

Diabetes and bone

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No disclosures relevant to this talk



A clustering of disease?

Double trouble!

Why is there a link?

T1DM vs. T2DM-related bone fragility - specific features

Treatment considerations



Diabetes & osteoporosis: clustering of disease?

- ▶ Both (type 2) diabetes & osteoporosis are:
 - ▶ considered epidemic by the WHO
 - ▶ chronic metabolic disorders, affecting quality of life, morbidity and mortality

- ▶ Estimated number of T2DM patients: 382 million (IDF, 2013)
- ▶ Estimated number women with osteoporosis: 200 million (IOF, 2013)
- ▶ Estimated number of fragility fractures: 9 million per year (IOF, 2013)



Diabetes & osteoporosis: clustering of disease?

- ▶ First suggestion in 1927:
 - ▶ Retarded bone development and bone atrophy described in children with type 1 diabetes (Morrison & Bogan)
- ▶ Since 1990s reports on increased fracture risk in T1DM & T2DM:
 - ▶ Especially hip fractures
 - ▶ Association most clear in women (WHI: postmenopausal women with T2DM adjusted RR 1.2 (Bonds et al. JCEM 2006))
 - ▶ Greater risk in insulin vs. non-insulin treated T2DM patients (Schwartz et al., Diabetes Care 2002)



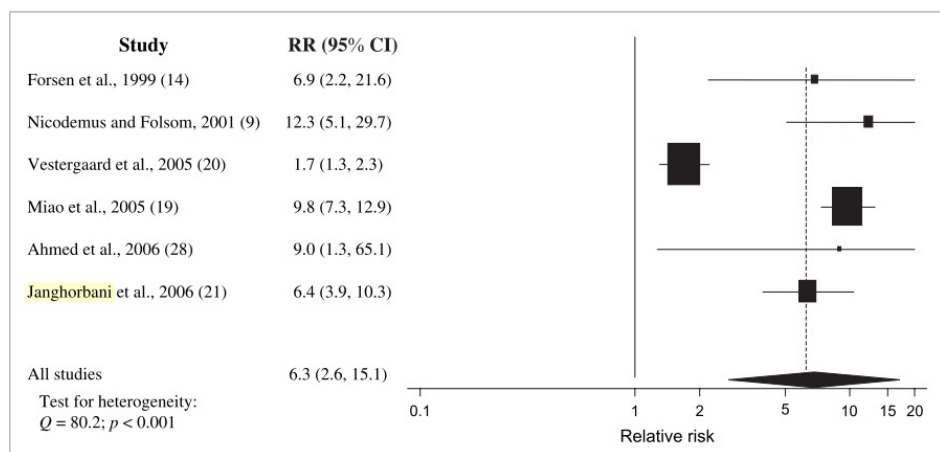
Diabetes & osteoporosis: hip fracture risk in T1DM and T2DM

- ▶ Systematic review in 2007:
 - ▶ 16 eligible studies (2 case-control studies and 14 cohort studies)
 - ▶ 836,941 participants
 - ▶ 139,531 incident cases of fracture



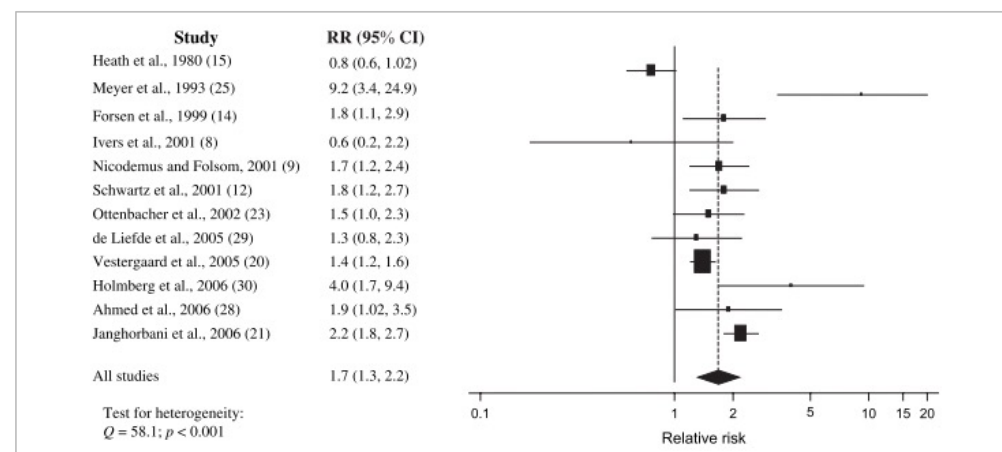
Diabetes & osteoporosis: hip fracture risk in T1DM and T2DM

▶ T1DM:



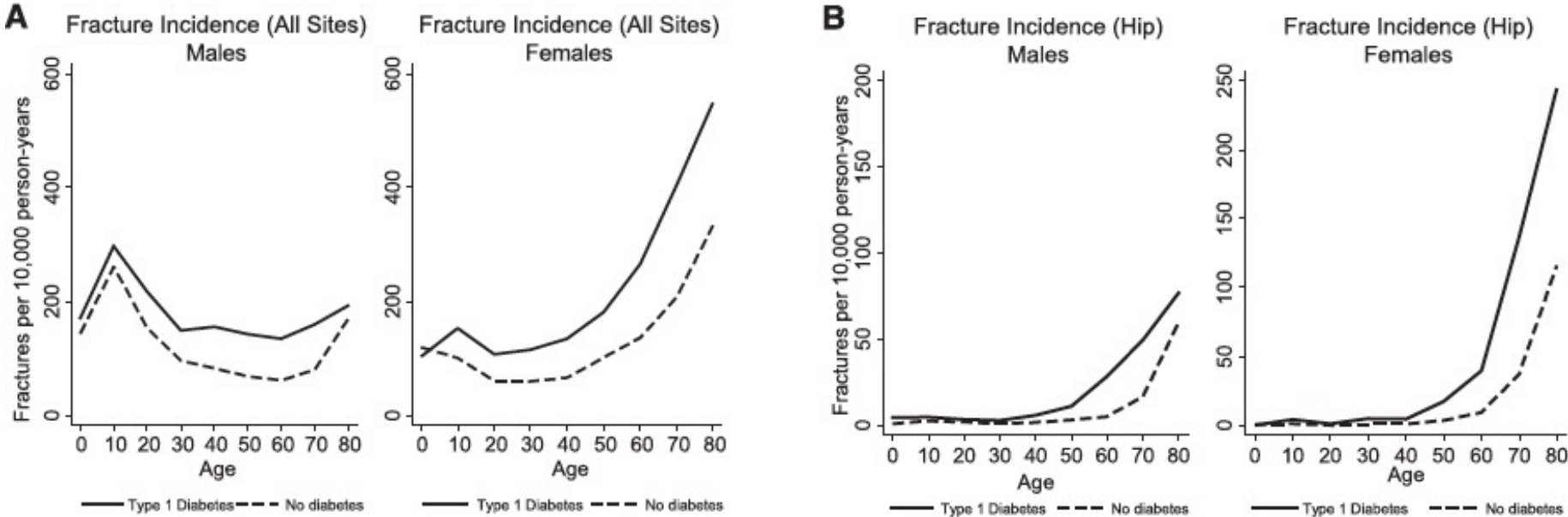
- ▶ 6 studies (1 case-control, 5 cohort)
- ▶ **6.3-fold increase** in hip fracture risk in men & women

▶ T2DM:

