Osteoporosis: The double threats of diabetes and fat to skeletal health

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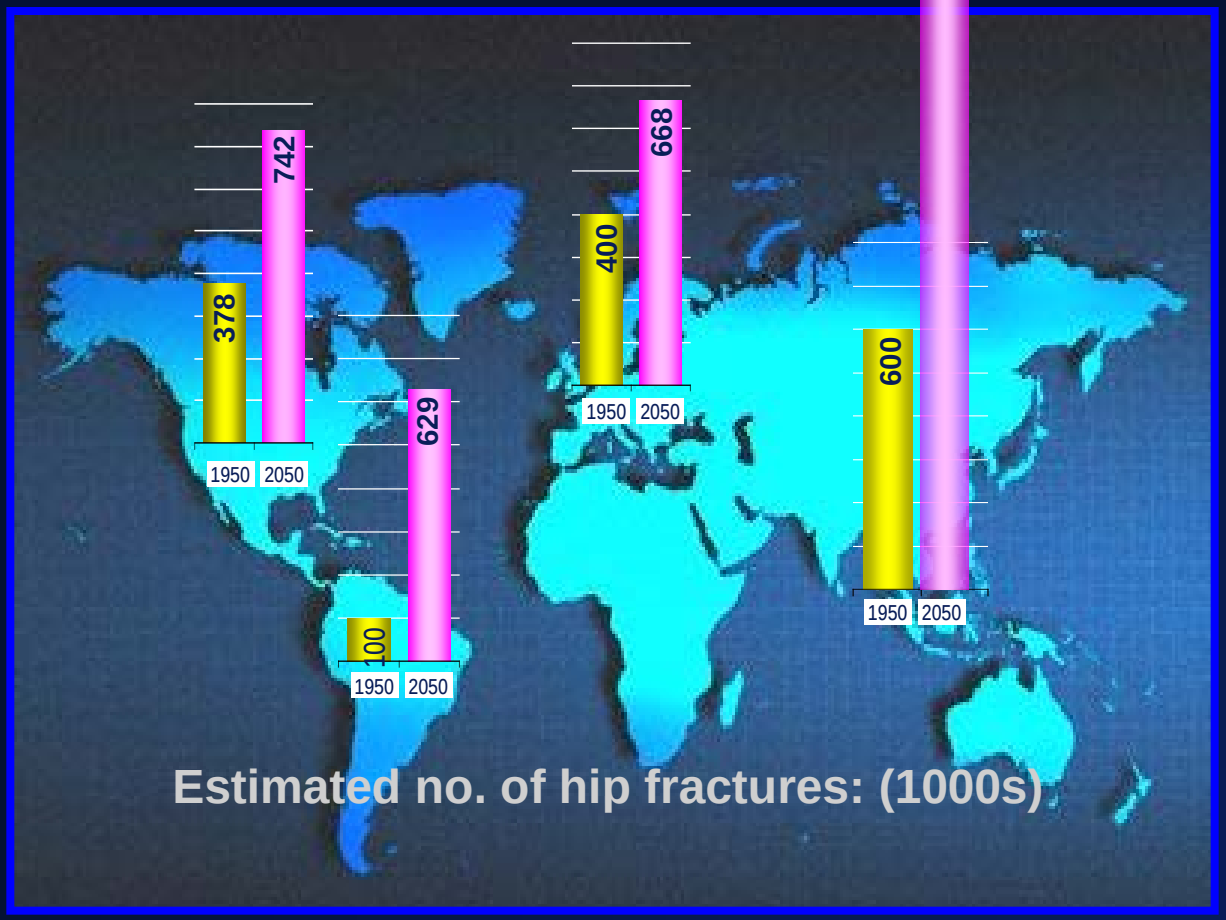
Outline

- Key aspects of osteoporosis
- The paradox of diabetes and skeletal health
- How is diabetes bad for bones?
- The paradox of fat and skeletal health
- How is fat bad for bone?

