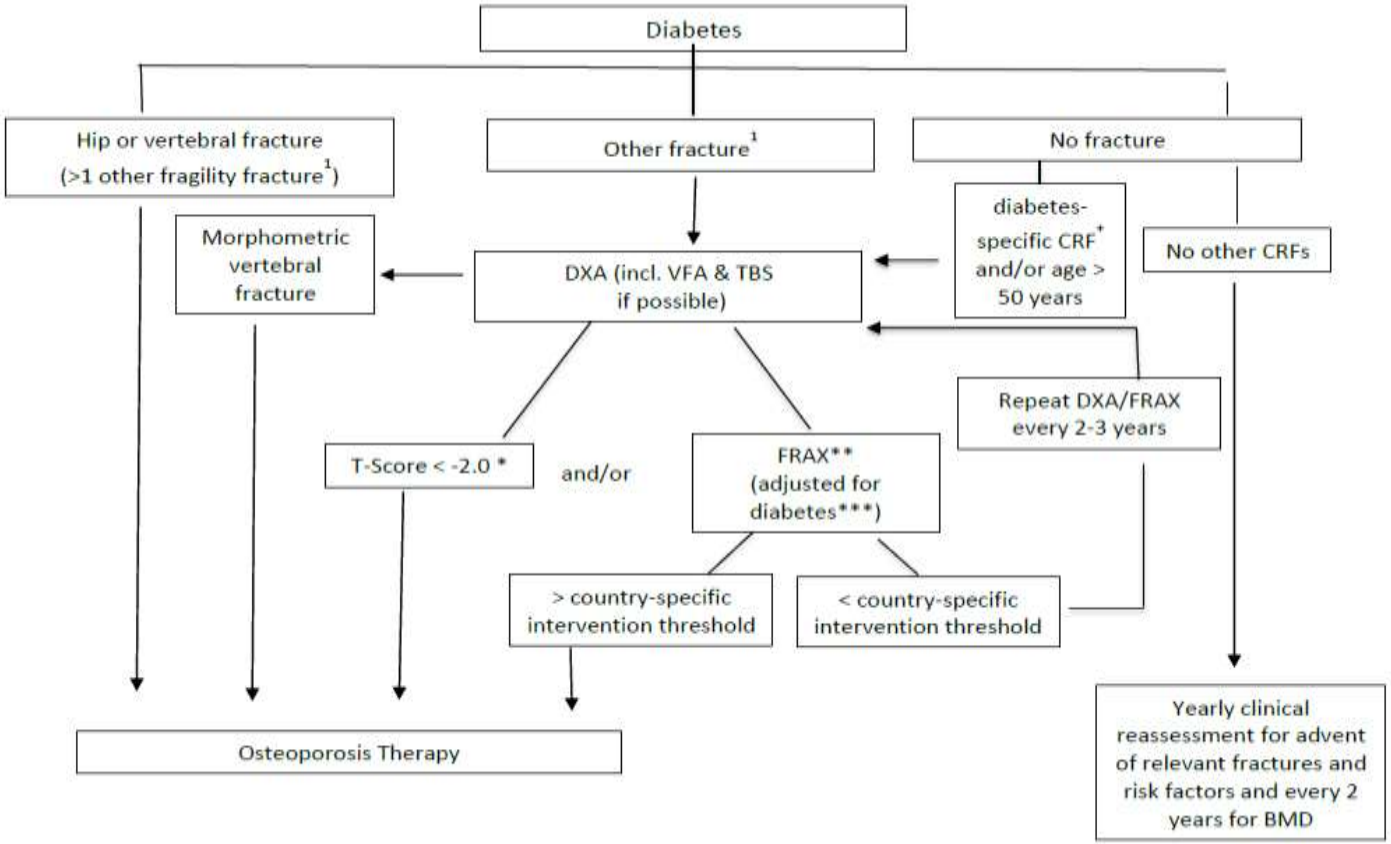
Napoli et al, Am Journ Clin Nutr, 2014

% Change in IW QUALITY OF LIFE



Napoli et al, Am Journ Clin Nutr, 2014

FRACTURE RISK PREVENTION IN DIABETIC SUBJECTS



Ferrari & Napoli, International Osteoporosis Foundation 2018 guidelines

Men using insulin had a higher risk of all non-vertebral fractures

Model	Diabetes, all[a]	IFG[b]	Diabetes, insulin use
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Unadjusted model	1.08 (0.91, 1.28)	0.93 (0.79, 1.08)	1.94 (1.35, 2.80)
2. Adjusted for age, race, clinic	1.12 (0.94, 1.34)	0.95 (0.81, 1.10)	2.24 (1.53, 3.27)
3. Adjusted for Model 1 plus total hip BMD	1.30 (1.09, 1.54)	1.04 (0.89, 1.21)	2.46 (1.69, 3.59)
4. Adjusted for Model 1 plus falls in the year before baseline	1.08 (0.91, 1.29)	0.95 (0.82, 1.11)	1.98 (1.34, 2.15)
5. Multivariable model[c]	–	1.00 (0.85, 1.18)	1.74 (1.13, 2.69)

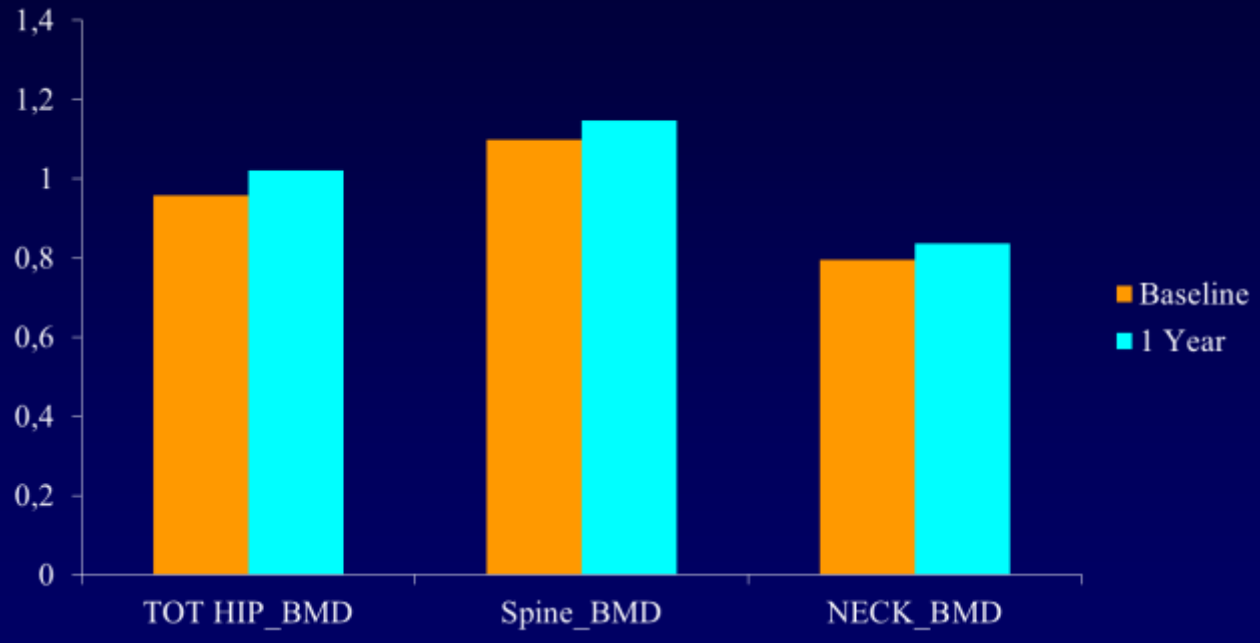
Napoli, Diabetologia, 2014

Risk factors for non-vertebral fracture in older men with diabetes

Variable	HR[a] (95% CI)
Age (per 5-year increase)	1.07 (0.88, 1.29)
Race/ethnicity	
White	1.00 (reference)
Black	0.90 (0.35, 2.29)
Hispanic	3.57 (1.44, 8.87)
Asian	1.44 (0.56, 3.77)
Total hip BMD (per 1 SD decrease[b])	1.69 (1.38, 2.06)
Fell in year before baseline (yes/no)	1.61 (1.06, 2.44)
Fasting glucose (per 1 SD increase[c])	1.02 (0.91, 1.11)
Insulin use (yes/no)	1.62 (0.78, 3.37)
Metformin use (yes/no)	0.96 (0.60, 1.54)
Sulfonylurea use (yes/no)	1.66 (1.09, 2.51)
TZD use (yes/no)	1.18 (0.64, 2.16)

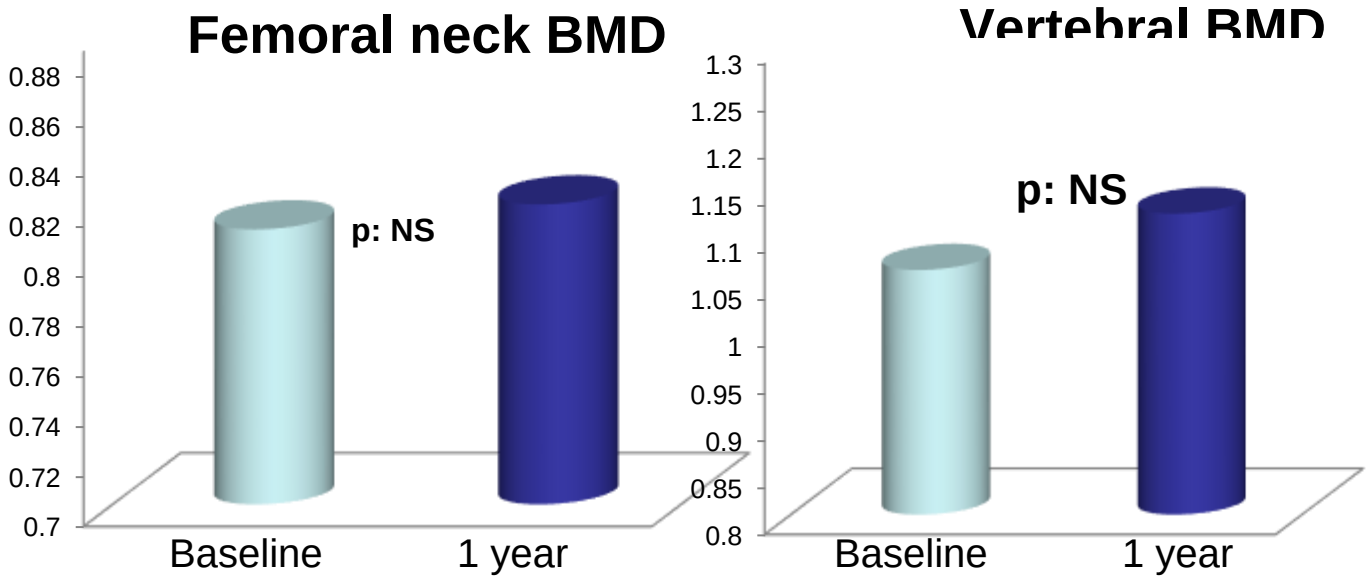
Napoli & Schwartz, Diabetologia, 2014

EFFECT OF LIRAGLUTIDE ON BMD



Napoli et al, unpublished

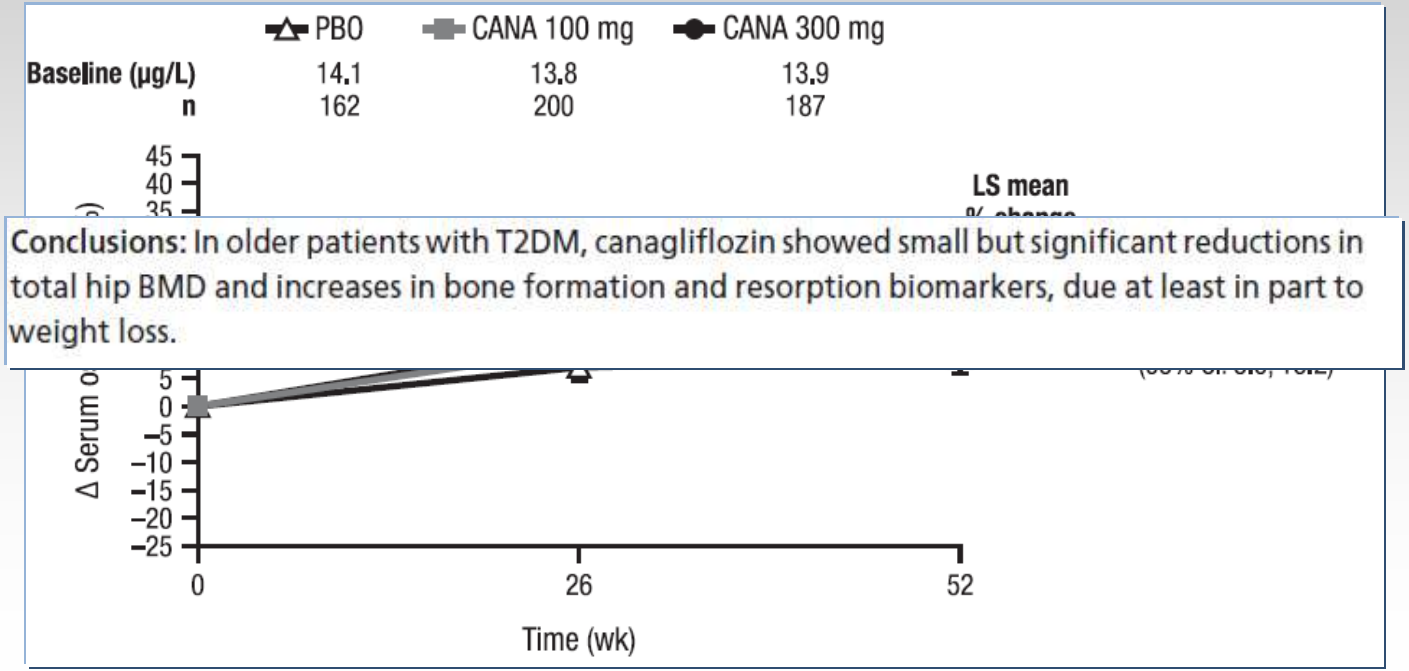
BMD changes: Sitagliptin



Evaluation of Bone Mineral Density and Bone Biomarkers in Patients With Type 2 Diabetes Treated With Canagliflozin