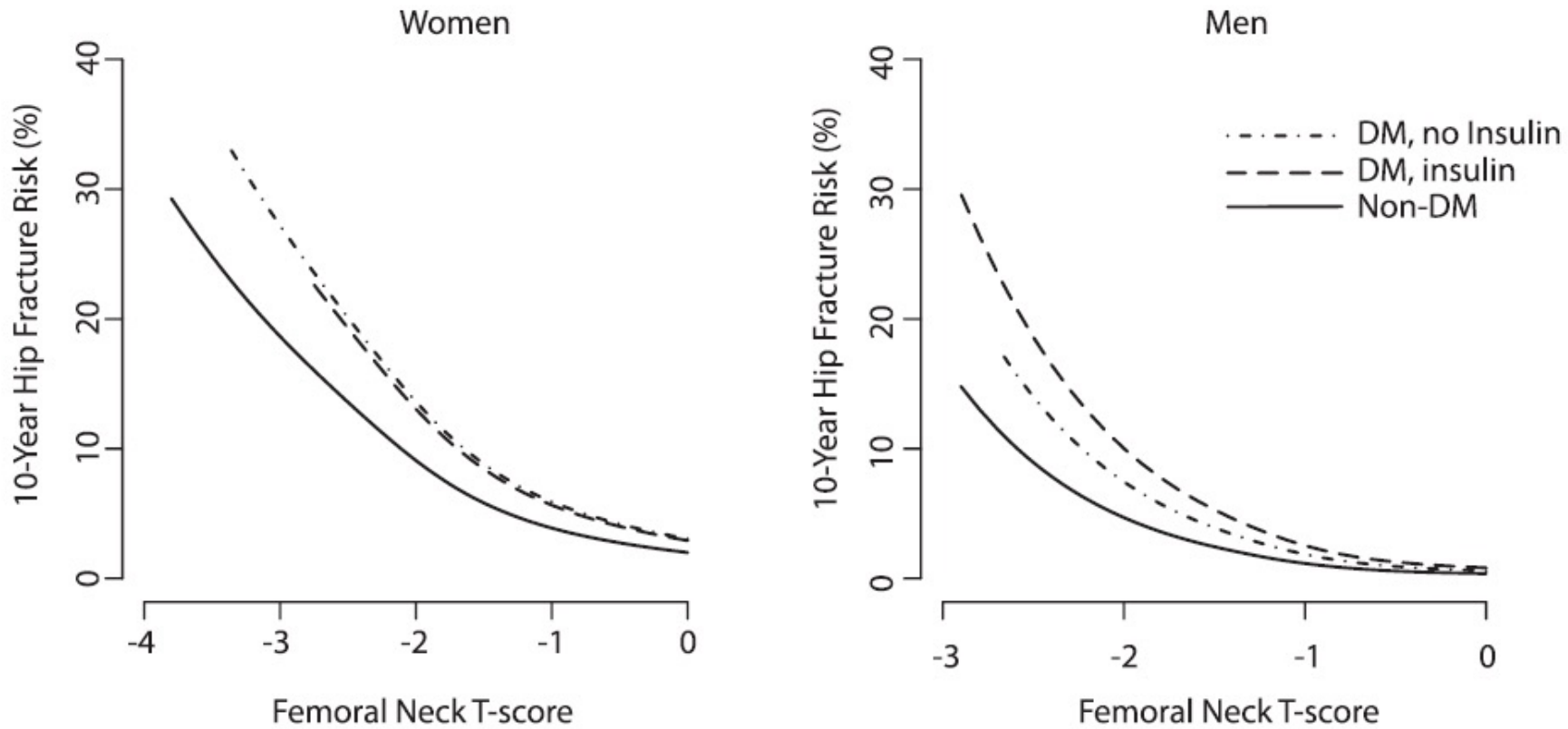


- ▶ 12 studies (1 case-control, 11 cohort)
- ▶ **1.7-fold increase** in hip fracture risk in men & women

Diabetes & osteoporosis: overall Fx risk in T1DM



An even higher fracture risk in diabetes patients?!



An even higher fracture risk in diabetes patients?!

Country: **Belgium** Name/ID: [About the risk factors](#)

T1DM / IDDM

Questionnaire:

1. Age (between 40 and 90 years) or Date of Birth
 Age: Date of Birth: Y: M: D:

2. Sex Male Female

3. Weight (kg)

4. Height (cm)

5. Previous Fracture No Yes

6. Parent Fractured Hip No Yes

7. Current Smoking No Yes

8. Glucocorticoids No Yes

9. Rheumatoid arthritis **T2DM** No Yes

10. Secondary osteoporosis No Yes

11. Alcohol 3 or more units/day No Yes

12. Femoral neck BMD (g/cm²)
 Select BMD

BMI: 25.9

The ten year probability of fracture (%)

without BMD

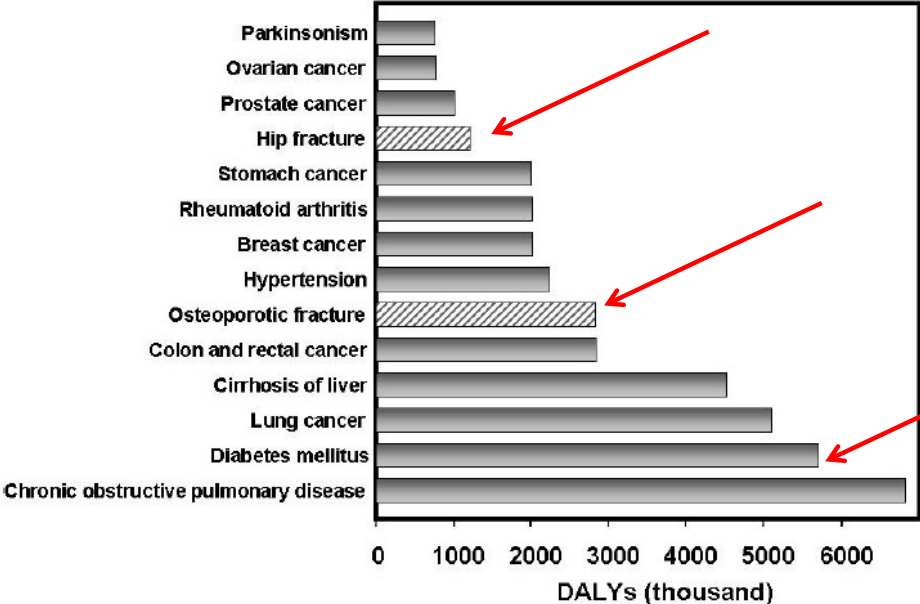
Major osteoporotic	11
Hip Fracture	2.0



Diabetes & osteoporosis: double trouble?

- ▶ In women > 45 years, osteoporosis accounts for more days spent in hospital than diabetes, myocardial infarction and breast carcinoma

Figure 1: Burden of diseases estimated as disability-adjusted life years (DALYs) in 2002 in the Americas and Europe combined



Diabetes & osteoporosis: double trouble?

- ▶ Patient outcomes worse in diabetic pts
 - ▶ Higher risk of Fx in hypoglycemia-related hospitalisations

Table 4. Distribution of number of morbid events in patients with and without a history of hypoglycemia-related hospitalizations over the calendar year.

	<i>n</i> events/year	With hypoglycemia (<i>n</i> = 2196)	Without hypoglycemia (<i>n</i> = 28 514)	<i>p</i> -value
Hospitalizations with traumatic fractures	No event	2023 (92.12%)	26,773 (93.89%)	
	At least one event (risk rate)	173 (7.88%)	1741 (6.11%)	
	OR [95% CI]†	1.247 [1.057–1.470]	–	0.009
	Event rate‡‡	0.063	0.064	<0.001
Hospitalizations with cardiovascular event	No event	2034 (92.62%)	26,424 (92.67%)	
	At least one event (risk rate)	162 (7.38%)	2090 (7.33%)	
	OR [95% CI]†	0.979 [0.829–1.157]	–	0.801
	Event rate‡‡	0.090	0.080	<0.001
Hospitalizations with depression	No event	2094 (95.36%)	27,807 (97.52%)	
	At least one event (risk rate)	102 (4.64%)	707 (2.48%)	
	OR [95% CI]†	1.900 [1.536–2.351]	–	<0.001
	Event rate‡‡	0.054	0.028	<0.001