Osteoporosis

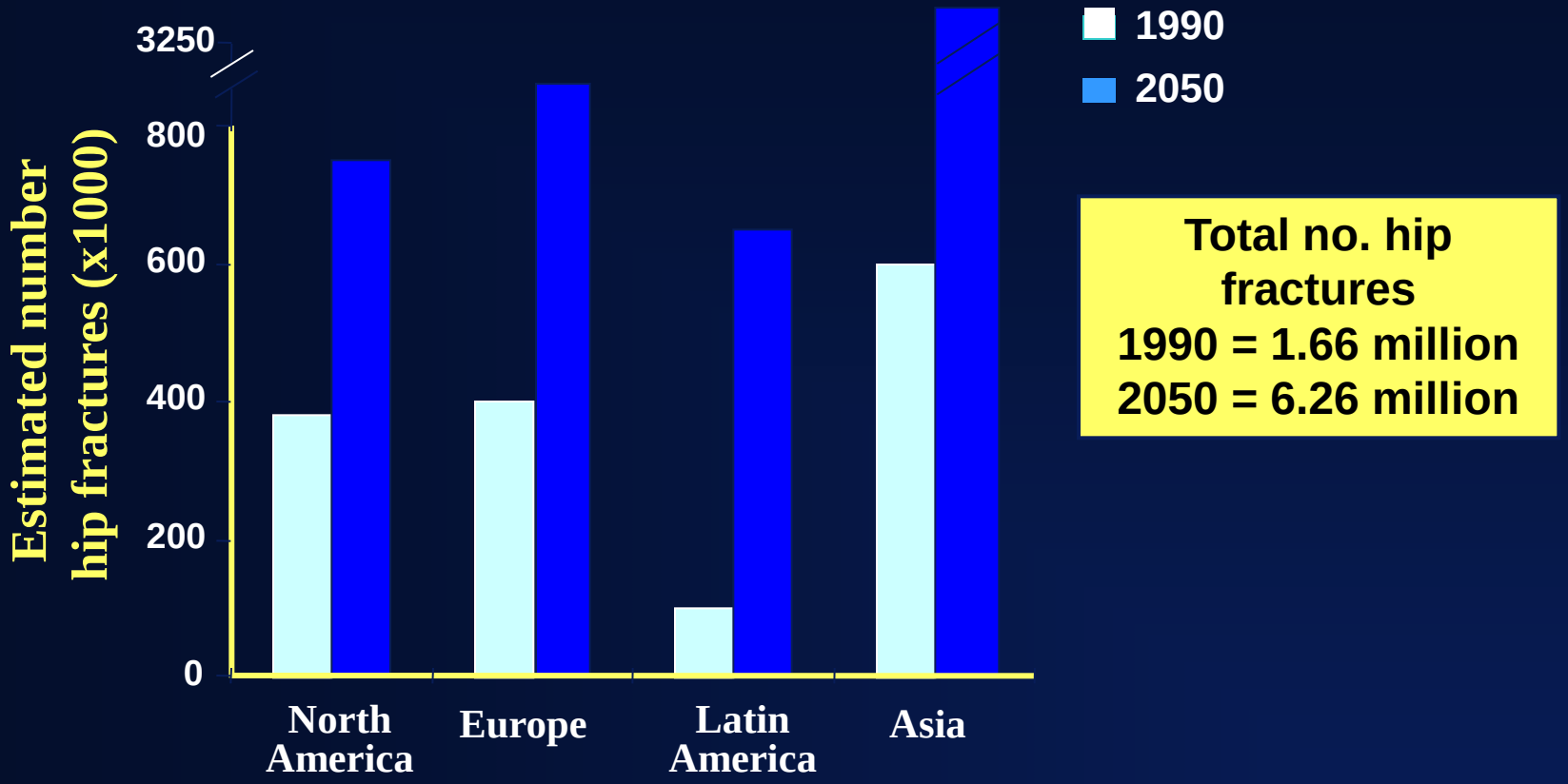
Projected Number of Hip Fractures

Total number of hip fractures:
1950 = 1.66 million
2050 = 6.26 million



Adapted from Cooper C et al. *Osteoporosis Int*. 1992;2:285-289.

Projected number of hip fractures worldwide



Total no. hip fractures
1990 = 1.66 million
2050 = 6.26 million

Cummings et al, 2002

Osteoporosis: Worldwide Prevalence

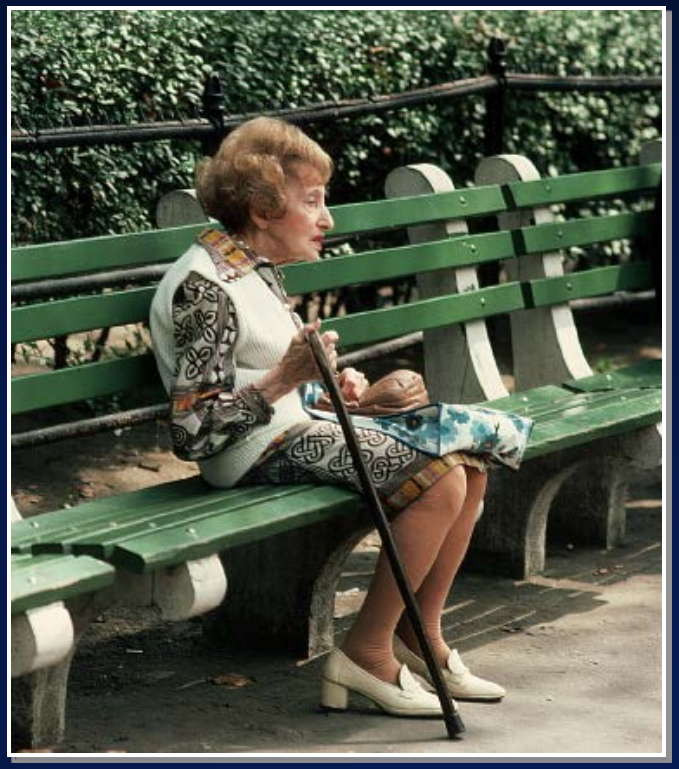
- **Affects 200 million women worldwide[1]**
  - **1/3 of women aged 60 to 70**
  - **2/3 of women aged 80 or older**