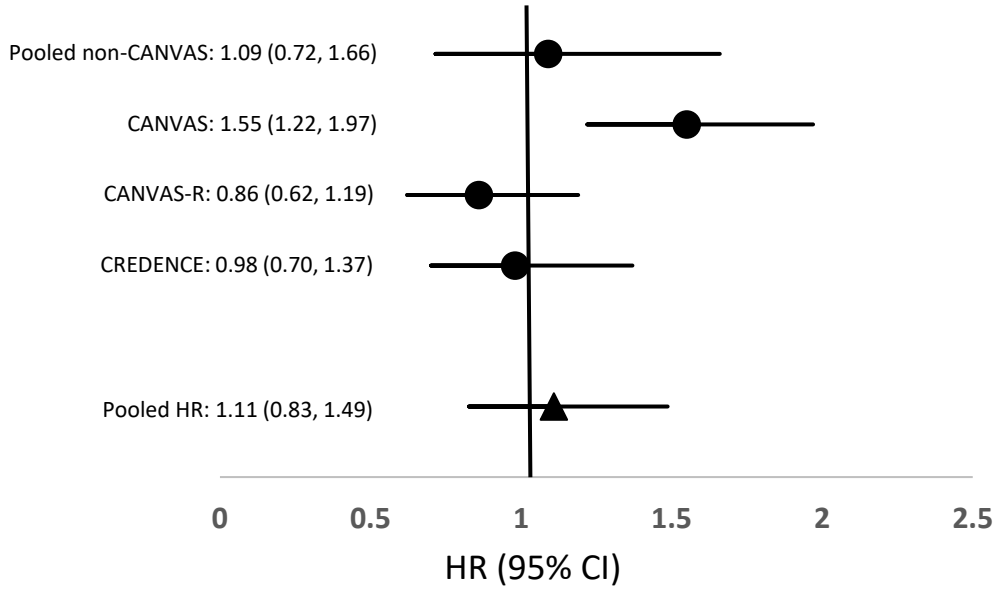
John P. Bilezikian[1], Nelson B. Watts[2], Keith Usiskin[3], David Polidori[4], Albert Fung[3], Daniel Sullivan[3], Norm Rosenthal[3]

JCEM 2015



Conclusions: In older patients with T2DM, canagliflozin showed small but significant reductions in total hip BMD and increases in bone formation and resorption biomarkers, due at least in part to weight loss.

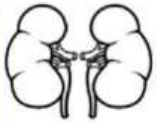
Canagliflozin and fracture risk



Napoli and Schwartz, 2020

SGLT2 Inhibitors

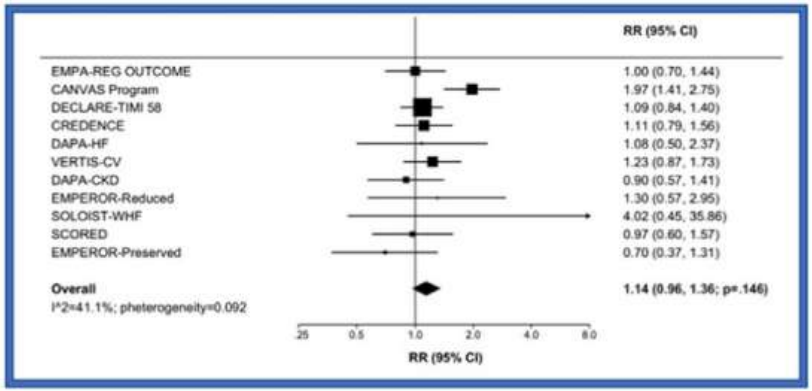
Broad cardiovascular and renal benefits in those with T2D, CKD and heart failure



Amputation

No increase in RR of amputation:

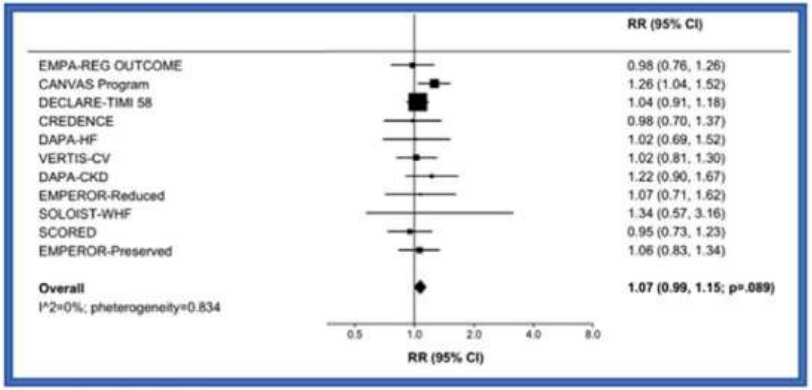
- Overall
- By individual drug
- By patient population



Fracture

No increase in RR of fracture:

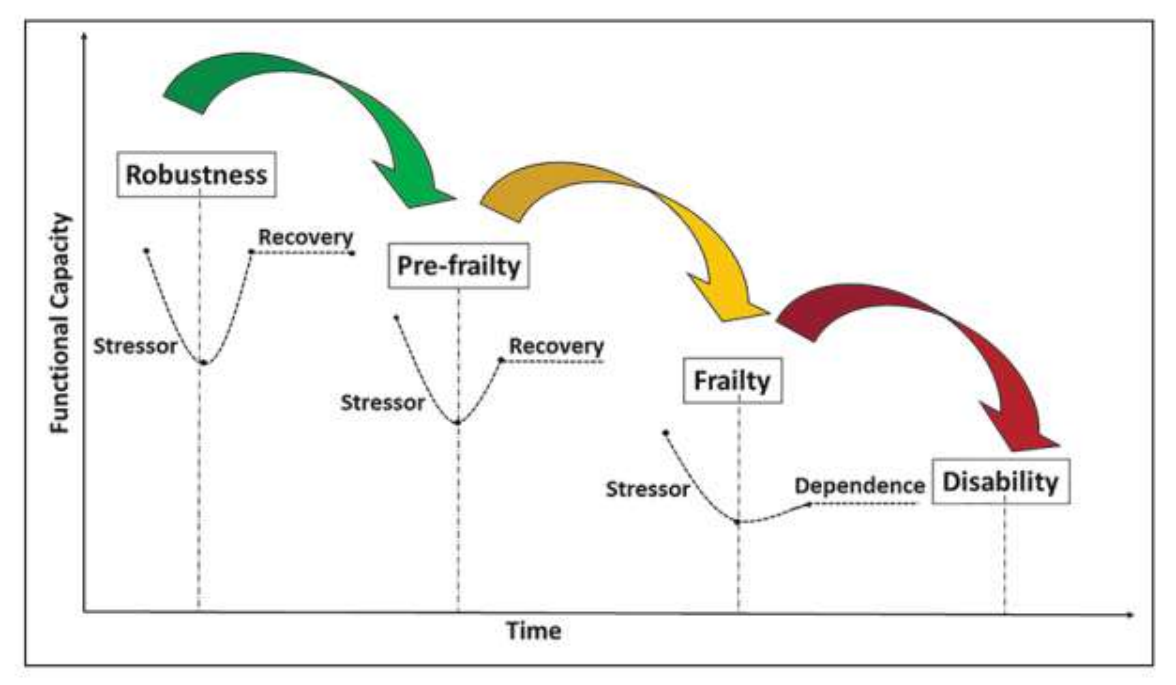
- Overall
- By individual drug
- By patient population



		Bone biomarkers		BMD	Fracture
		Bone formation	Bone resorption		
Metformin		↓/=	↓/=	=/↑	↓/=
Sulfonylureas		↑/=	↓/=	--	↓/=
Thiazolidinediones		↓↓/=/↑	↑↑/=	↓↓/=	↑↑/=
Incretin	GLP-1 analogue	=	↓↓*	↑/=	=
	DPP-4 inhibitor	↓/=	=	--	↓/=
SGLT2		=	=/↑	=	=/↑
Insulin		=	=	=	↑

Palermo, Napoli, Ost Inter 2015

Prevention of falls and frailty



Anti-osteoporosis treatment

Archives of Osteoporosis (2021) 16: 102
https://doi.org/10.1007/s11657-021-00954-1

POSITION PAPER

The Indian Society for Bone and Mineral Research (ISBMR) position statement for the diagnosis and treatment of osteoporosis in adults

Sanjay K. Bhadada[1] · Manoj Chadha[2] · Usha Sriram[3] · Rimesh Pal[1] · Thomas V. Paul[4] · Rajesh Khadgawat[5] · Ameya Joshi[6] · Beena Bansal[7] · Nitin Kapoor[4] · Anshita Aggarwal[8] · Mahendra K. Garg[9] · Nikhil Tandon[5] · Sushil Gupta[10] · Narendra Kotwal[11] · Shriraam Mahadevan[12] · Satinath Mukhopadhyay[13] · Soham Mukherjee[1] · Subhash C. Kukreja[14] · Sudhaker D. Rao[15] · Ambrish Mithal[16]

- A vertebral fracture (clinically apparent or found on vertebral imaging) or non-vertebral fracture (hip, wrist, and humerus)
- In individuals > 50 years of age with T-score ≤ − 2.5 at femoral neck or total hip or lumbar spine measured by DXA
- In individuals with osteopenia (T-score between − 1.0 and − 2.5 at the femoral neck or lumbar spine) with clinical risk factors or a 10-year probability of a hip fracture ≥ 3.5% or a 10-year probability of a major osteoporosis-related fracture ≥ 10.5% based on the FRAX tool (based on limited data in Indians)
- In individuals with type 2 diabetes mellitus, the intervention threshold should be increased to T-score ≤ − 2.0 at femoral neck or total hip or lumbar spine measured by DXA [76]

Archives of Osteoporosis (2021) 16: 102
https://doi.org/10.1007/s11657-021-00954-1

POSITION PAPER

The Indian Society for Bone and Mineral Research (ISBMR) position statement for the diagnosis and treatment of osteoporosis in adults

- Maintain serum 25-hydroxyvitamin D (25[OH] D) ≥ 20 ng/mL in all patients with osteoporosis. However, we feel that a level of 30–40 ng/mL would be ideal.
- Supplement with vitamin D3 if needed; 1000 to 2000 international units (IU) of daily maintenance therapy is typically required to maintain an optimal serum 25(OH)D level in Indians.
- Higher doses of vitamin D may be necessary in the presence of certain factors (e.g., obesity, malabsorption, older individuals)
- Counsel patients to maintain adequate dietary intake of calcium with a total intake (including diet plus supplement, if needed) of at least 1000 mg/day for women > 50 years [3]

- Approved agents with efficacy to reduce hip, non-vertebral, and spine fractures include alendronate, risedronate, zoledronic acid, and denosumab, and these are appropriate as initial therapy for most patients at risk of fracture. Often, oral bisphosphonates are preferred in low and moderate risk cases.

Recommendations for initial first-line therapy for individuals with prevalent vertebral fractures

- Teriparatide is an effective anabolic agent to initiate therapy in these cases, which to be continued for 24 months and followed by antiresorptives.
- Intravenous zoledronic acid or denosumab are also effective options. Since the protocol for discontinuing denosumab is still not firmly established, zoledronic acid is usually preferred as initial therapy for 3–5 years.
- Oral bisphosphonates can be used if the patient wants to avoid injectable therapies.