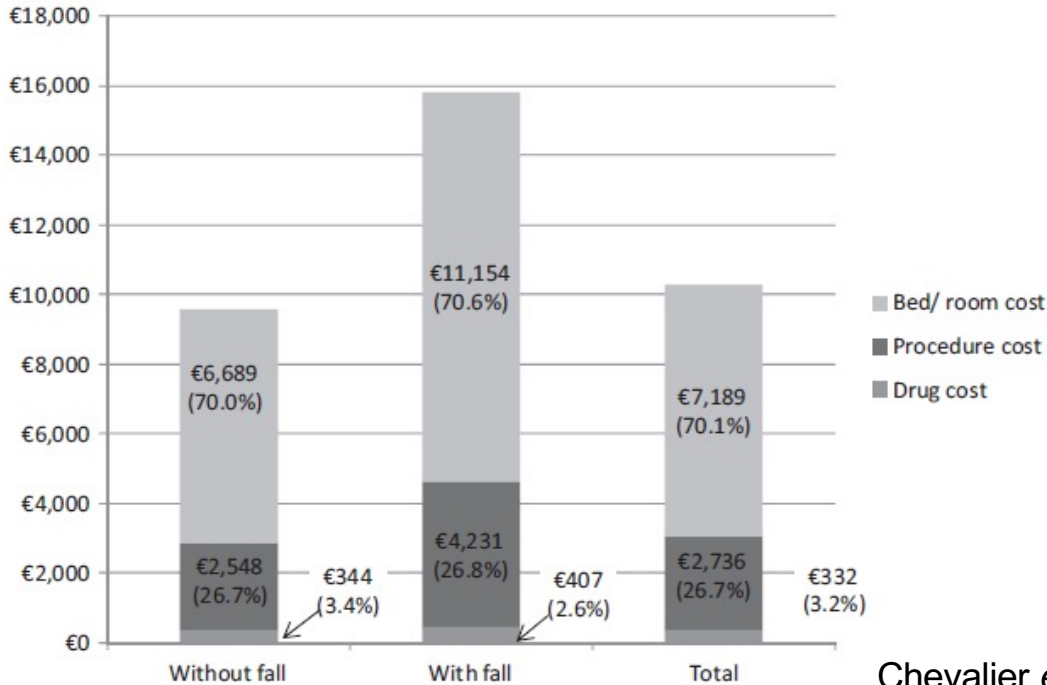
†Odd-ratios, adjusted for age and sex.

‡‡In number of events/patient-calendar year.



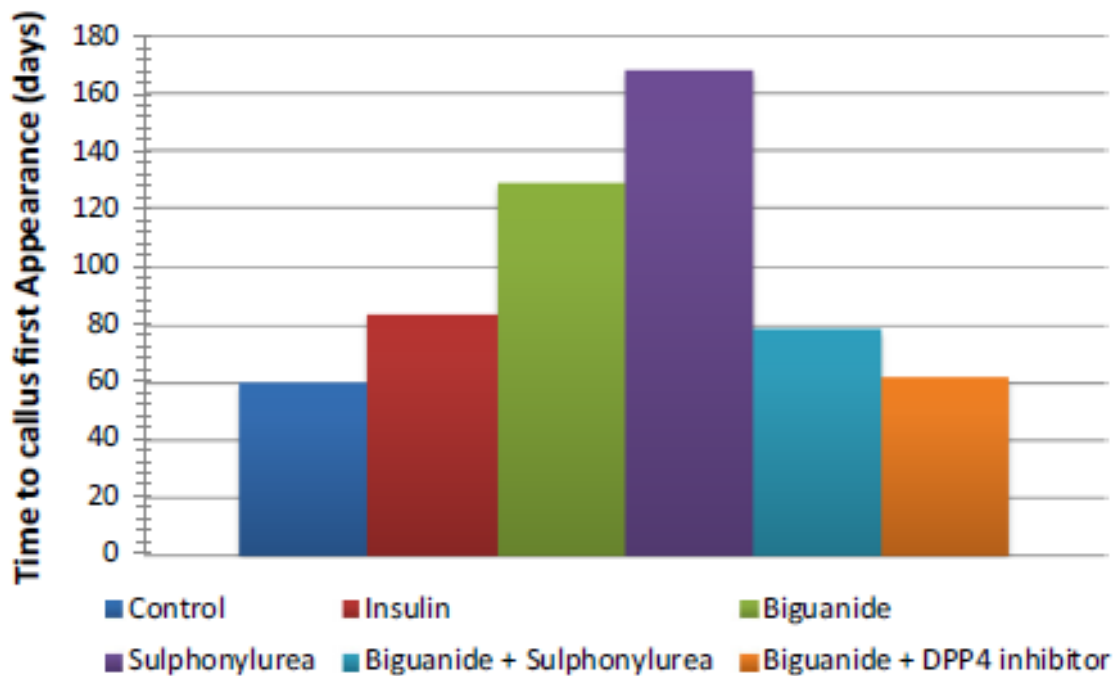
Diabetes & osteoporosis: double trouble?

- ▶ Patient outcomes worse in diabetic pts
 - ▶ Longer length of stay, higher health care cost



Diabetes & osteoporosis: double trouble?

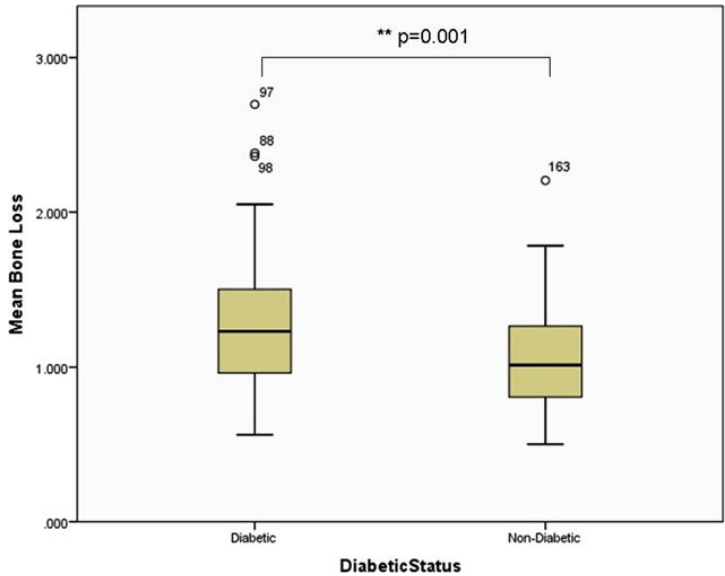
- ▶ Delayed Fx healing described in both type 1 and type 2 DM
 - ▶ Mostly in patients with displaced fractures or treated by open reduction



Diabetes & bone: double trouble?



▶ A Scottish bitewing radiographic study



	Diabetes participants (N = 108)	Non-diabetes participants (N = 66)
Bone Loss	%(n)	% (n)
≥2mm	65.70% (n = 71)	53.0% (n = 35)
≥3mm	29.6% (n = 32)	22.7% (n = 15)
≥4mm	13.0% (n = 14)	3.0% (n = 2)



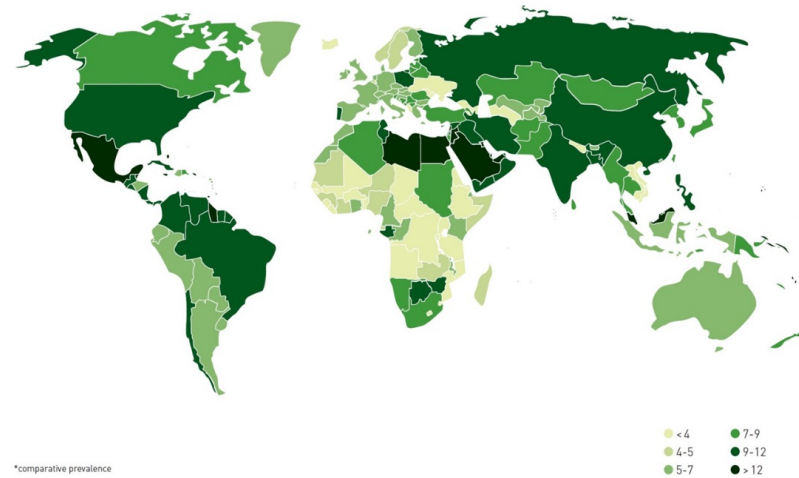
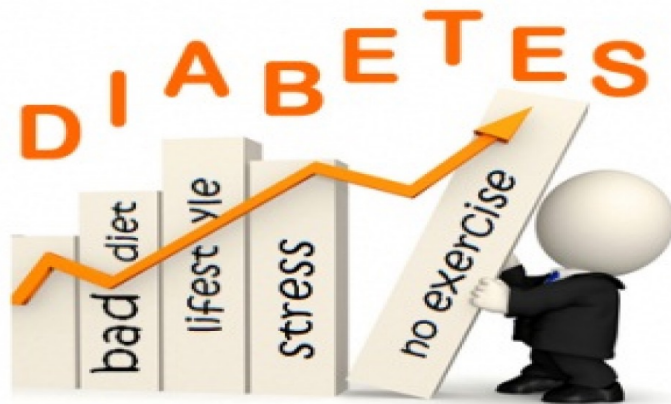
Diabetes & osteoporosis: double trouble?