- **Approximately 30 % of women over the age of 50 have one or more vertebral fractures[2]**

1. International Osteoporosis Foundation Osteoporos Int 1996, 6:233
2. Dennison,2000

Human Costs of Osteoporosis

- Impaired function, decreased mobility
- More bone loss due to decreased activity
- Compressed abdomen, reduced appetite
- Reduced pulmonary function
- Sleep disorders
- Shortened survival
- Poor self esteem



Ross PD et al. *Ann Intern Med* 1991;114-23.
Silverman SL. *Bone* 1992;13 (suppl 2):S27-31.
Cooper C, et al. *Am J Epidem* 1993;137:1001-5.
Lyles et al. *Am J Med* 1993;94:595-601.
Schlaich C, et al. *Osteoporos Int* 1998;8:261-7.

Photo courtesy of the National Osteoporosis Foundation

The Physical Signs of Severe Osteoporosis

Ross PD et al. *Ann Intern Med* 1991;114-23.
Silverman SL. *Bone* 1992;13 (suppl 2):S27-31.
Cooper C, et al. *Am J Epidem* 1993;137:1001-5.
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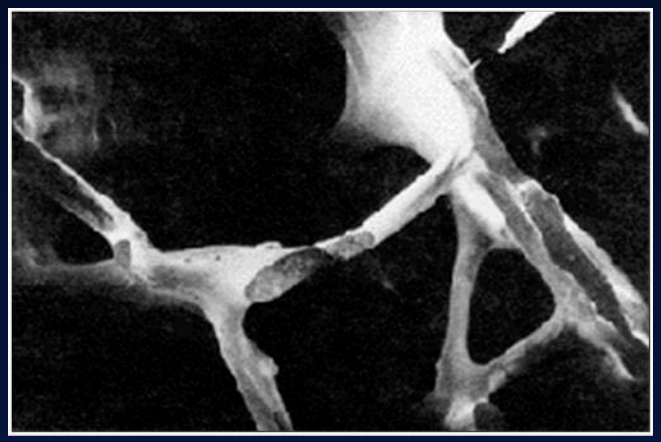
Schlaich C, et al. *Osteoporos Int* 1998;8:261-7.

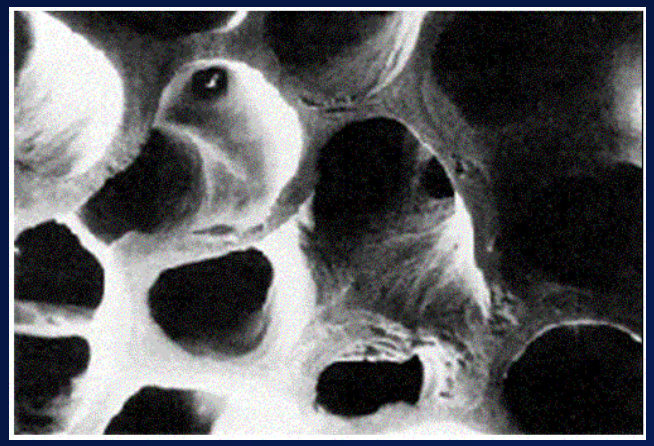
Photo courtesy of the National Osteoporosis Foundation

Osteoporosis: Identifying the Problem

" A skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture."