Original Article

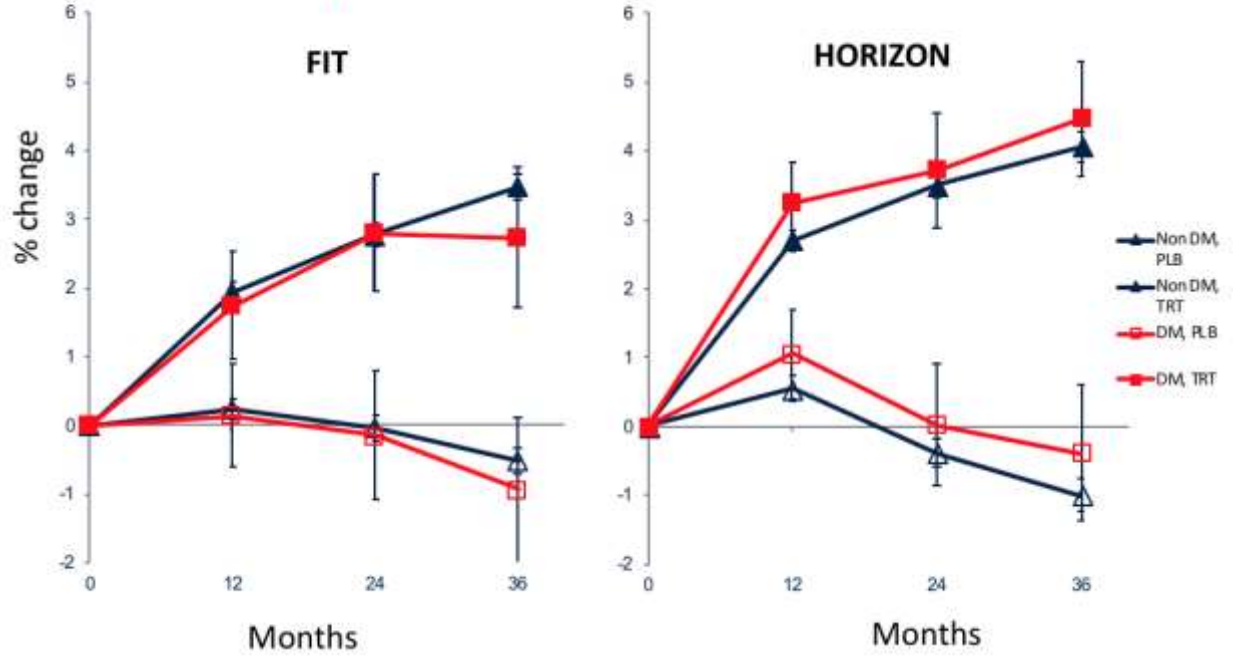
Osteoporosis in a Rural Community – Long-Term Effects of a Community Level Program of Calcium and Vitamin D Supplementation – A Prospective Observational Study

Mandalam S. Seshadri, Manigandan Gopi, Priyanka Murali, Kaliyaperumal Kumar
Department of Medicine and Endocrinology, Thirumalai Mission Hospital, Vanapadi Road, Ranipet, Vellore, Tamil Nadu, India

Editorial

Falls, Fractures, and Mortality: The Role of Calcium and Vitamin D Replacement in Rural India

Femoral Neck BMD – Placebo v Treatment, by Trial and Diabetes status

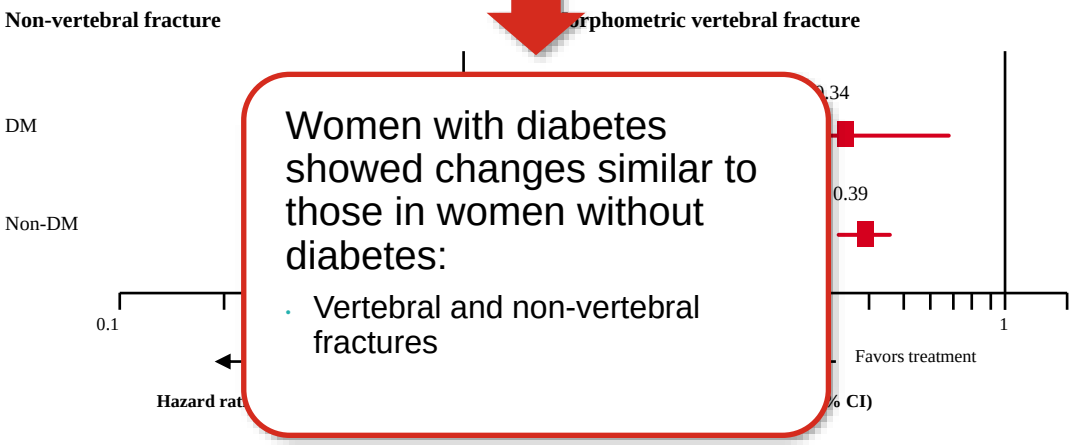


Schwartz A. Bisphosphonates reduce fracture risk in postmenopausal women with diabetes: Results from FIT and HORIZON trials. Presented at: American Society for Bone and Mineral Research,

- Bisphosphonates

Post hoc combined subgroup analysis

Alendronate (FIT) and zoledronic acid (HORIZON)



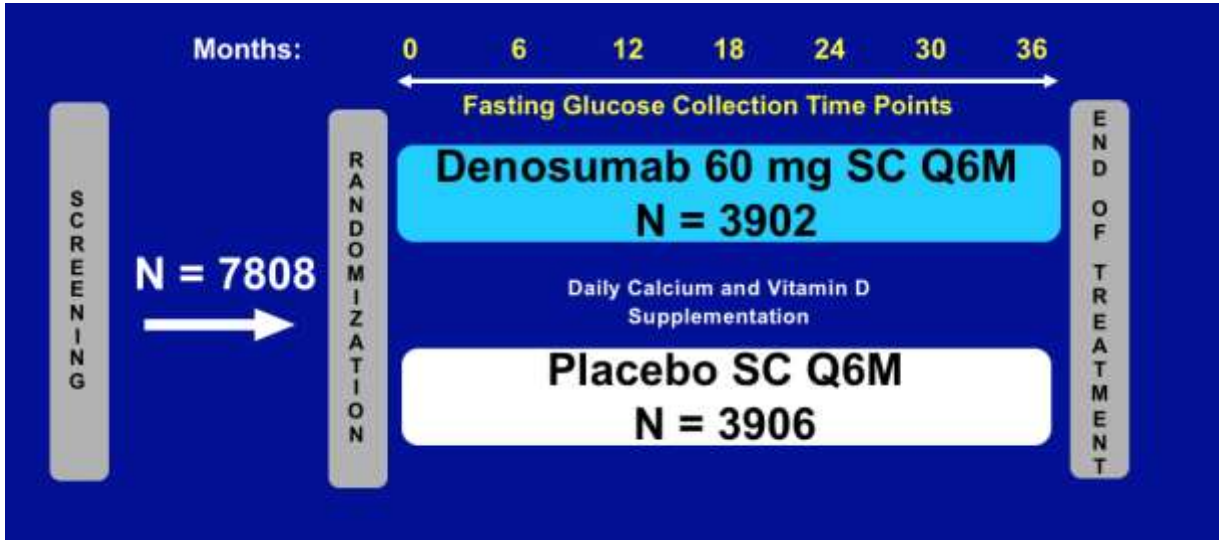
Women with diabetes showed changes similar to those in women without diabetes:

- Vertebral and non-vertebral fractures

FIT=Fracture Intervention Trial; HORIZON=Health Outcomes and Reduced Incidence with Zoledronic Acid

Schwartz A. Bisphosphonates reduce fracture risk in postmenopausal women with diabetes: Results from FIT and HORIZON trials. Presented at: American Society for Bone and Mineral Research,

FREEDOM Study Design

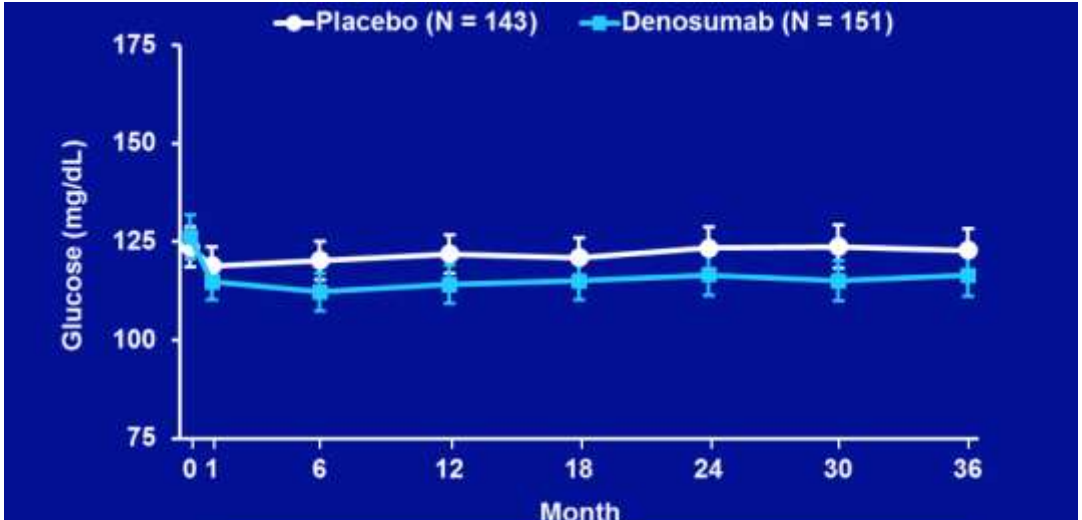


Key Inclusion Criteria

- Postmenopausal women age 60 to 90 years
- T-score < –2.5 at the lumbar spine or total hip, but not < –4.0 at either site
- No severe and ≤ 2 moderate vertebral fractures
- Vitamin D level ≥ 12 ng/mL and calcium within normal range

Cummings SR, et al. *N Engl J Med* 2009;361:756-765.

Subjects With Diabetes treated with denosumab have lower fasting glucose than those treated with placebo

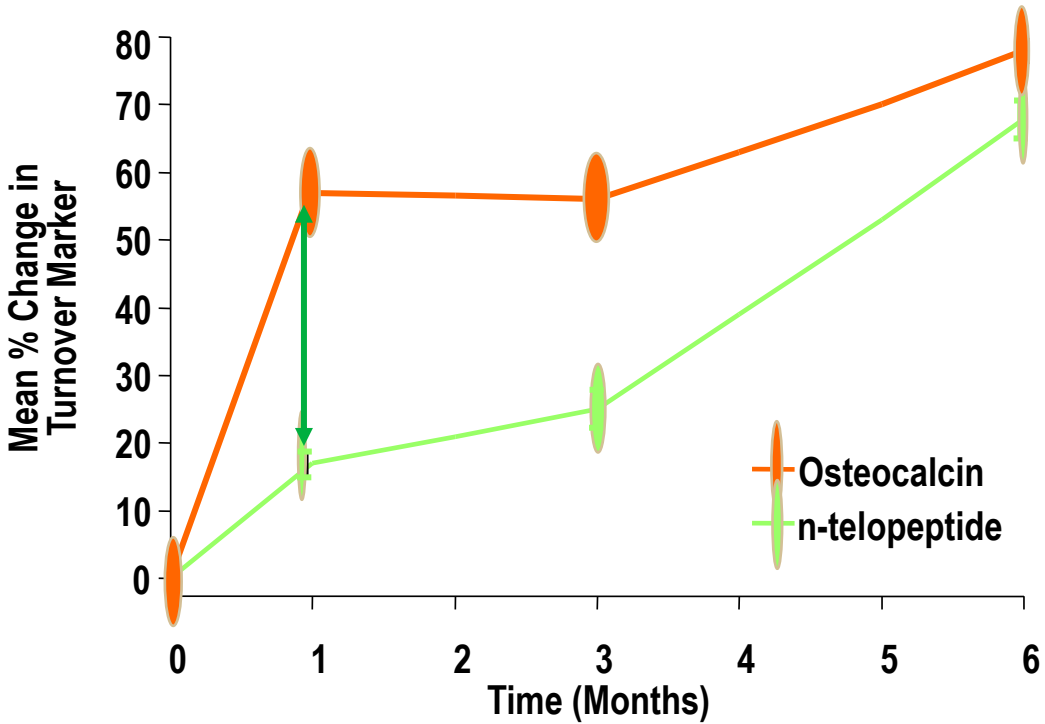


Difference in Post-baseline FSG (Denosumab – Placebo)[a]		
LS Mean	95% CI	*p* value
– 6.8	– 12.6, –1.0	0.022

Napoli et al, DMRR 2018

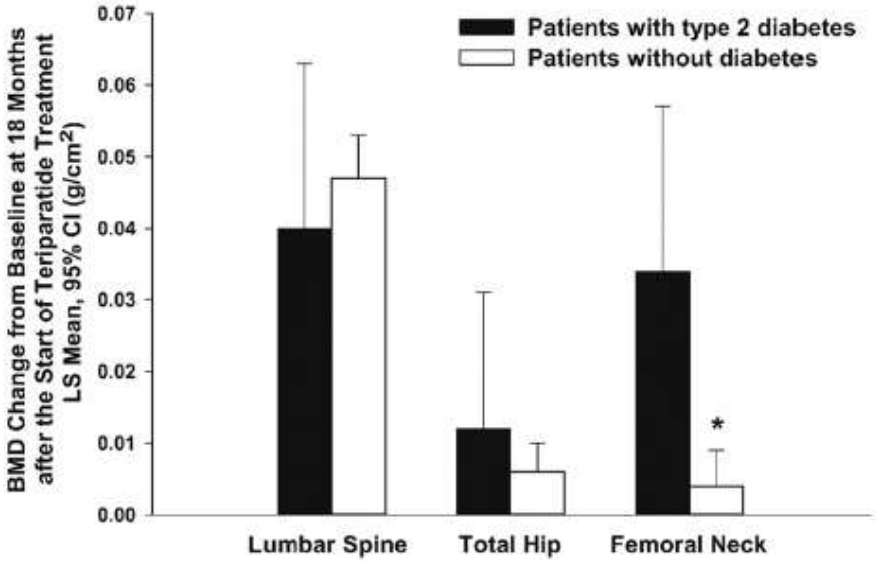
TERIPATIDE is anabolic:

Bone Formation Markers increase before Bone Resorption Markers



Lindsay R, et al. Lancet. 1997;350(9077):550-555.