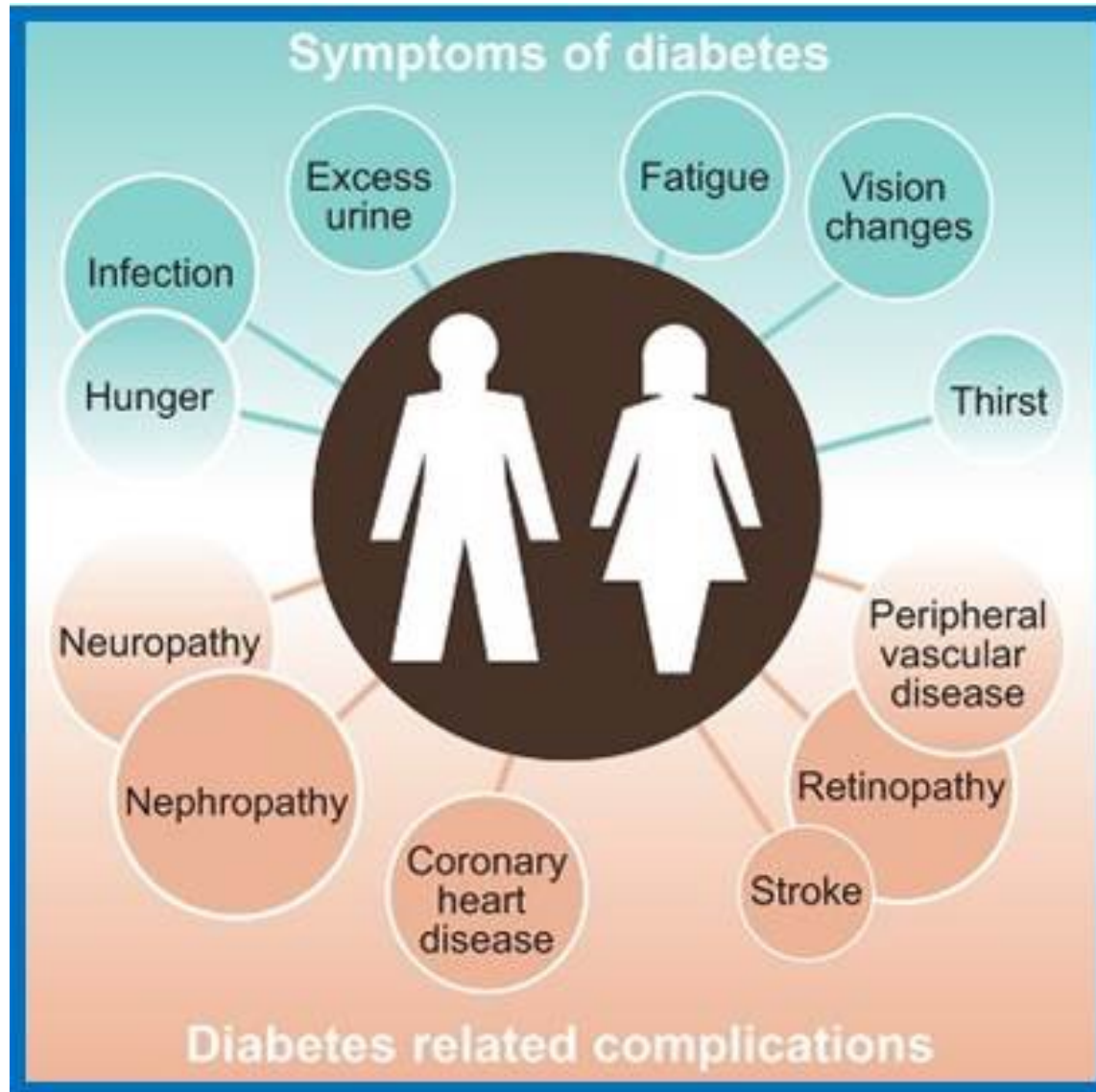
- ▶ But how come?
- ▶ And why is there a link in the first place?



But first something on diabetes

- ▶ Diabetes mellitus = heterogeneous group of chronic disorders who share 1 unifying principle:
 - ▶ Elevated blood glucose levels (hyperglycemia) leading to micro- and macrovascular damage
 - ▶ Associated with disability & premature mortality
 - ▶ Rising incidence & prevalence (esp. T2DM)





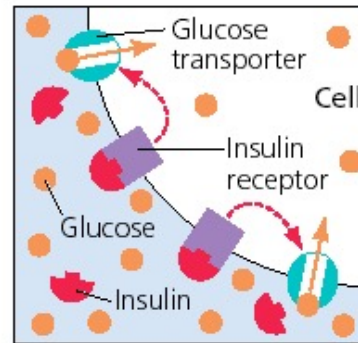
But first something on diabetes

- ▶ Type 1 diabetes (5-10%)
 - ▶ Auto-immune disease, onset during childhood/young adulthood, clustering with other AI diseases
 - ▶ Strictly insulin dependent
- ▶ Type 2 diabetes (>90%)
 - ▶ Characterized by insulin resistance with ultimately beta cell failure leading to hyperglycemia; clustering with obesity & other CV risk factors
 - ▶ Lifestyle central, oral drugs, insulin
- ▶ Monogenic & syndromic diabetes; secondary diabetes



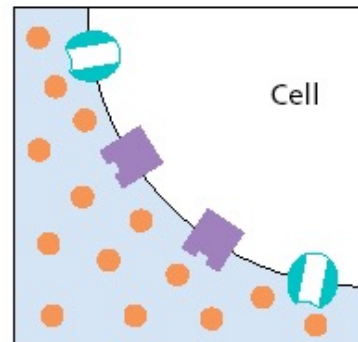
Normal:

Insulin binds to receptors on the surface of a cell and signals special transporters in the cell to transport glucose inside.



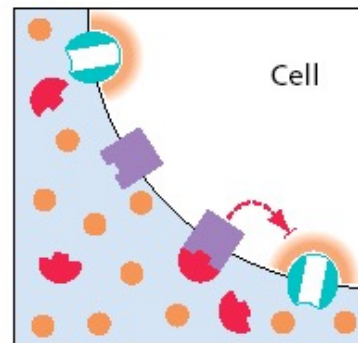
Type 1 diabetes:

The pancreas produces little or no insulin. Thus, no signal is sent instructing the cell to transport glucose, and glucose builds up in the bloodstream.



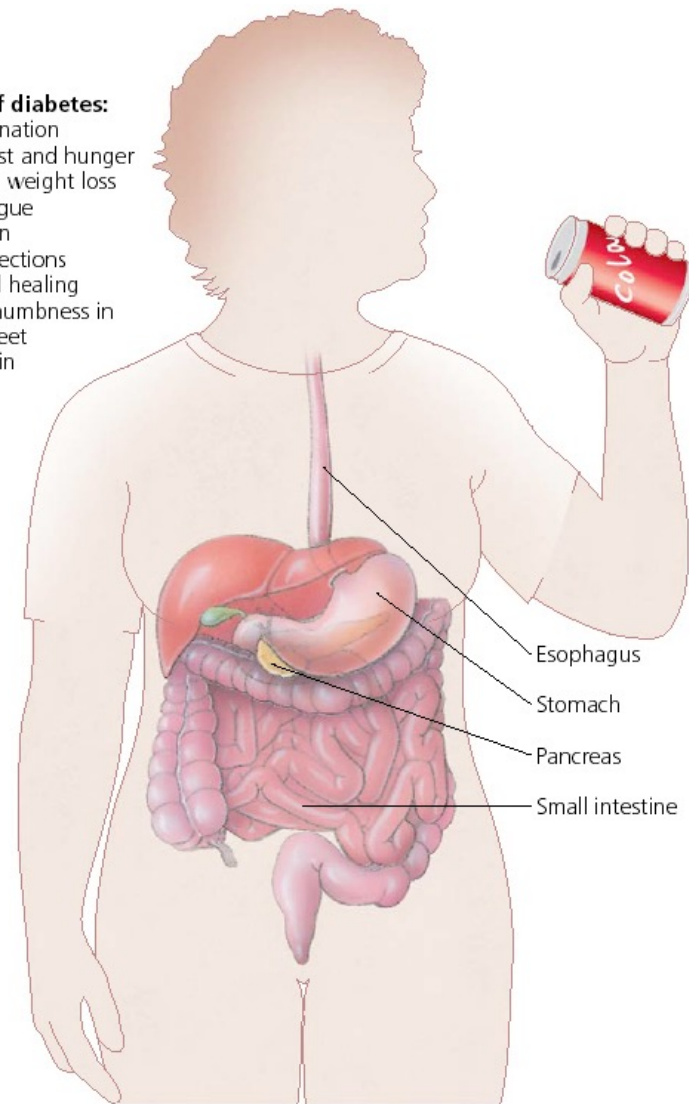
Type 2 diabetes:

The pancreas produces too little insulin and/or the body's cells are resistant to it. Some insulin binds to receptors on the cell's surface, but the signal to transport glucose is blocked. Glucose builds up in the bloodstream.