Osteoporotic bone



Healthy bone

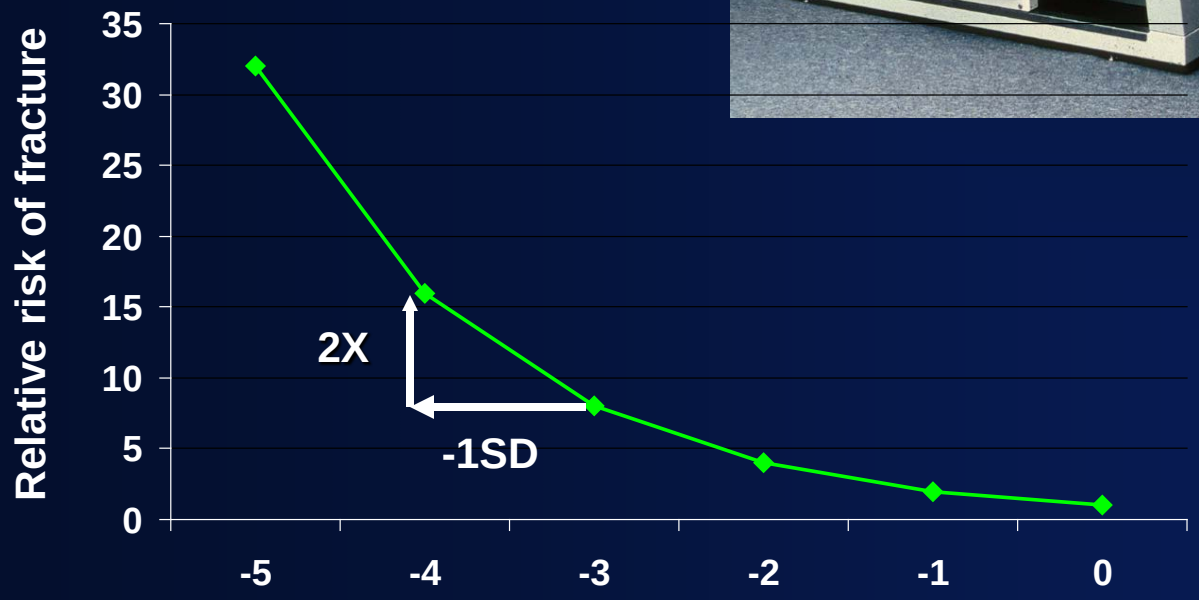
NIH Consensus Development Conference on Osteoporosis, 2000.

Osteoporosis can be identified before the fracture occurs by dual energy X-ray absorptiometry (DXA)

- Safe
- Accurate
- Precise
- Normative population databases
- Correlates with fracture risk
- A diagnostic standard for osteoporosis

Osteoporosis can be identified before the fracture occurs by dual energy X-ray absorptiometry (DXA)