Change from baseline in BMD 18 months after teriparatide initiation

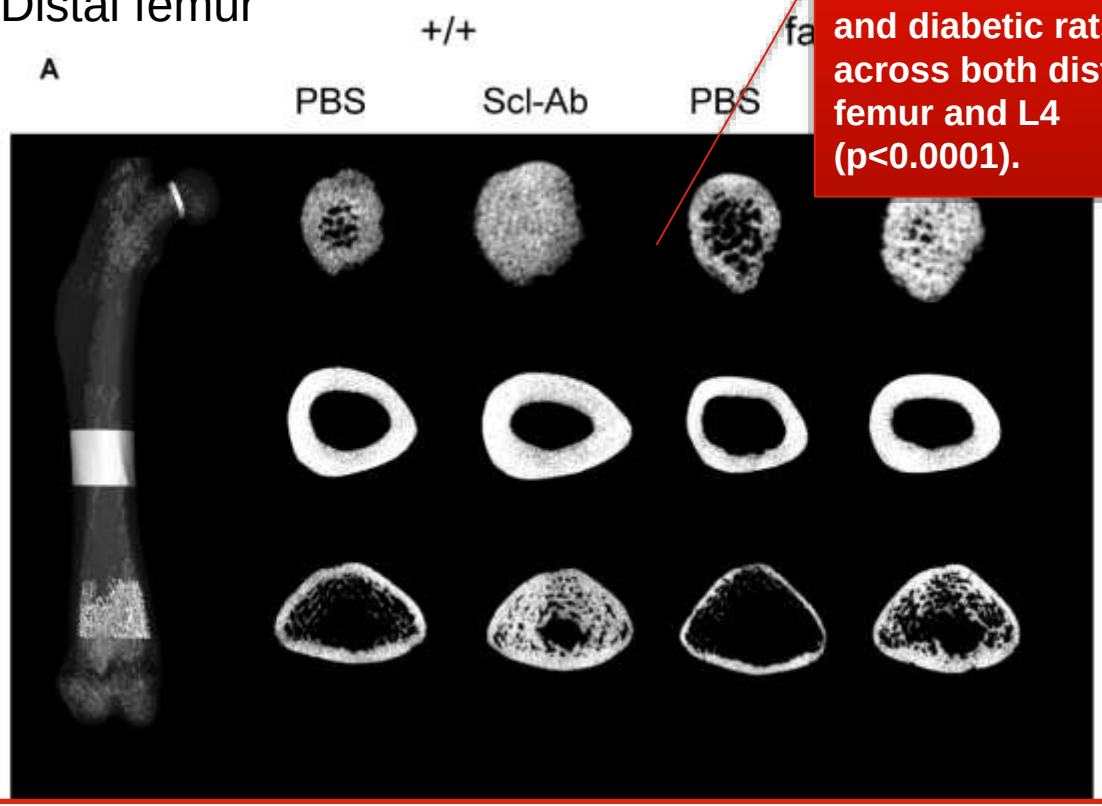


DXA	n	n	n	n	n	n
Baseline	60	1052	51	883	61	1053
6 months	3	130	2	124	3	137
12 months	30	479	25	402	30	471
18 months	30	594	27	514	31	607

Schwartz AV et al. Bone. 2016 Oct;91:152-8

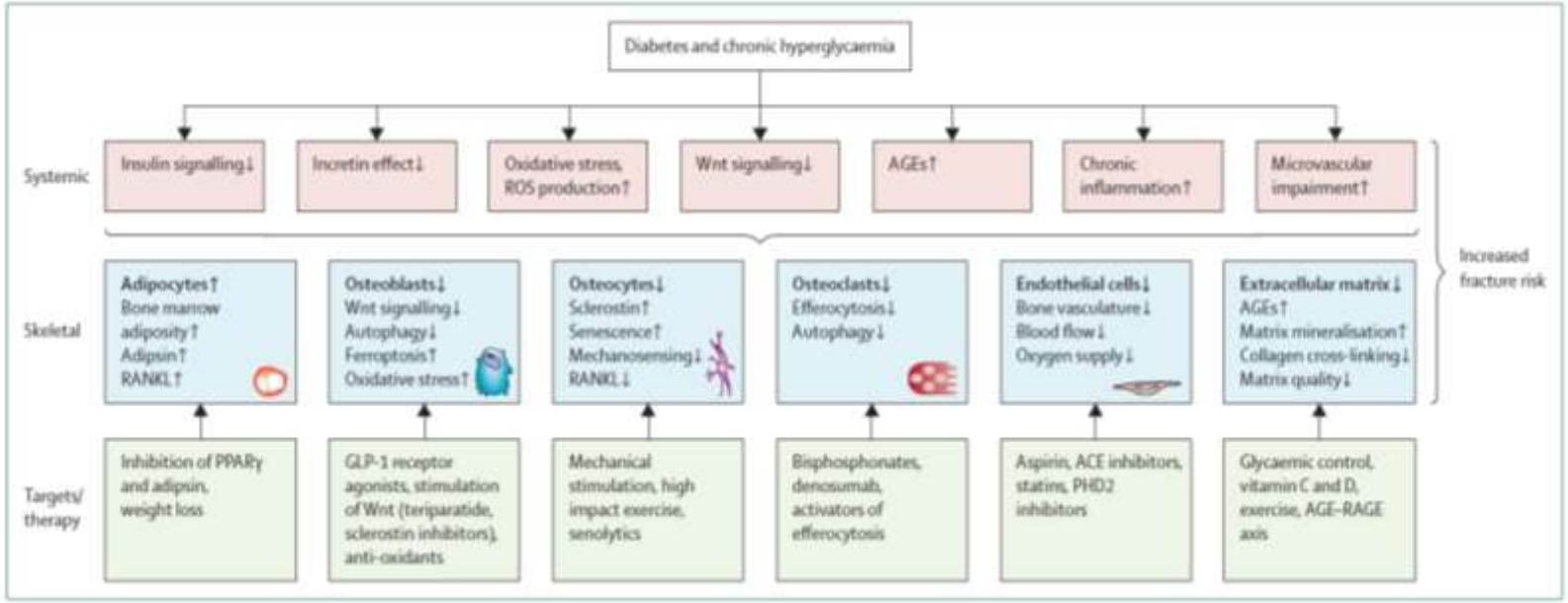
Sclerostin Antibody Treatment

- Distal femur



Treatment with Scl Ab significantly increased trabecular bone in nondiabetic and diabetic rats across both distal femur and L4 ($p<0.0001$).

C. Hamann et al. *J Bone Miner Res*. 2013 Mar;28(3):627-38.



Hofbauer, Napoli, Rauner, Lancet DE 2022

The impact of diabetes

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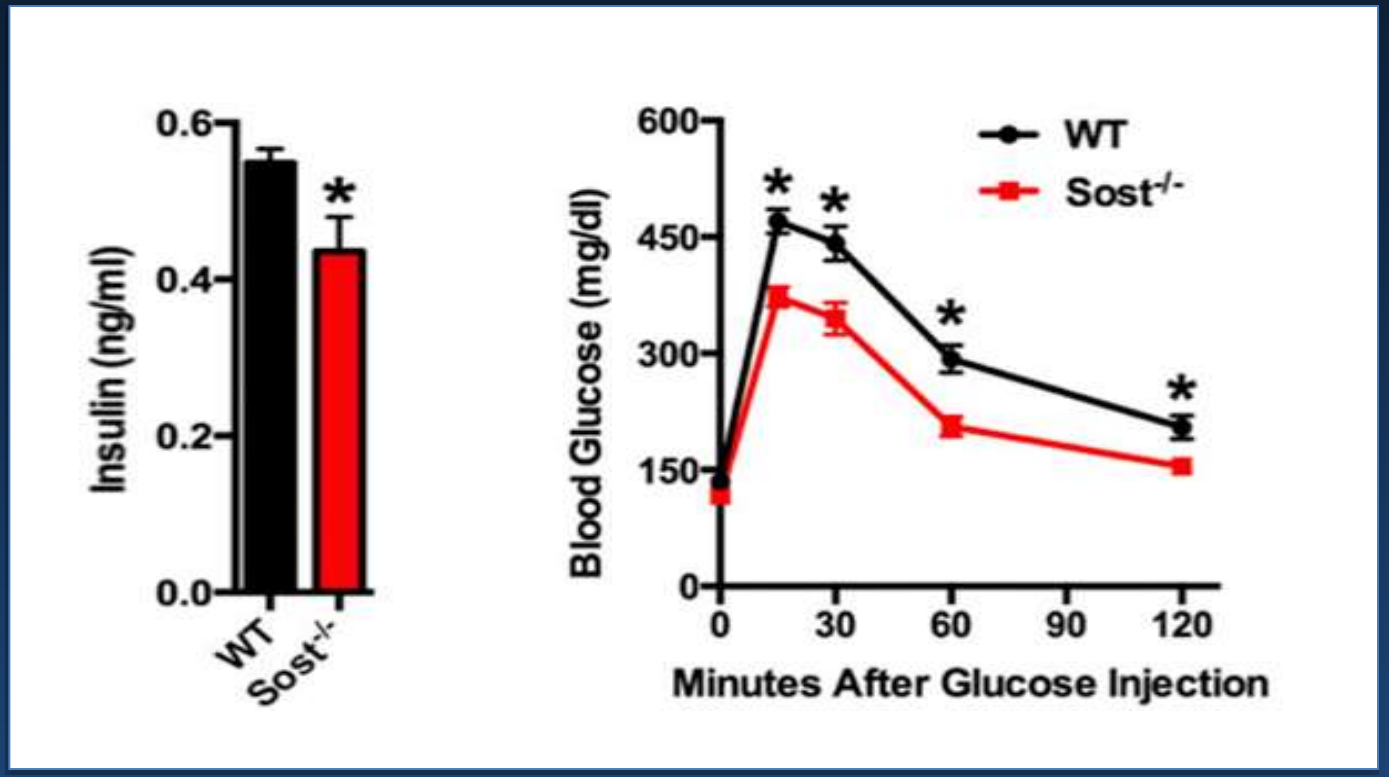
Flavia Tramontana

Ann Schwartz
Dennis Black

Prof. R. Papalia
Prof. V Denaro
Prof. G Vadalà
Prof CIVITELLI LAB
Prof Matt Silva

CAN WE REVERT WNT FATE?

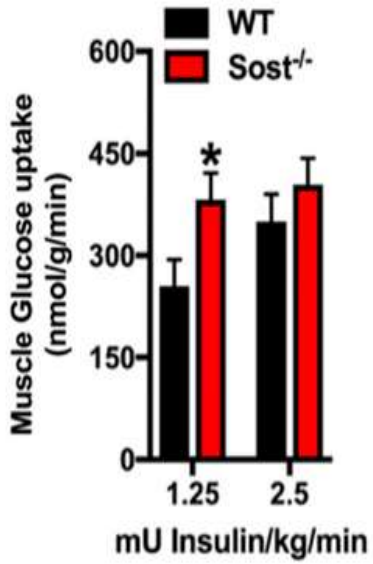
Increased glucose tolerance in Sost$^{-/-}$ mice

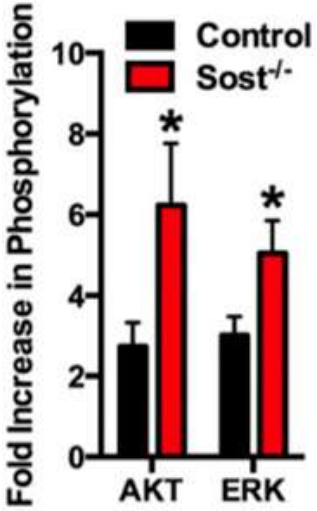


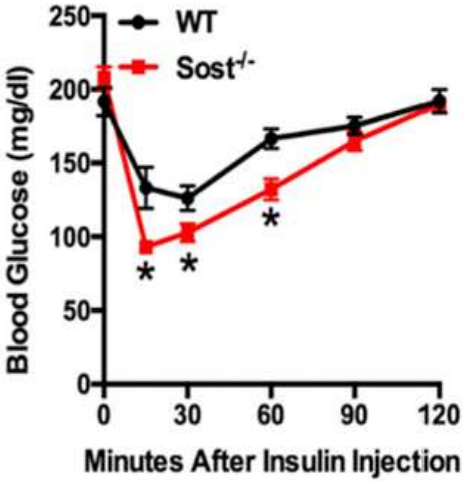
16-week-old; n= 6-8 mice/group

Kim SP et al., PNAS 2017

Increased insulin sensitivity in Sost$^{-/-}$ mice







Kim SP et al., PNAS 2017

Premise

Wnt signaling inhibition (by higher sclerostin production) contributes to reduced bone mass and strength in T1D

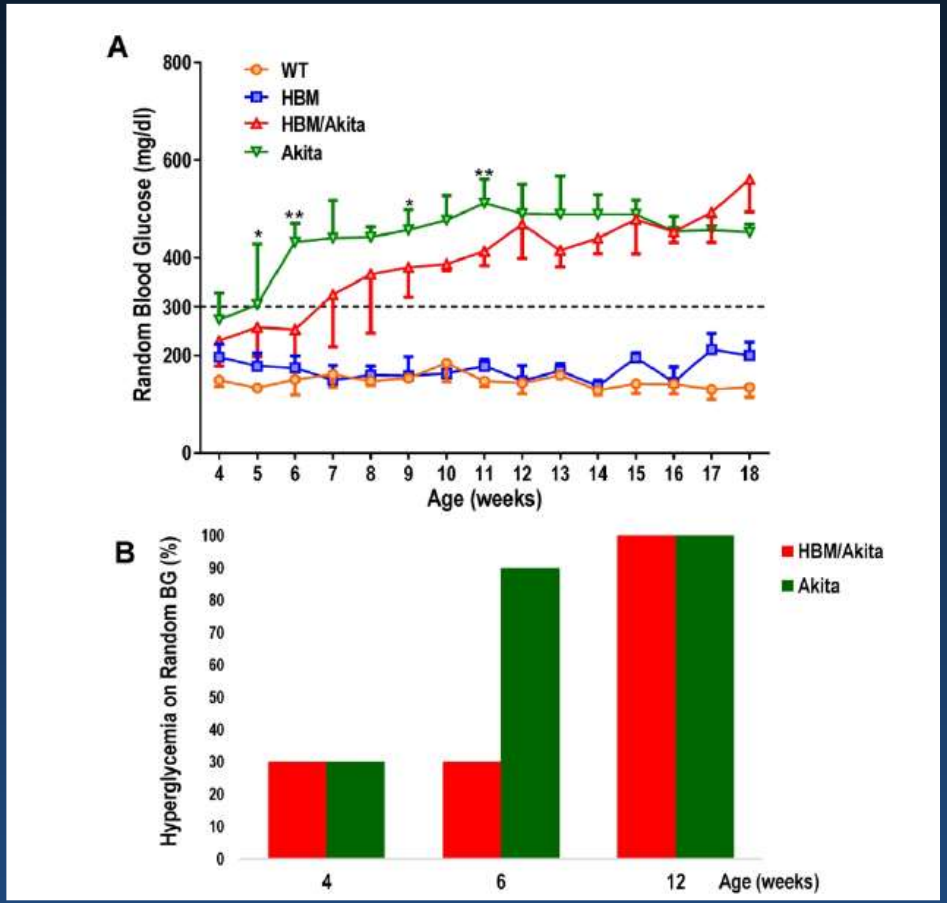
Hypothesis

Wnt signaling hyperactivation by a sclerostin-insensitive Lrp5 mutation protects bone mass, architecture and strength in T1D