Symptoms of diabetes:

- Frequent urination
- Extreme thirst and hunger
- Unexplained weight loss
- Extreme fatigue
- Blurred vision
- Frequent infections
- Slow wound healing
- Tingling or numbness in hands and feet
- Dry, itchy skin



	T1DM	T2DM
Usual age of onset	< 20 yrs	> 40 yrs
Pace of onset	Rapid	Slow
Body mass	Low (wasted)	Obese
Insulin levels	Low or absent	Variable
Glucagon levels	High, suppressible	High, unsuppressible
Glucose levels	Increased	Increased
Insulin sensitivity	Normal	Reduced
Therapy	Insulin	Weight loss, oral antidiabetic drugs, incretins, insulin



So why are patients with DM at higher risk of Fx?



- ▶ Do diabetic patients just fall more?
 - ▶ Increased risk factors for falling: visual impairment, peripheral & autonomic neuropathy, foot deformities
 - ▶ BP lowering drugs
 - ▶ Sedentarism
 - ▶ Hypoglycemia!





So why are patients with DM at higher risk of Fx?

Table 2—Frequency of falls and proportion of fallers among older women by diabetes and insulin use

	No diabetes	Non-insulin-treated diabetes	Insulin-treated diabetes
n	8,620	530	99
Incidence of falls (per person-year)			
70–74 years old	0.43	0.56*	1.26*†
75–79 years old	0.52	0.74*	0.82*
80–84 years old	0.66	0.89*	1.31*†
≥ 85 years old	0.98	1.32*	1.37*
All ages	0.62	0.85*	1.12*†
Fell more than once a year (%)	17.0	25.7*	35.4*†
Fell more than twice a year (%)	6.8	10.6*	15.2*
Follow-up (years)	7.2 ± 1.9	6.6 ± 2.2*	6.2 ± 2.4*

Data for follow-up are means ± SD. *P < 0.05 compared with women without diabetes; †P < 0.05 compared with women with non-insulin-treated diabetes.

So why are patients with DM at higher risk of Fx?

- ▶ Diabetic patients fall more!
- ▶ Do diabetic patients have increased bone fragility?
 - ▶ Mineralisation deficit due to reduced bone formation or increased bone resorption?
 - ▶ Matrix abnormalities?
 - ▶ Abnormal bone acquisition during growth in pts with T1DM?
 - ▶ Alterations in bone size or geometry



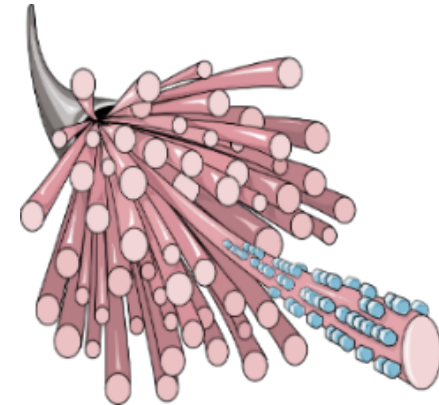
Diabetes & bone: why is there a link?

- ▶ Diabetes = metabolic disorder with imbalance in macronutrient oxidation patterns
- ▶ Bone has a relatively high energy demand
 - ▶ 17% of body weight
 - ▶ 9% of tissue bulk
 - ▶ bone protein accounts for ~8% of whole body protein synthesis
 - ▶ bone receives +/-9% of cardiac output
- ▶ Imbalances in substrate metabolism will probably affect bone metabolism as well



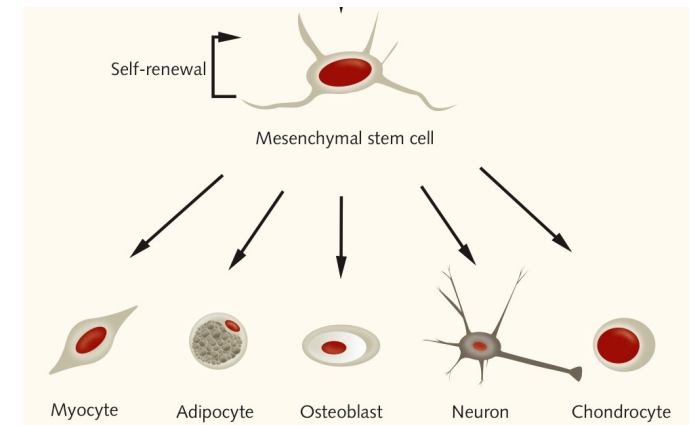
Diabetes & bone: why is there a link?

- ▶ Chronic hyperglycemia
 - ▶ ↓ osteoblast and osteoclast activity
 - ▶ Accumulation of AGEs
 - Impaired collagen formation affecting mechanical properties
 - ↓ osteoblast, osteoclast, osteocyte function
- ▶ Micro- and macrovascular complications
 - ▶ Altered vascular supply
 - ▶ Chronic inflammation
 - ▶ Altered in mineral metabolism in patients with nephropathy



Diabetes & bone: why is there a link?

- ▶ Changes in fat content & distribution
 - ▶ Obesity & increased body fat in T2DM
 - ▶ Increased bone marrow adiposity in T1DM & T2DM
 - ▶ Osteoblasts, myocytes and adipocytes share a common progenitor; the mesenchymal stem cell
- ▶ Energy metabolism and bone mass are regulated by the same hormones e.g. leptin, NPY, substance P, adiponectin, osteocalcin, ...
- ▶ Effects of antidiabetic drugs?



Diabetes & bone: why is there a link?

- ▶ Fractures & DM have shared risk factors, impact of diabetic complications

TABLE 3. Multivariable proportional hazards model of baseline characteristics associated with incident hip fracture risk among women without hip osteoporosis (total hip bone mineral density > -2.5) at start of observation

Characteristics	Multivariable HR (95% CI)
Age (per yr) ^a	1.08 (1.05–1.12)
Walking for exercise: no other activity	0.73 (0.48–1.09)
Other activity: alone or in addition to walking	0.50 (0.32–0.78)
Contrast sensitivity, low frequency: lowest quartile	1.54 (1.06–2.25)
Any falls in last year	1.64 (1.15–2.34)
Prevalent vertebral fracture	1.86 (1.28–2.71)
Total hip bone mineral density (per SD decrease)	1.95 (1.53–2.46)

28 /



T1DM-related bone fragility – specific features

- ▶ Absolute insulin deficiency:
 - ▶ Impaired osteoblast function possibly through low IGF-1?
- ▶ Hypercalciuria & hypomagnesemia
 - ▶ Due to bone mineral loss & functional hypoparathyroidism?
 - ▶ Improves upon insulin treatment
- ▶ Contribution of other auto-immune diseases?
 - ▶ Low bone mass in celiac disease; high bone turnover during thyrotoxicosis



DM-related bone fragility: bone mass

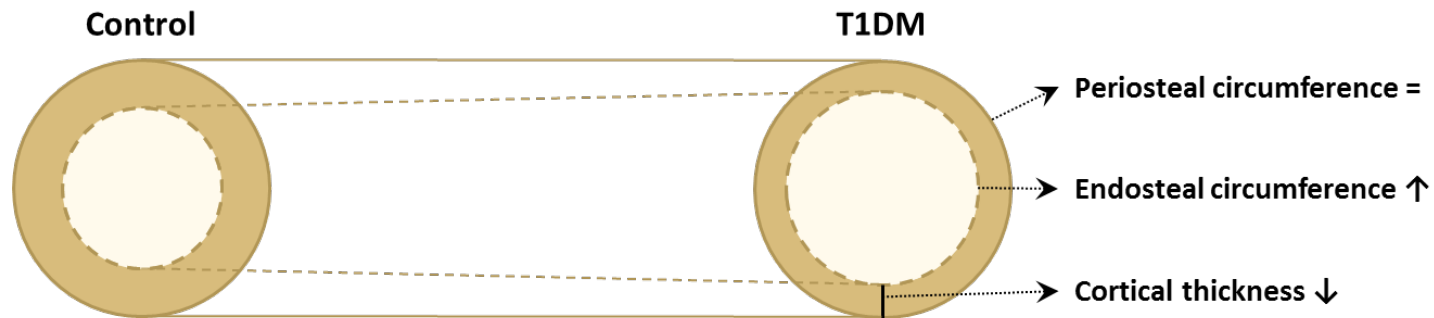
Table 4 Observed changes in BMD and expected change in fracture risk