DXA is one of the most powerful predictors of fracture risk

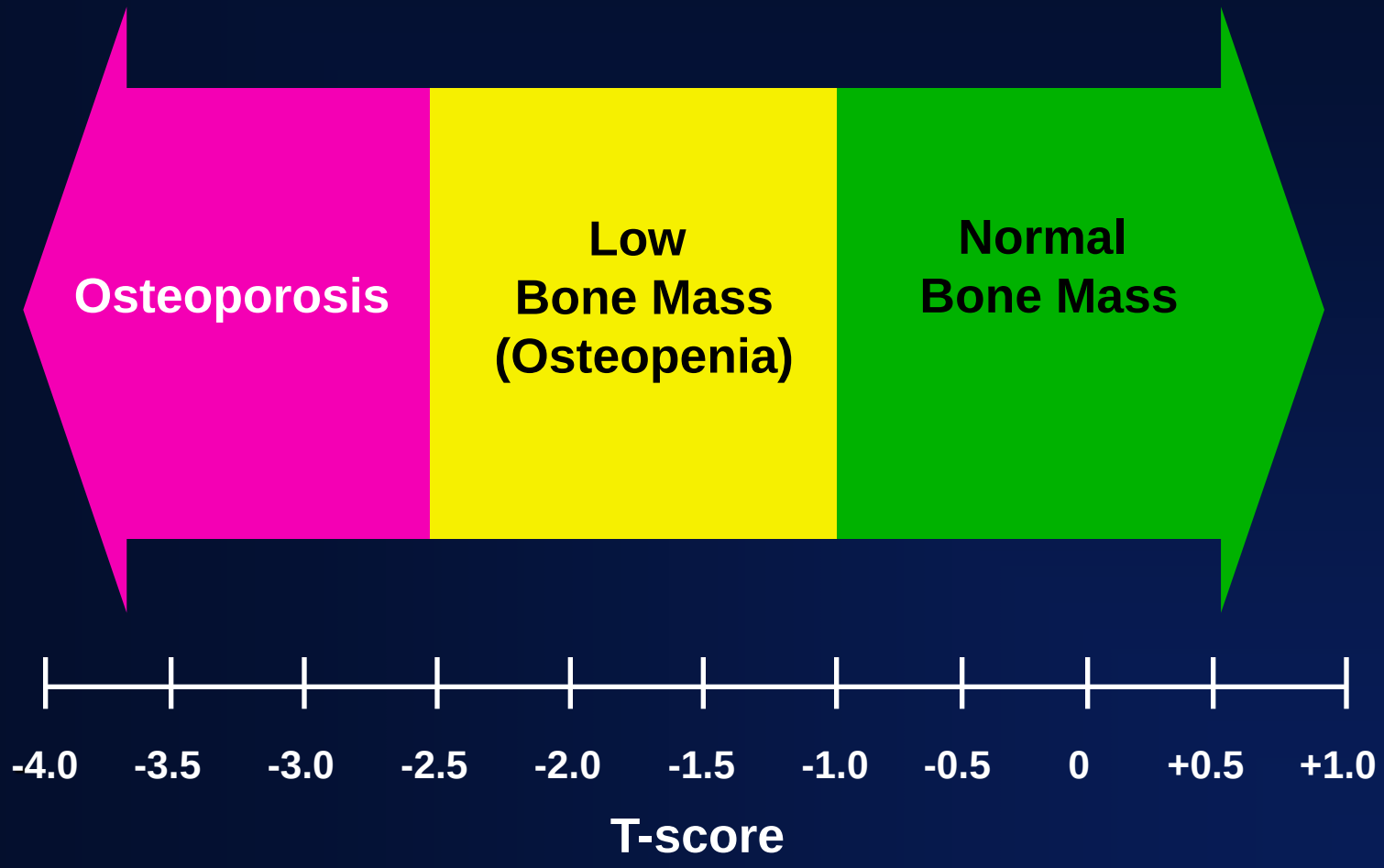


- **Without DXA**….It is exceedingly difficult to diagnose osteoporosis before the osteoporotic fracture occurs

- **With DXA**… .Osteoporosis can be identified before the fracture occurs and plans for prevention and treatment can be implemented

Diagnosing Osteoporosis by DXA: the T-score

Correlates with life time fracture risk for Caucasian Women



Major Points Leading To Osteoporosis Programs in Armenia

- **Recognition:** Osteoporosis is a world wide health problem

- Lack of diagnostic testing equipment in Armenia. In 2007, there was only 1 bone densitometer to measure bone density (bone calcium) in the entire country!

- The Hologic Corporation's generous donations of 7 bone densitometers (6 DXAs and 1 ultrasound instrument) in the past 9 years: (Markarian, YSMU, Erebouni Hospital, Traumatology Hospital, Gyumri, and Karabagh)

- **In 2016: Two more Bone Densitometers will be placed, one in Vanadzor and one in Kapan!**

Historical View

- In 2006, Armenia was among the countries with the **fewest bone density (DXA) instruments/capita in the world**

- In 2013, Armenia gained enough DXA instruments to be placed in the **middle rankings of all countries in the world!**

- **In 2016, Armenia will be above the average in comparison to all other countries in the world per capita!**

Progression (or Consequence) of Osteoporosis

Patient at age 50...

and 25 years later

How did this Happen?

Used with permission of the National Osteoporosis Foundation, *Osteoporosis: The Silent Disease*, National Osteoporosis Foundation, Partners in Prevention Slide Presentation, 1993.

Risk Factors for Osteoporosis

- Age
- Family (genetics)
- The menopause
- Certain medications like glucocorticoids
- Other diseases (rheumatoid arthritis, COPD, Type 1 Diabetes mellitus)
- Nutrition (anorexia, vitamin D deficiency)
- Lifestyle issues (smoking, excessive alcohol, lack of exercise)

Risk factors for Osteoporosis

- Not on most lists:
- **Type 2 Diabetes mellitus**

WHO Estimate for diabetes in different parts of the world

382 million adults (8.3%) worldwide are living with diabetes
By 2035 the number will increase to 592 million

Country	2000	2030
Albania	86,000	188,000
Andora	6,000	18,000
Armenia	120,000	206,000
Austria	239,000	366,000
Azerbaijan	337,000	733,00