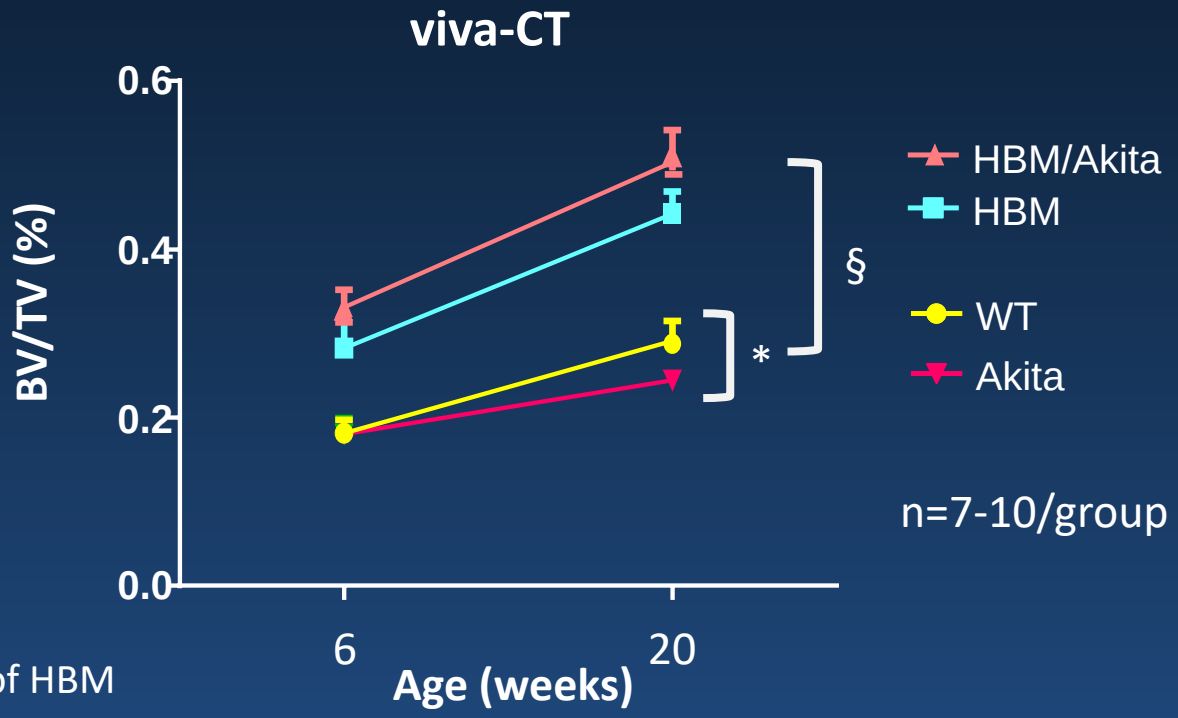
Experimental Approach

We used only male littermates

HBM Mutation delays onset of hyperglycaemia



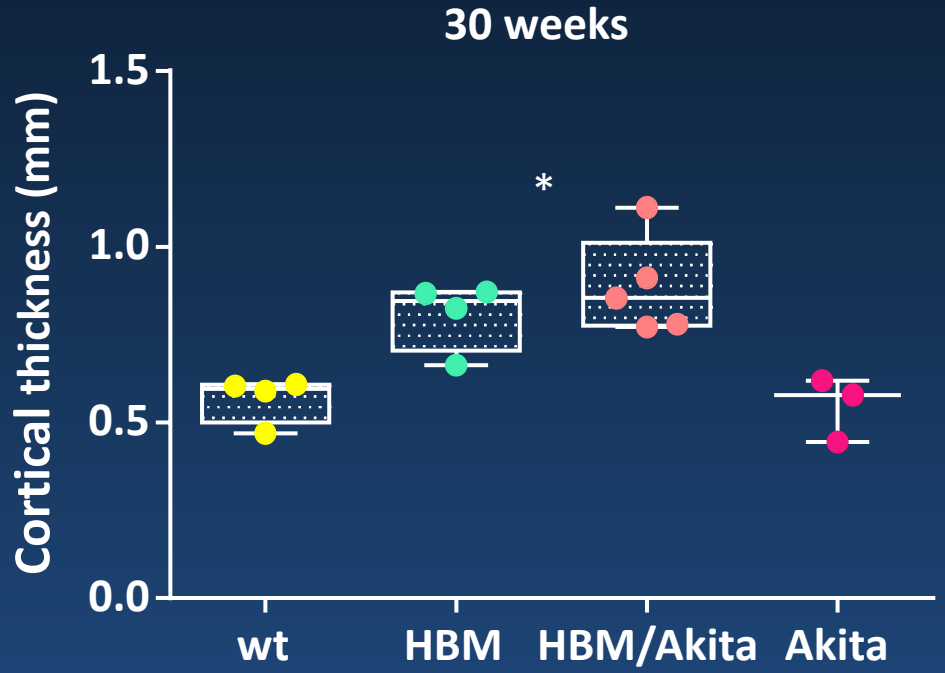
HBM/Akita Maintain High Volumetric Trabecular Bone Mass Despite Diabetes



§p<0.001 for the effect of HBM

*p<0.05 for the interaction between wt and Akita

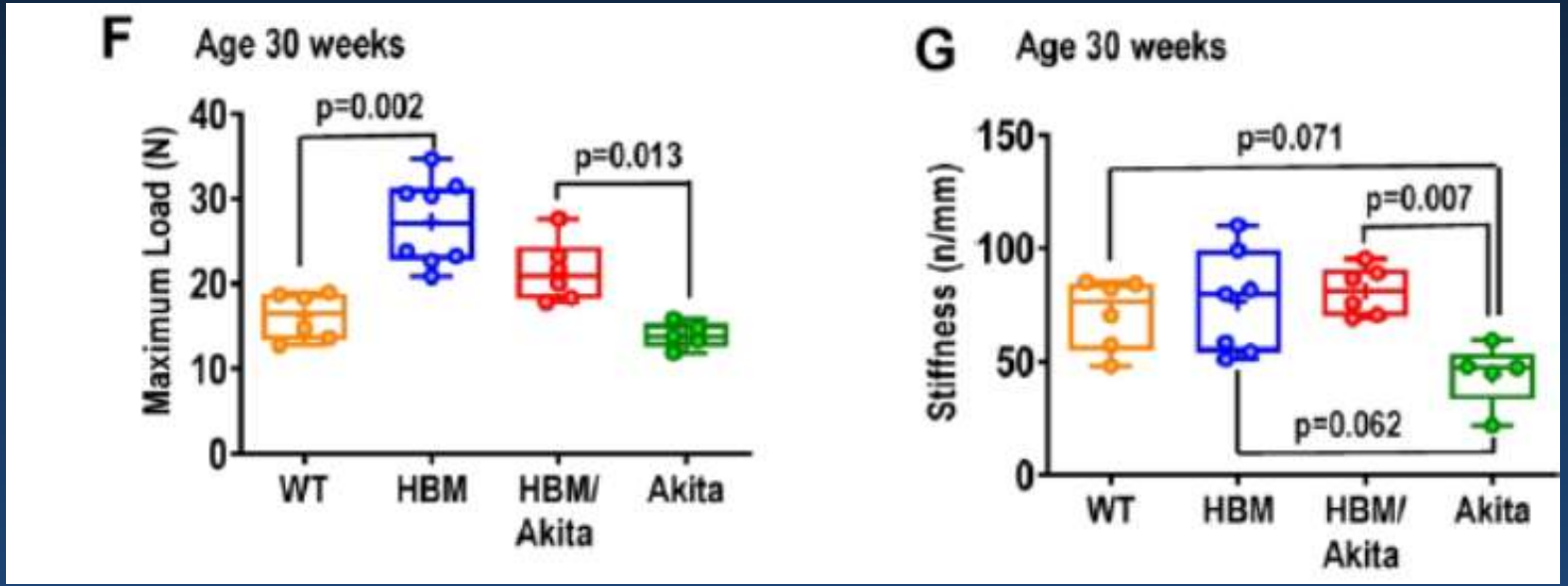
HBM/Akita Maintain High Volumetric Cortical Bone Mass Despite Diabetes



*p<0.001 for the effect of HBM

HBM/Akita Maintain Elevated Bone Strength Despite Diabetes

30 weeks



*p<0.001 for the effect of HBM

Summary

Genetic Wnt signaling activation

- ✓ Overrides the effect of T1D on bone mass and bone strength
- ✓ Retards the onset of glucose abnormalities, despite lack of insulin

Conclusions

- Wnt signaling may provide a common thread between bone and energy metabolism.
- Activated Wnt signaling improves bone mass, microarchitecture and strength in insulin-deficient diabetes and has positive effects on glucose homeostasis.

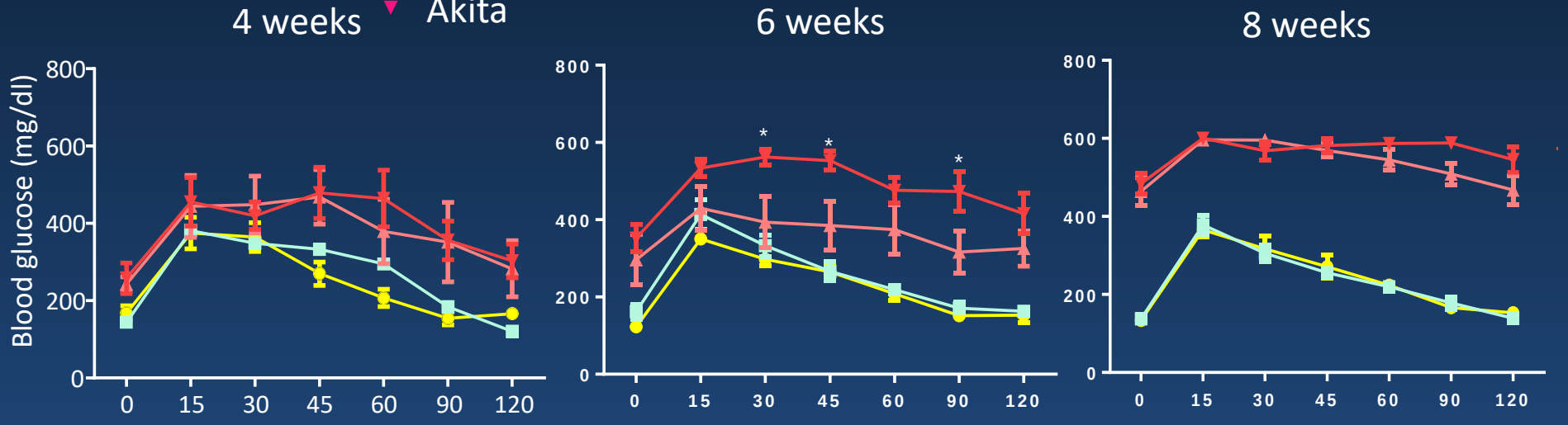
Does Wnt signaling hyperactivation through sclerostin-insensitive Lrp5 mutation improve glucose metabolism in T1D?