Type of diabetes	Spine Z-score	Hip Z-score
T1D	-0.22±0.01*	-0.37±0.16*
T2D	0.41±0.01*	0.27±0.01*
Expected relative fracture risk	Any fracture	Hip fracture
T1D	1.09	1.42
T2D	0.85	0.77

Meta-analyses are based on a minimum of three studies

*: 2p<0.05, # Includes studies with T2D patients who were only diet or tablet treated, P: test for heterogeneity

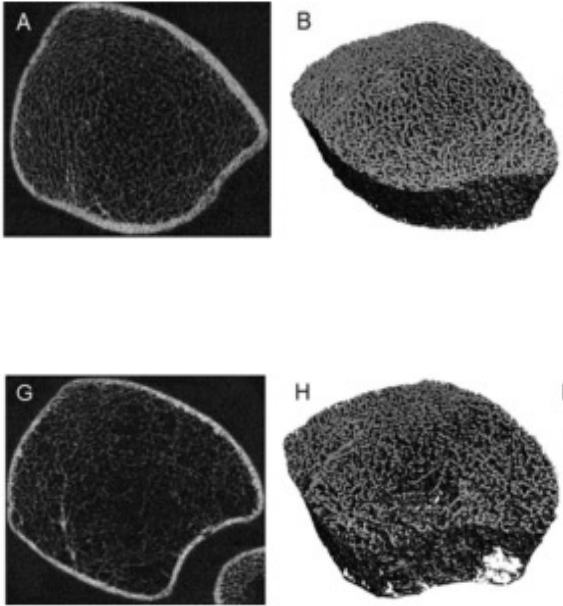
T1DM-related bone fragility: bone size



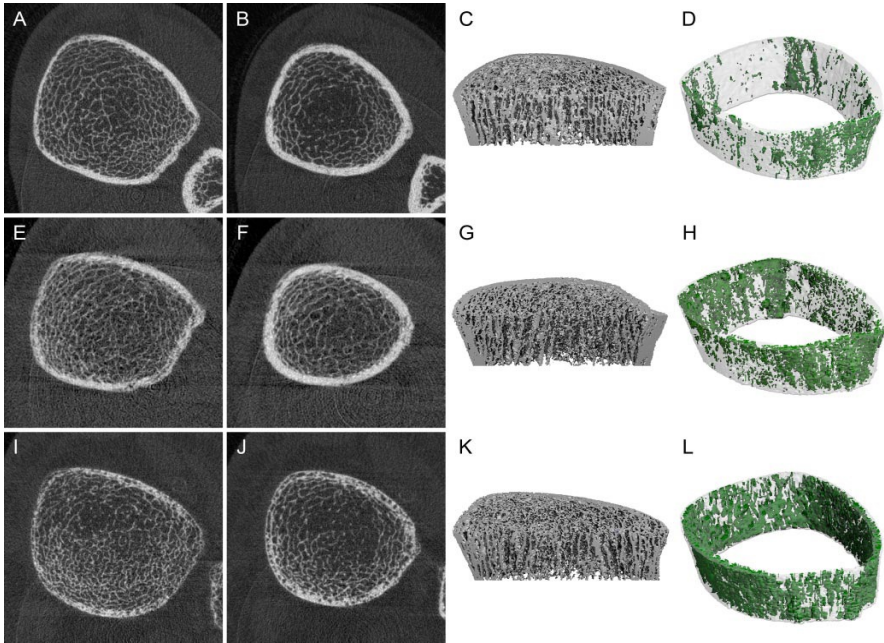
- ▶ **Cortical bone size deficit in T1DM** characterized by
 - ▶ 6.1% larger endosteal circumference
 - ▶ 4.3% smaller cortical thickness
 - ▶ 9.1% lower cortical / total bone area ratio