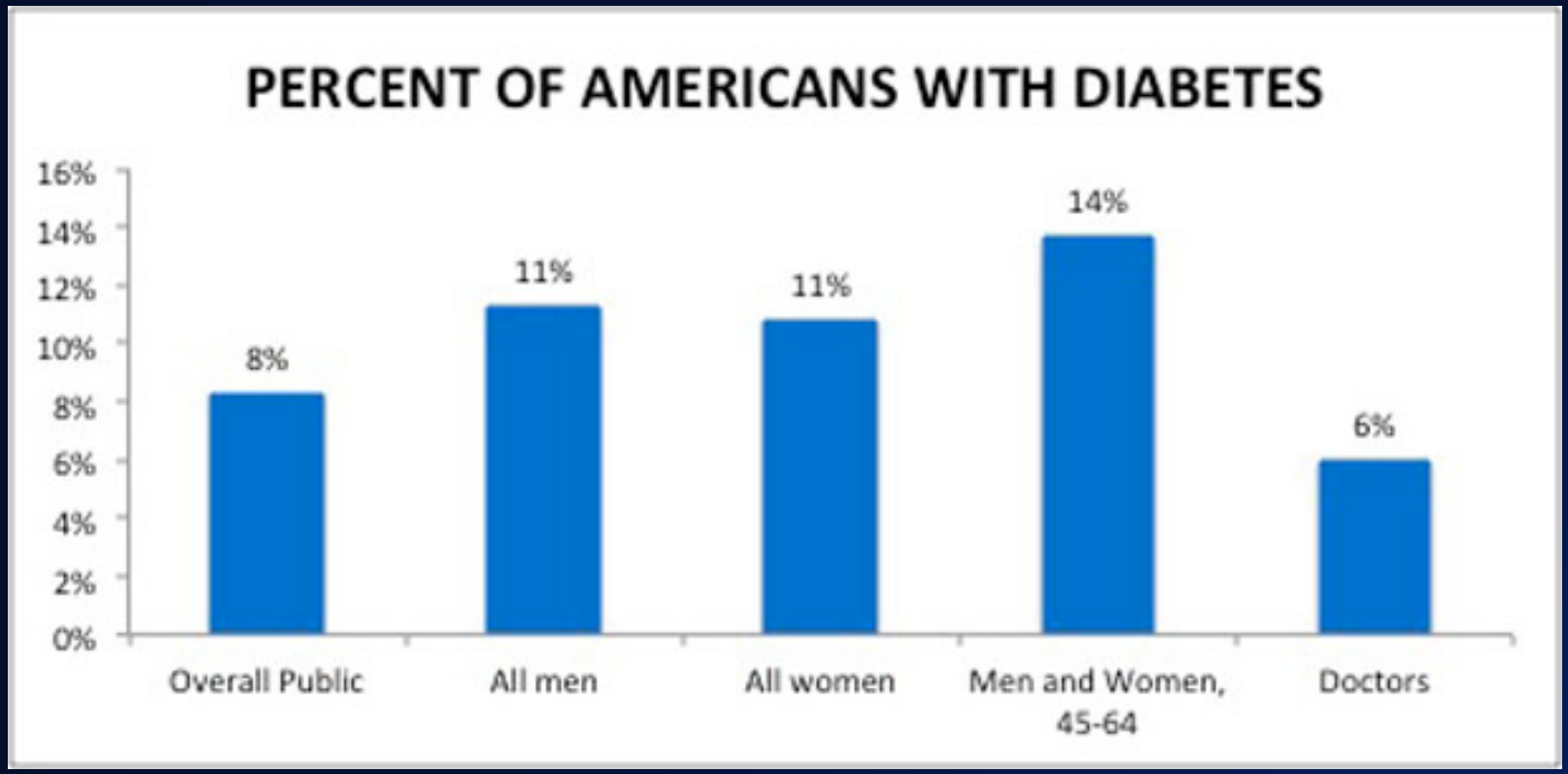
http://www.who.int/diabetes/facts/world_figures/en/index4.htm

Prevalence of Diabetes and Prediabetes

- In 2012 - 29.1 million Americans, or 9.3% of the population, had diabetes.
  - The vast majority have type 2 Diabetes
  - Approximately 1.25 million American children and adults have type 1 diabetes.

- Seniors: The percentage of Americans age 65 and older with diabetes is 25.9%, or 11.8 million (diagnosed and undiagnosed).

Diabetes Prevalence in 2013



National Diabetes Statistics Report, June, 2013
http://www.diabetes.org/diabetes-basics/statistics/

Diabetes cases reach 422 million as poorer countries see steep rises

- Between 1980 and 2014, diabetes has become more common among men than women.
- Diabetes rose significantly in many low and middle income countries, including China, India, Indonesia, Pakistan, Egypt and Mexico
- Northwestern Europe has the lowest rates of diabetes, lower than 4 percent among women and at around 5 to 6 percent among men in Switzerland, Austria, Denmark, Belgium and the Netherlands.
- No country saw any meaningful decrease in diabetes prevalence.