HBM Mutation Improves Glucose Tolerance in Diabetic Mice

ip Glucose Tolerance Test (IPGTT)

n=5-9/group

wt
HBM
HBM/Akita
Akita

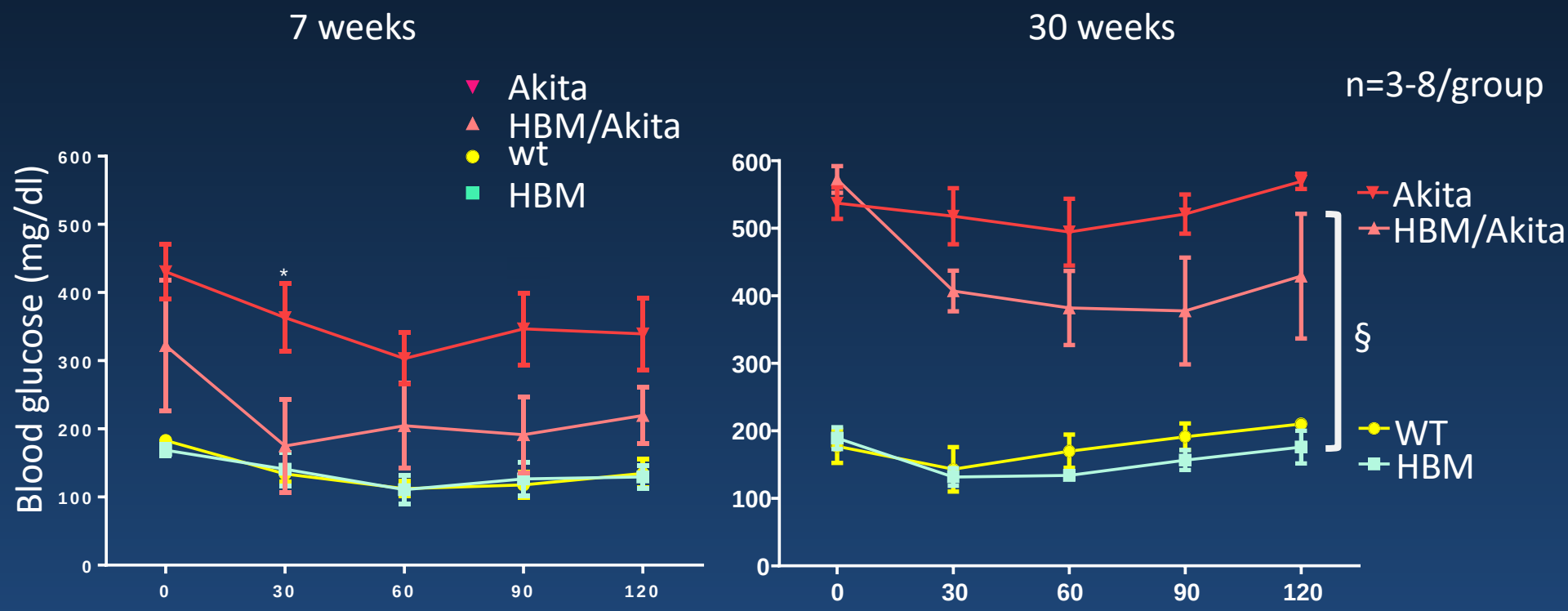


Time (minutes)

*p<0.05 for interaction Akita/HBM vs Akita

HBM Mutation Improves Insulin Sensitivity In Diabetic Mice

ip insulin tolerance test (ipITT)



Time (minutes)

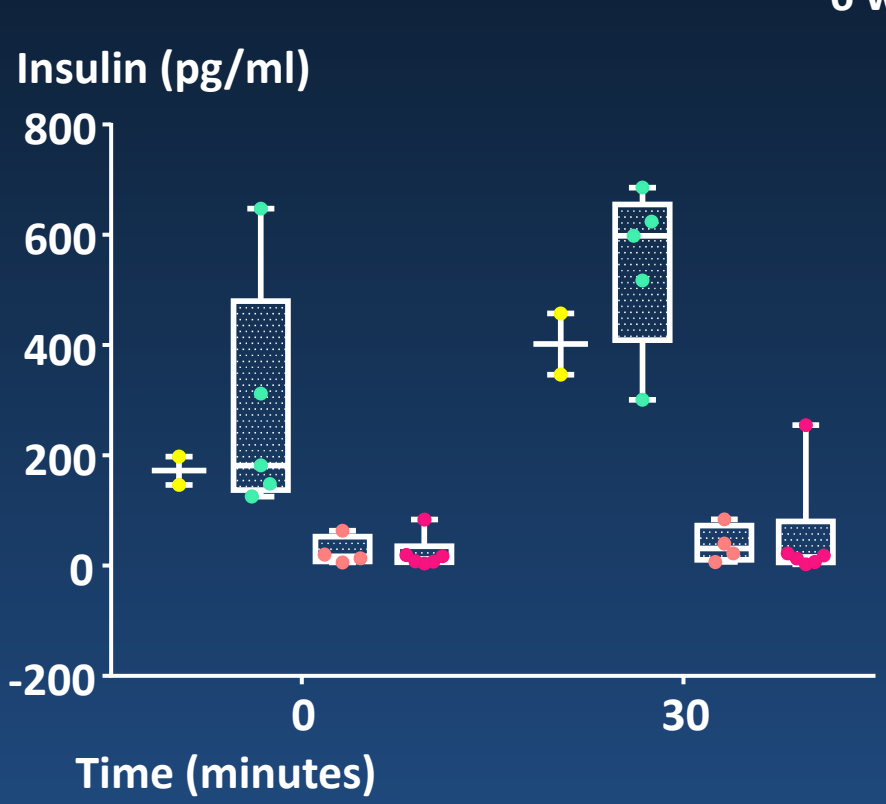
*p<0.05 for interaction HBM/Akita vs Akita

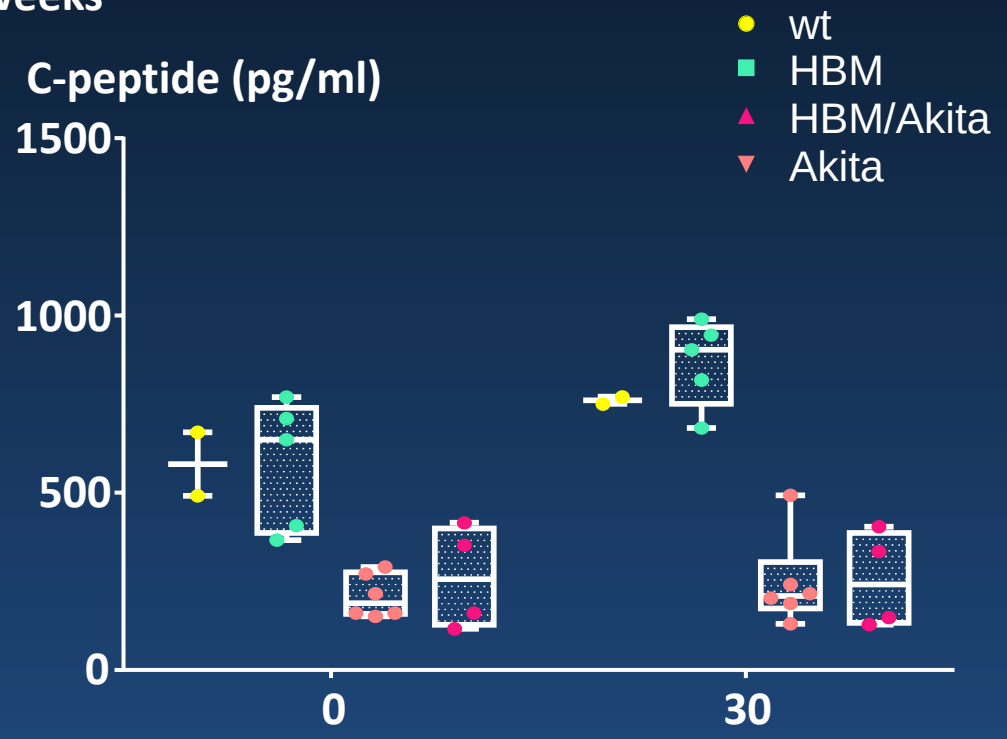
§p<0.001 for the effect of Akita

HBM Mutation Does Not Improve Insulin Secretion in Akita Mice

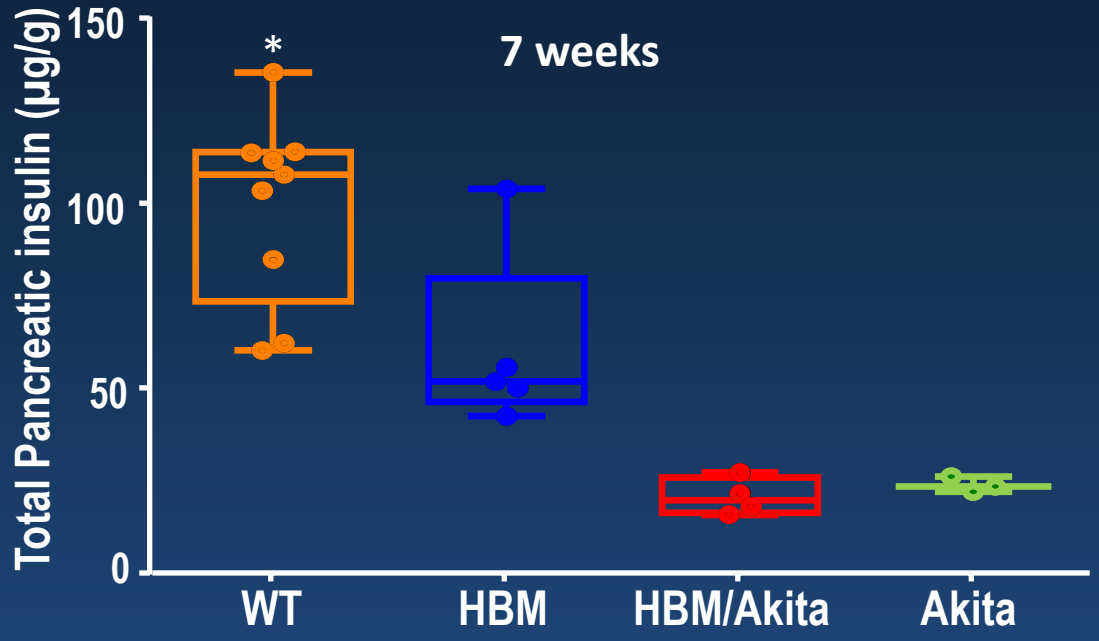
Serum hormones assay after a glucose load

6 weeks



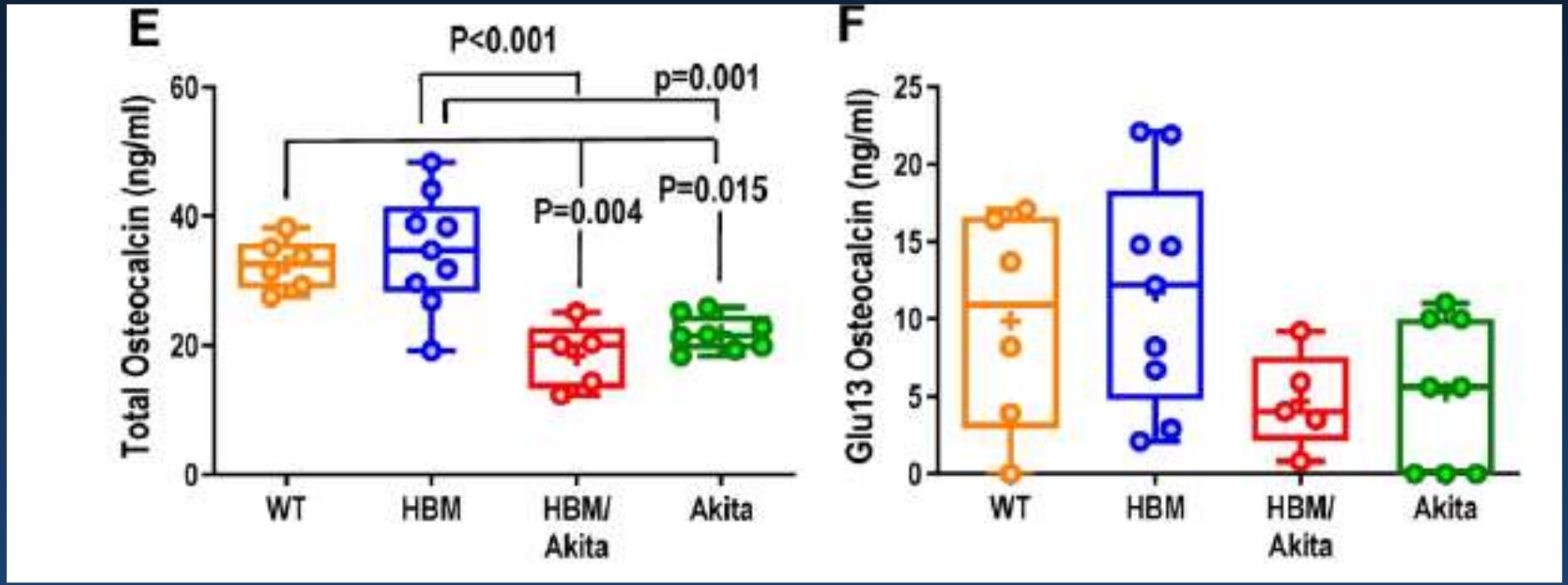


HBM Mutation Reduces Pancreatic Insulin Content

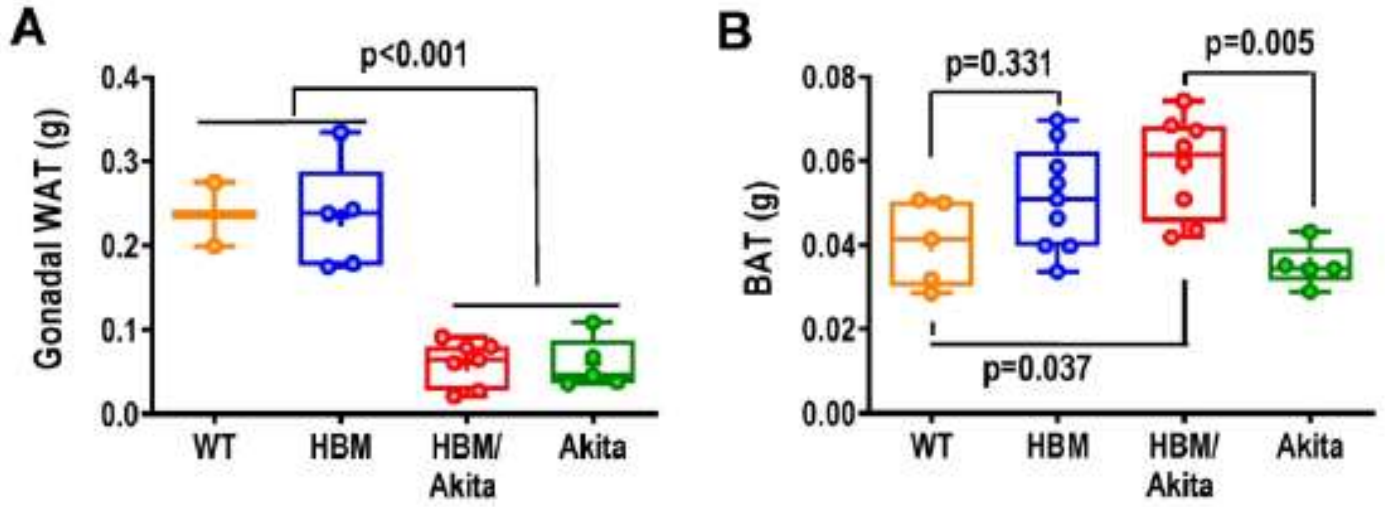


*p<0.05 vs. all other groups (post-hoc multiple t-test)