DM-related bone fragility: bone microarchitecture

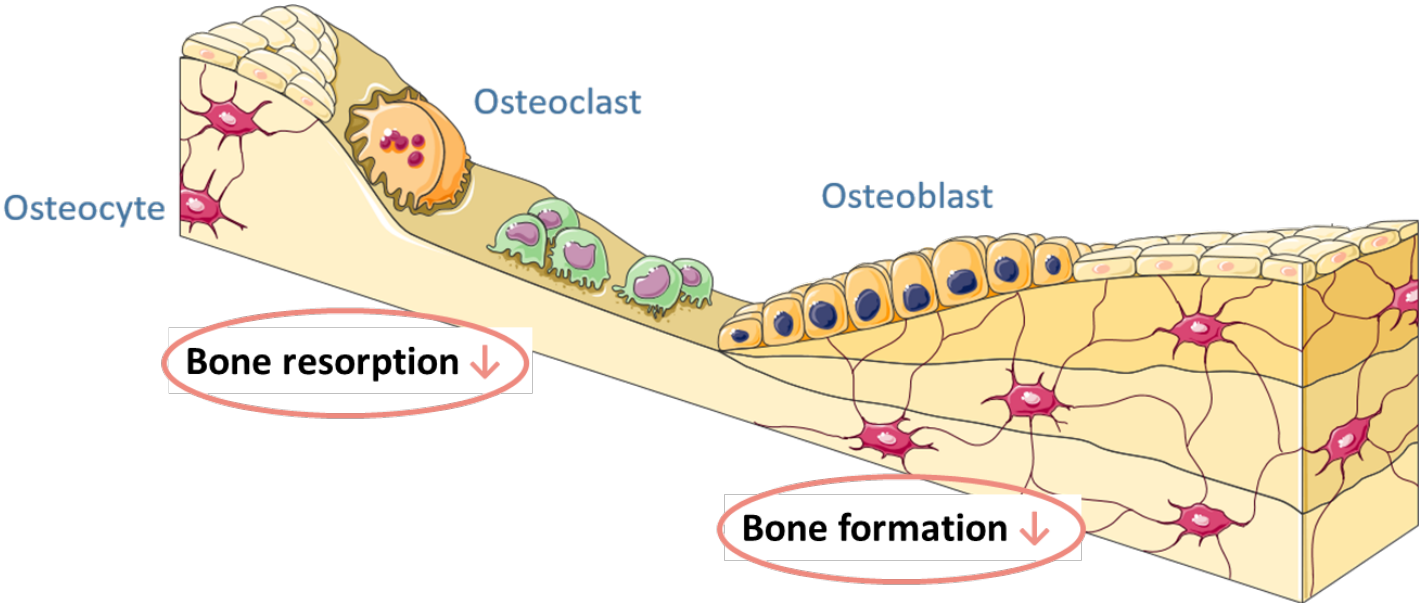
Control vs. T1DM



Control vs. T2DM with / without fracture

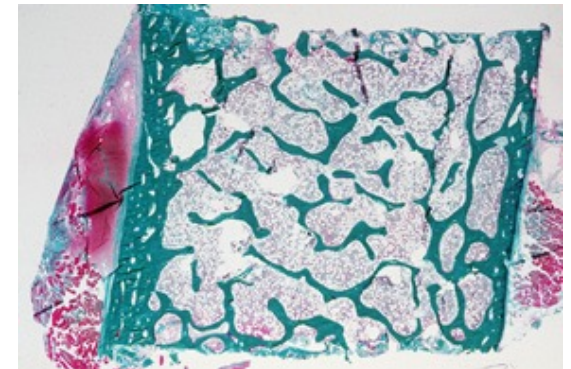


DM-related bone fragility: bone turnover

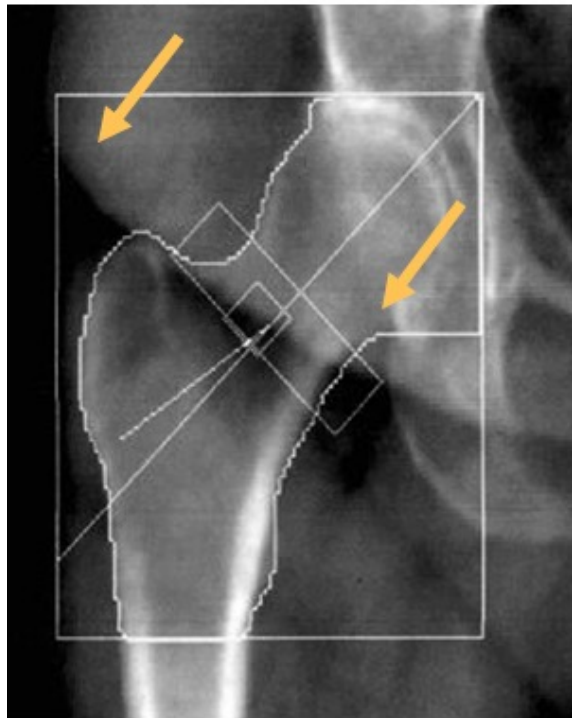


T1DM-related bone fragility: bone turnover

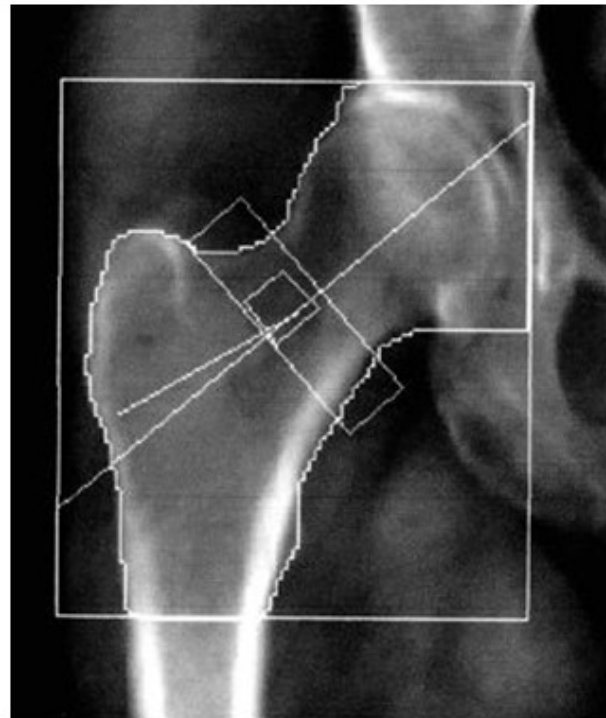
- ▶ Bone histomorphometry:
 - ▶ Low turnover with reduced bone formation & resorption (Bouillon, 1999)
 - ▶ No differences (McNair, 1988)
- ▶ Serum markers of bone turnover
 - ▶ Resembling functional hypoparathyroidism
 - ▶ Lower osteocalcin levels ~ bone formation
 - ▶ Higher serum tartrate resistant acid phosphatase and urinary hydroxyproline ~ bone resorption



T2DM-related bone fragility – effects of adiposity?



Total femur BMD Pre:
0.899 g/cm²

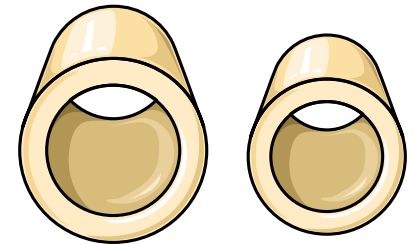


Total femur BMD Post:
0.794 g/cm²



T2DM-related bone fragility – effects of insulin resistance?

- ▶ Effects of insulin resistance?
 - ▶ associated with smaller periosteal & endosteal circumference, smaller cortical area, (smaller cortical thickness)
 - ▶ Not explained by body composition or physical activity level



- ▶ Bone phenotype already appreciable early in T2DM disease course?
- ▶ Direct consequence of impaired insulin signaling in bone – indirect effects through modulation of the muscle-bone relationship – related to physical activity ?



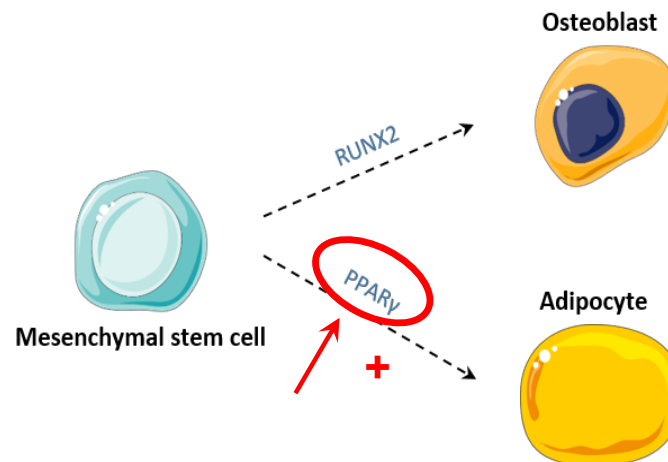
T2DM-related bone fragility

- ▶ What about those drugs?



The glitazone experience

- ▶ Thiazolidinediones (TZD's) bind to and activate one or more peroxisome proliferator-activated receptors (PPARs)
 - ▶ regulate gene expression
 - ▶ improve insulin responsiveness of skeletal muscle and hepatocytes
 - ▶ affect adipokine secretion + adipocyte proliferation & differentiation



The glitazone experience

- ▶ Increased risk of heart failure with rosiglitazone – or not?
- ▶ TZD use associated with decreases in BMD and increases in fracture risk
 - ▶ Health ABC Study: women (not men) taking TZD had greater bone loss
 - ▶ ADOPT: higher rate of fractures in women treated with rosiglitazone as compared to metformin or glyburide
 - ▶ RECORD trial: RR 1,57 [1,26-1,97]; mainly fractures of the extremities
 - ▶ UK-GPRD: increased risk of fragility fractures in both men and women with rosiglitazone (OR 2,38 [1,39-4,09]) and pioglitazone (OR 2,59 [0,96-7,01])
- ▶ **FDA: glitazones should be avoided in patients with high fracture risk!**



T2DM-related bone fragility – effects of drugs?

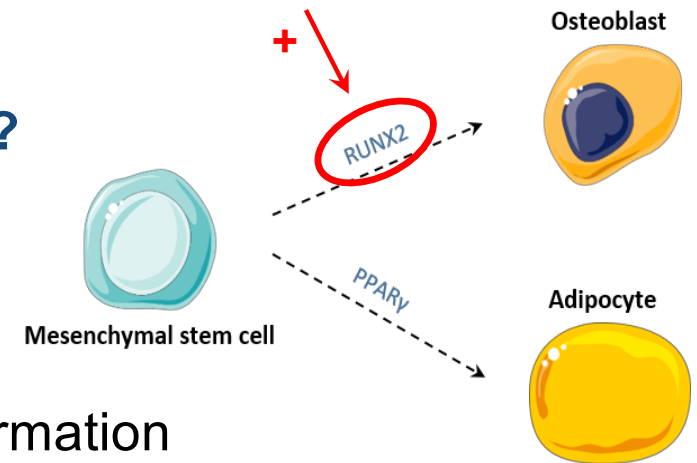
- ▶ Metformin

- ▶ ↓ or = fracture risk
- ▶ effect on osteoblast differentiation: ↑ bone formation

- ▶ Sulfonylurea:

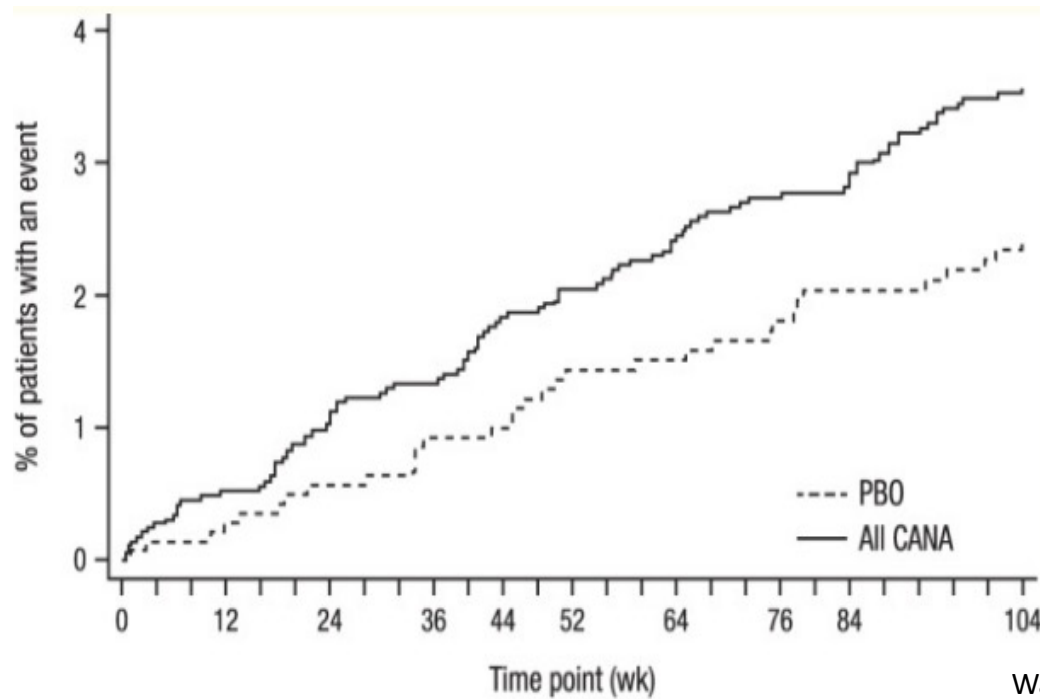
- ▶ Probably no direct effect (understudied)
- ▶ Reports of higher fracture risk < increased hypoglycemia risk

- ▶ No signals from DPP-IV-i or GLP-1 analog studies



T2DM-related bone fragility – effects of drugs?

- ▶ SGLT2-inhibitors: great CV profile! But ...
 - ▶ Natriuresis drives calciuresis, so 6 excess Fx per 1000 pt/yr!



T2DM-related bone fragility – effects of drugs?

- ▶ SGLT2-inhibitors: pathophysiology of increased fracture risk
 - ▶ Natriuresis – calciuresis?
 - ▶ Reduced mechanical loading through weight loss?
 - ▶ Reduced circulating volume → compromising microcirculation?
 - ▶ BP lowering effects → increased fall frequency?

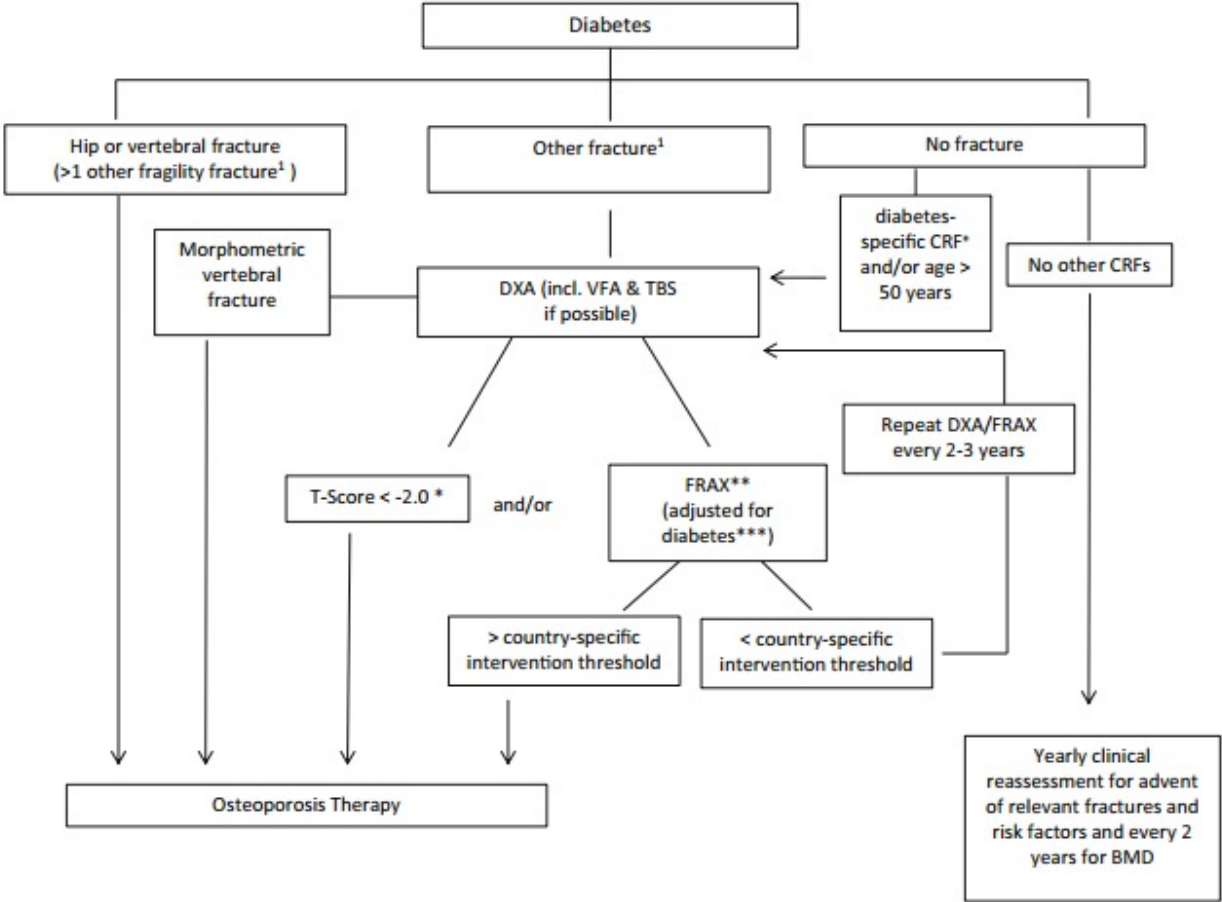


Diabetes & osteoporosis – treatment considerations

- ▶ **Consider** bone fragility as another complication of T1DM & T2DM !
 - ▶ In addition to retinopathy, nephropathy, neuropathy, cardiovascular disease,
- ▶ **General recommendations** for prevention of osteoporosis and fractures are also applicable to postmenopausal women and men with diabetes
 - ▶ Healthy lifestyle, exercise
 - ▶ Calcium (800-1200 mg/d) and vitamin D (800-1000 IU/d) intake / supplementation
 - ▶ Fall prevention!
 - ▶ Avoid smoking and excessive alcohol intake



Diabetes & osteoporosis: treatment considerations



Diabetes & osteoporosis: treatment considerations

- ▶ Diabetes patients with **hip or vertebral fracture** (or > 1 fragility fracture)
 - ▶ Initiate osteoporosis therapy
- ▶ Diabetes patients with **other fragility fracture**
- ▶ Diabetes patients without fracture but with **clinical risk factors**
 - ▶ Perform DXA & calculate FRAX (adjusted for diabetes)
- ▶ **T-score < -2 or vertebral fracture**
 - ▶ Initiate osteoporosis therapy
 - ▶ Otherwise repeat DXA every 2 or 3 years



Diabetes & osteoporosis: treatment considerations

▶ Bisphosphonates

- ▶ Probably as effective in diabetic as compared to non-diabetic patients
- ▶ Studies mostly with alendronate, no data on IV bisphosphonates

▶ Denosumab

- ▶ No data in diabetic patients
- ▶ Cave rapid decline in BMD and increase in fracture risk after discontinuation

▶ SERMs & teriparatide

- Possibly as effective in diabetic as compared to non-diabetic patients



Conclusions

- ▶ Both T1DM and T2DM are associated with increased fracture risk
 - ▶ Increased fall risk
 - ▶ Changes in bone metabolism, structure and mineral density due to metabolic abnormalities
- ▶ Bone disease in T1DM is different from that in T2DM
 - ▶ Early age of onset in T1DM → effects on peak bone mass
 - ▶ Effects of adiposity and insulin resistance in T2DM
 - ▶ Underestimation of risk using DXA in T2DM
 - ▶ Effects of antidiabetic drugs in T2DM
- ▶ Bone health should be within the scope of every physician treating patients with diabetes



Conclusions

- ▶ More knowledge needed on:
 - ▶ Pathophysiology of diabetes-related bone fragility
 - ▶ Better risk prediction, esp. in T2DM – other diagnostic procedures?
 - ▶ Relation with diabetic complications
 - ▶ Natural history in aging
- ▶ Don't break anyone's heart, they have only one!
- ▶ Break their bones, they have 206!



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