http://mobile.reuters.com/article/idUSKCN0X31BL

Diabetes: Complications/Co-Morbid Conditions

- **Hypoglycemia** –In 2011, about **282,000** emergency room visits for adults aged 18 years or older had hypoglycemia (BG < 70 mg/dl).
- **Hypertension**- In 2009–2012, of adults aged 18 years or older with diagnosed diabetes**, 71%** had blood pressure greater than or equal to 140/90
- **Dyslipidemia-** In 2009–2012, of adults aged 18 years or older with diagnosed diabetes, **65%** had LDL cholesterol > 100 mg/dL
- **Kidney Disease**- Diabetes was listed as the primary cause of kidney failure in **44%** of all new cases in 2011

http://www.diabetes.org/diabetes-basics/statistics

Diabetes: Complications/Co-Morbid Conditions

- **CVD Death Rates:** In 2003–2006, after adjusting for population age differences, CVD death rates were about **1.7 times** higher than in general population
- **Heart Attack Rates:** In 2010, after adjusting for population age differences, hospitalization rates for heart attack were **1.8 times higher**
- **Stroke:** In 2010, hospitalization rates for stroke were **1.5 times higher**
- **Amputations:** In 2010, about **73,000** non-traumatic lower-limb amputations were performed in adults aged 20 years or older with diagnosed diabetes.

http://www.diabetes.org/diabetes-basics/statistics

With all the bad news about diabetes…

We have thought, until recently, that one thing we didn't have to worry about was an increased risk of osteoporosis in Diabetes…..

A paradox: Type 2 Diabetes Mellitus should protect against osteoporosis

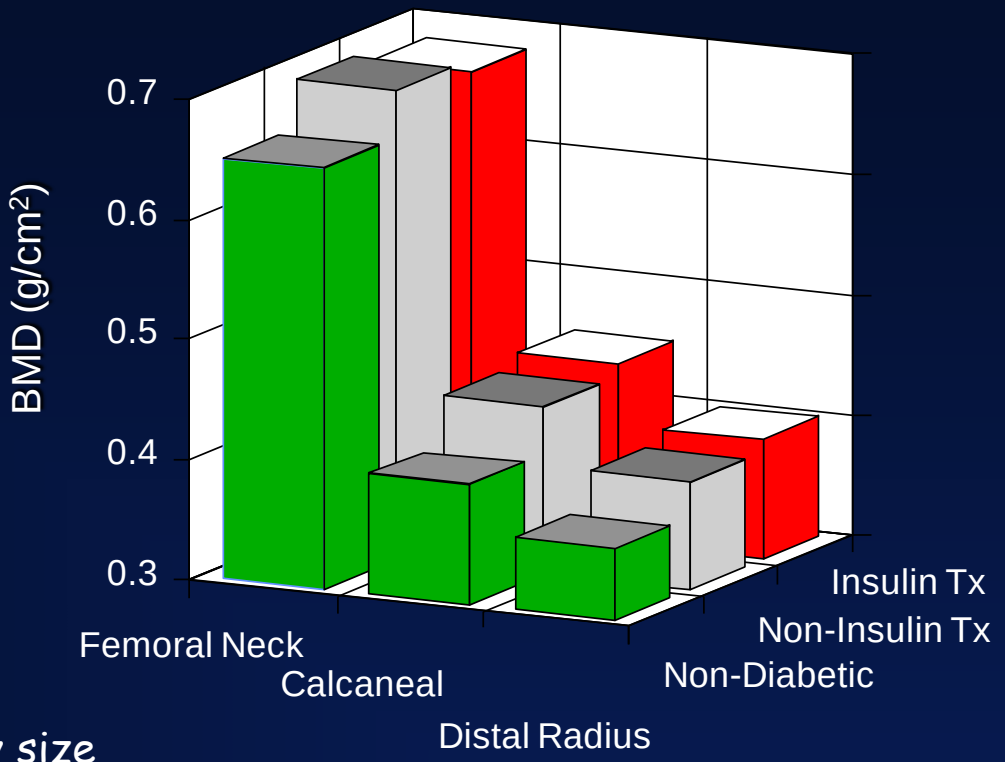
- Protective Factors:
  - Average or higher BMD than age-matched controls
  - Greater weight in general

In Type 2 Diabetes Mellitus, BMD is higher

Study of Osteoporotic Fractures
(n=9654 women, ≥65 yo)
BMD in T2D:

- 5% higher at radius
- 5% higher at calcaneus
- 3% higher at femoral neck

With or without insulin, adjusted for body size



Schwartz JCEM 2001

T-scores in T2D are 0.3-0.8 higher than those in controls

Hanley J Bone Miner Res 2003
Bonds J Clin Endocrinol Metab 2006
Melton J Clin Endocrinol Metab 2008

Expectations of fracture risk in Diabetes Mellitus based upon bone mineral density