Role of osteocalcin

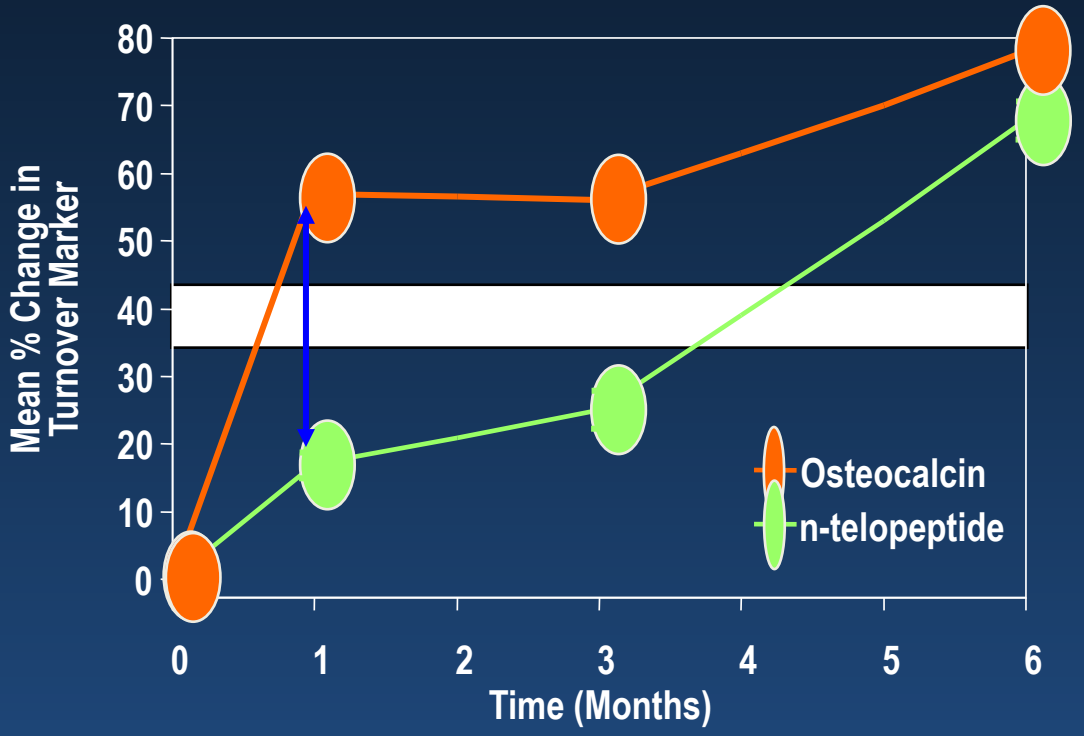


HBM Mutation Increases Brown Adipose Tissue



TERIPATIDE is anabolic:

Bone Formation Markers increase before Bone Resorption Markers

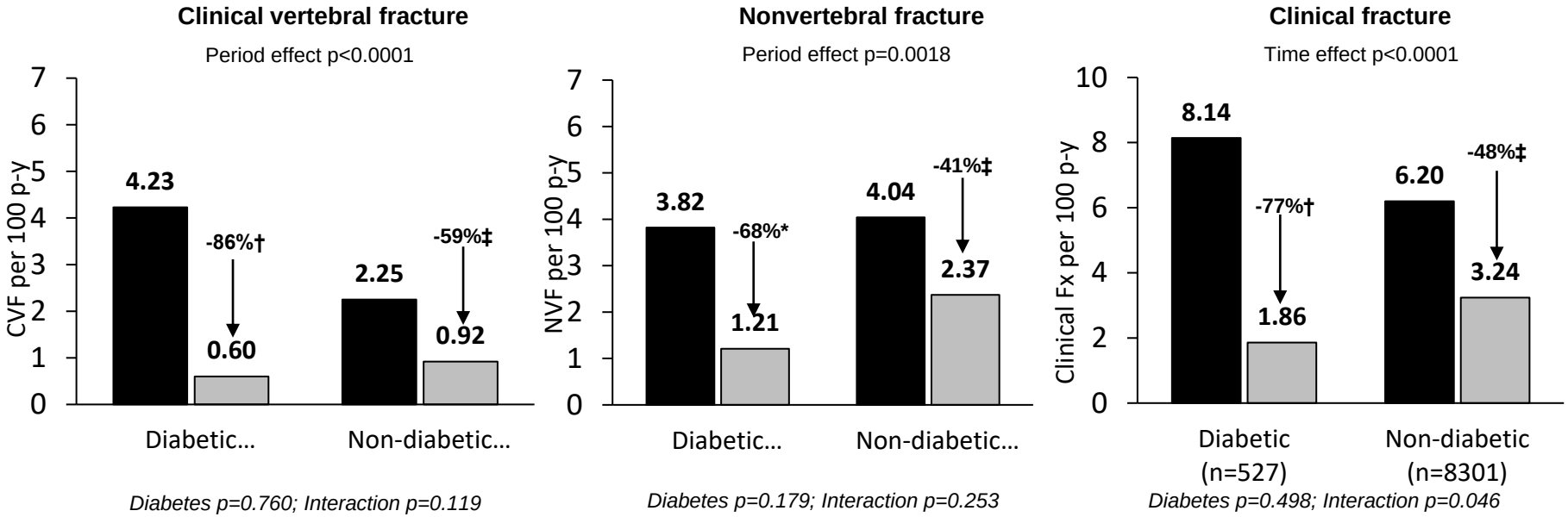


Lindsay R, et al. *Lancet.* 1997;350(9077):550-555.

Fracture Rates by Diabetes Mellitus with Teriparatide

0-6 months
>6 months

*p<0.05; †p<0.005; ‡p<0.0001 between periods



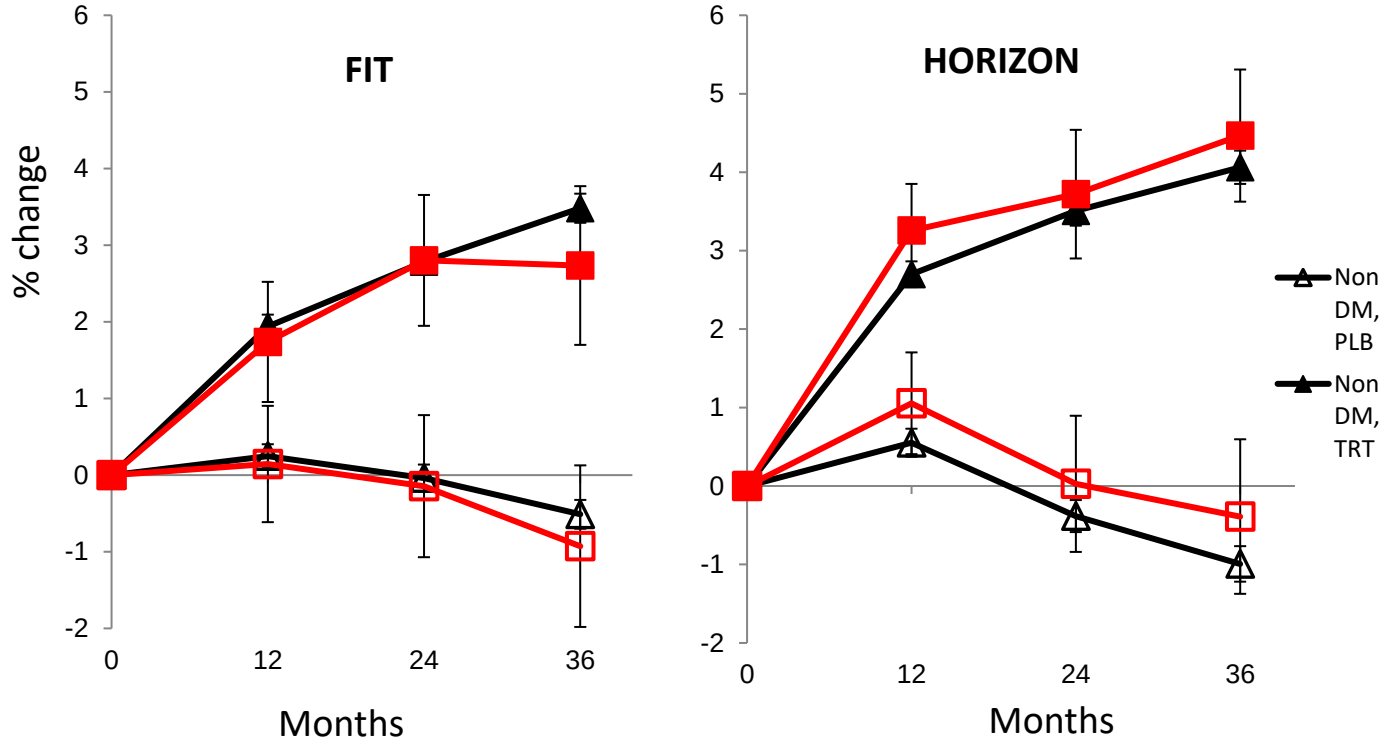
CVF, clinical vertebral fracture; Fx, fractures; NVF, nonvertebral fracture; p-y, patient-years of treatment.

Fracture rates per 100 patient-years for the reference period (0 to 6 months) versus postreference period (>6 months) for subgroup based on diabetes mellitus presence at baseline. Time effect compares fracture rate between the 2 treatment periods irrespective of subgroup; interaction assesses whether time effect varied between subgroups; subgroup compares fracture rate between subgroups irrespective of period effect.

Period and subgroup significant at p<0.05; interaction significant at p<0.10.

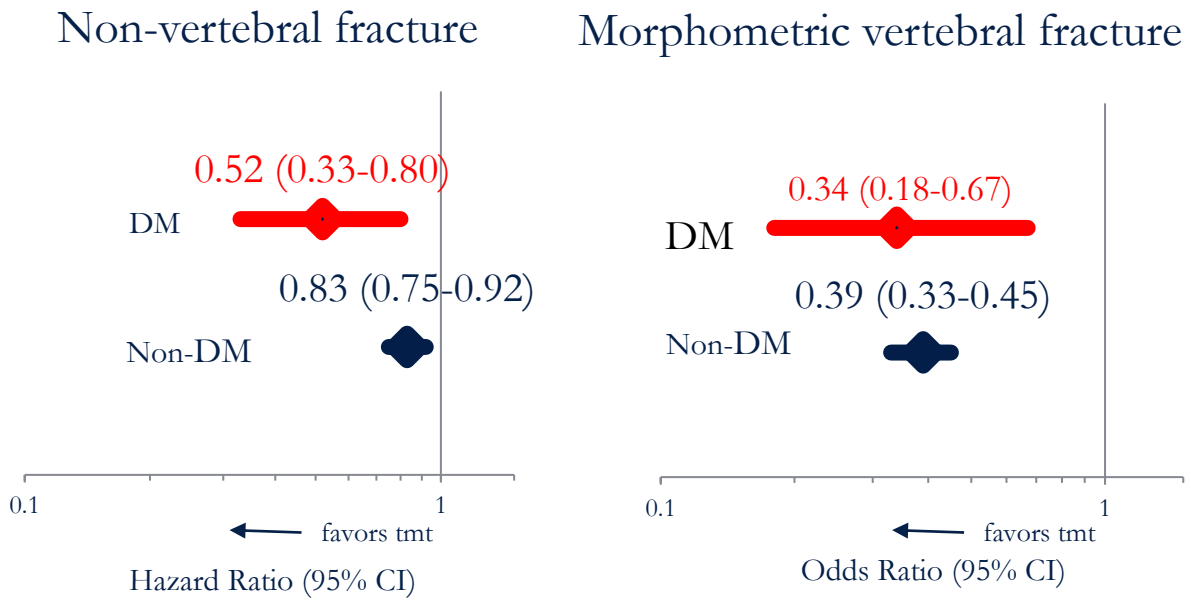
Langdahl BL, et al. Bone (2018);116:58-66.

Femoral Neck BMD – Placebo v Treatment with Alendronate or Zoledronate



Schwartz and Napoli, ASBMR 2018

Relative risk of fracture, comparing bisphosphonates with placebo, in DM and non-DM women

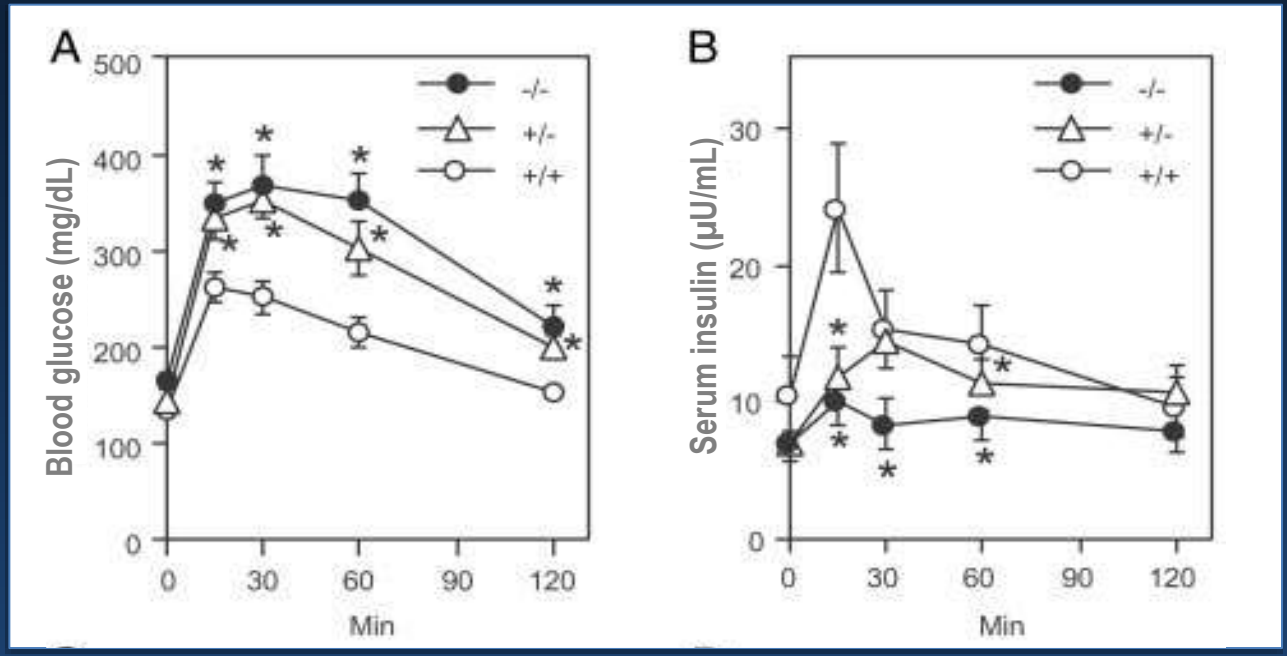


Schwartz and Napoli, ASBMR 2018

Conclusions

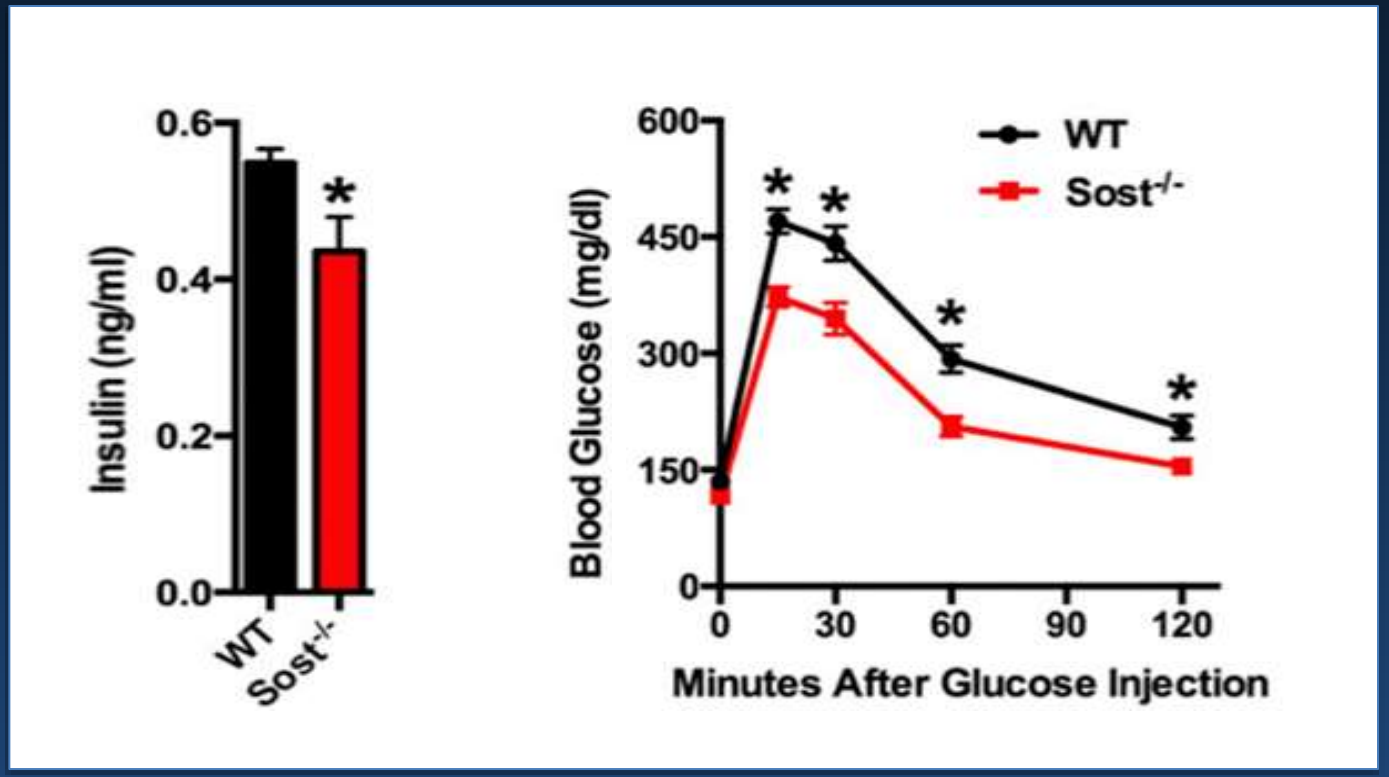
- Anabolic agents may be a first choice treatment in diabetic patients with fragility fractures
- Alendronate and zoledronic acid preserved bone density and reduced fracture risk.
- Anti-fracture efficacy of these bisphosphonates is not inferior to their efficacy in women without diabetes.

Loss-of-Function Lrp5$^{-/-}$ Reduces Glucose Tolerance and Insulin Production



N= 4/group
6-month-old mice

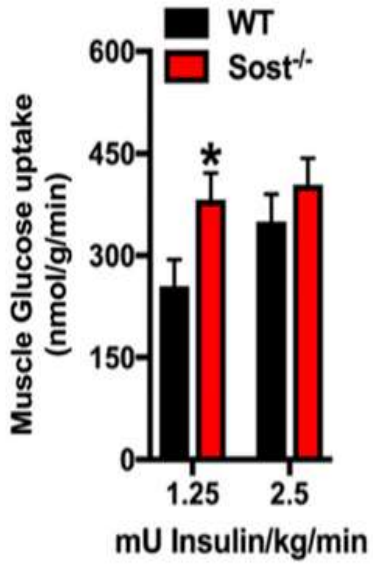
Increased glucose tolerance in Sost$^{-/-}$ mice

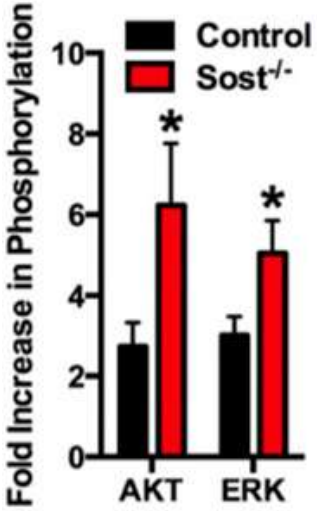


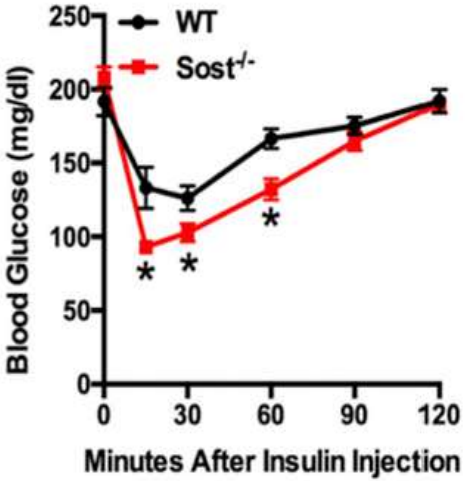
16-week-old; n= 6-8 mice/group

Kim SP et al., PNAS 2017

Increased insulin sensitivity in Sost$^{-/-}$ mice

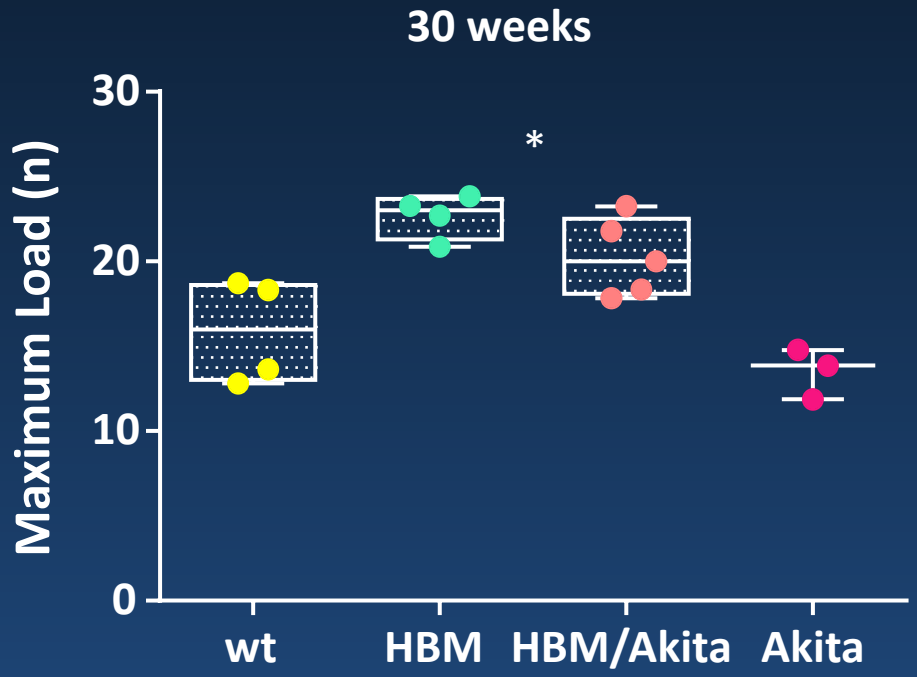






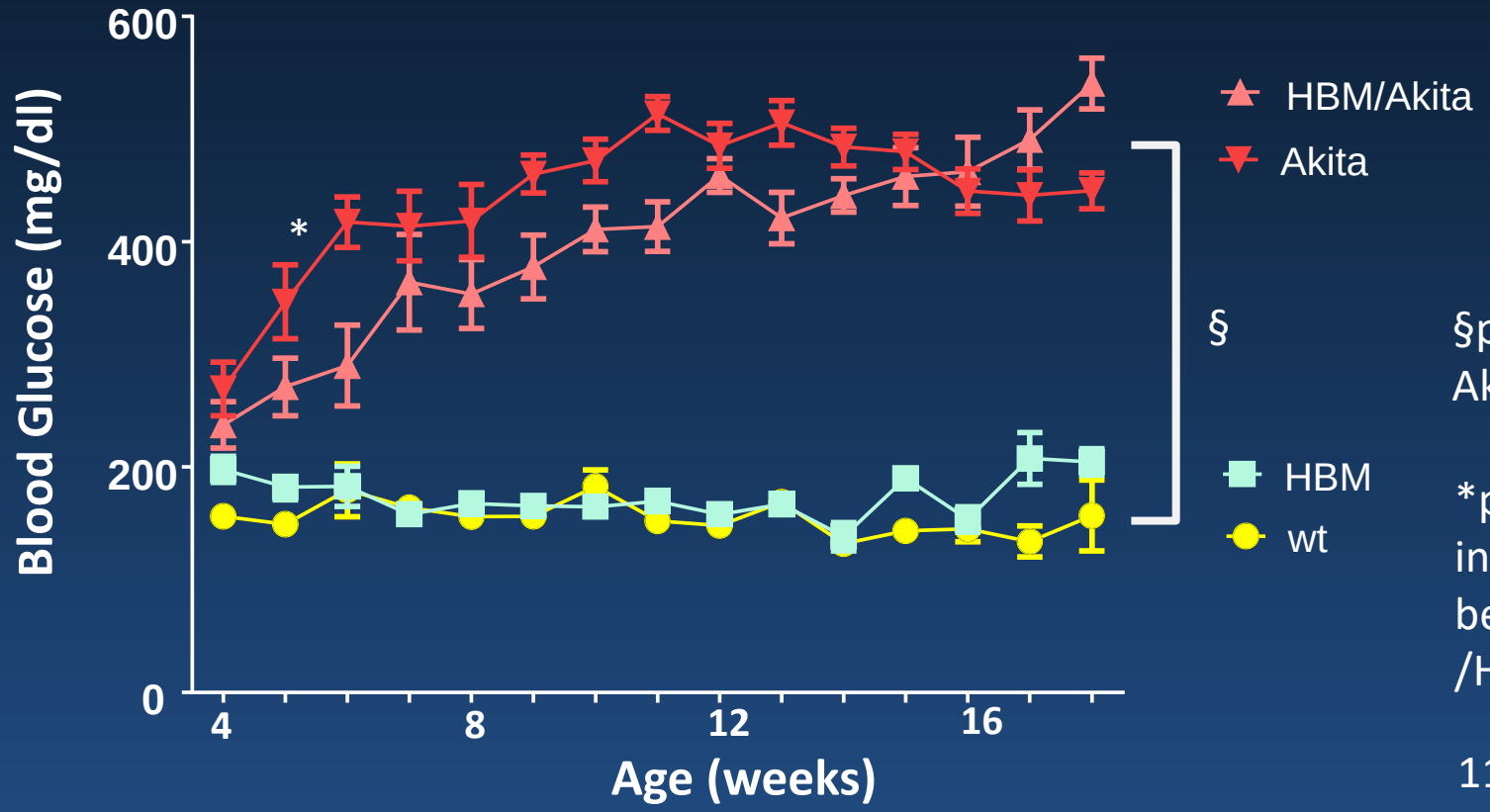
Kim SP et al., PNAS 2017

HBM/Akita Maintain Elevated Bone Strength Despite Diabetes



*p<0.001 for the effect of HBM

Akita/HBM Develop Hyperglycemia with Different Onset Timing



§p<0.01 for Akita effect

*p<0.05 for the interaction between Akita /HBM vs Akita

11-16/group