Should be lower than age- and weight-matched controls

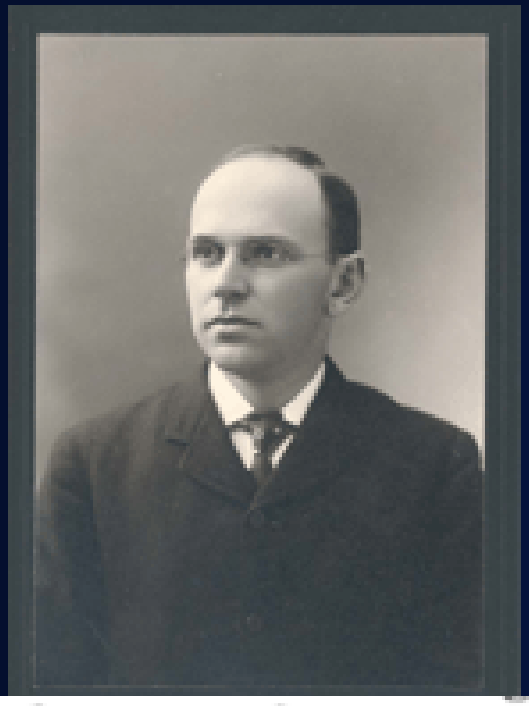
Type 2 Diabetes

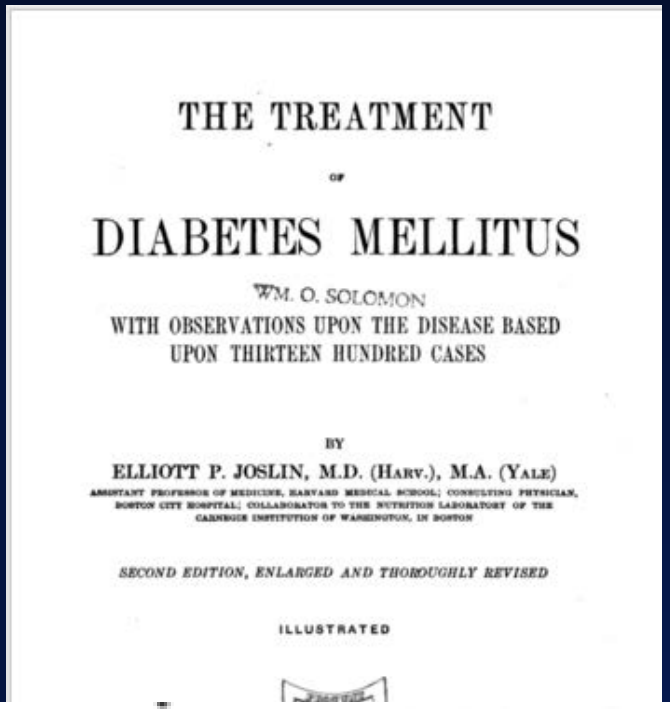
- Expectation:
  - Lower Fracture Risk

but….

- **Fracture risk is higher**

History of Diabetes and Fractures





THE TREATMENT

OF

DIABETES MELLITUS

WM. O. SOLOMON

WITH OBSERVATIONS UPON THE DISEASE BASED UPON THIRTEEN HUNDRED CASES

BY

ELLIOTT P. JOSLIN, M.D. (HARV.), M.A. (YALE)

ASSISTANT PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL; CONSULTING PHYSICIAN, BOSTON CITY HOSPITAL; COLLABORATOR TO THE NUTRITION LABORATORY OF THE CARNEGIE INSTITUTION OF WASHINGTON, IN BOSTON

SECOND EDITION, ENLARGED AND THOROUGHLY REVISED

ILLUSTRATED

The fracture of an extremity is often accompanied by glycosuria. Among 61 cases at the Surgical Clinic at Kiel, 24 showed alimentary glycosuria, and in 3 unsuspected diabetes was discovered. Hyperglycemia was present in 31 out of 36 of the cases examined.[1] It

Type 2 Diabetes and Fracture Risk Meta-analyses

- Vestergaard et al. 2007 (8 Studies)
  - Age-adjusted
  - By BMD alone, the RR would be expected to be lower, approximately 0.77
  - **But RR for hip fracture is higher, 1.38 (1.25-1.53)**
- Janghorbani et al.2007 (8 Studies)
  - Adjusted for multivariables
  - **Hip fracture RR=1.7 (1.3-2.2)**
  - **Any fracture RR=1.2 (1.01-1.5)**

Increased Fractures are at Multiple Sites in T2D

WHI (n=93,676; 7 years follow-up)
RR for fracture in T2D:

- Hip 1.41
- Foot 1.44
- Upper arm 1.30
- Ankle 1.34
- Spine 1.28
- Forearm 0.98

Bonds JCEM 2006

Fractures and Diabetes

Table 2—Risk of fracture for cohorts with and without diabetes

	n	Person-years	Fracture events	Incidence*	HR	95% CI
No diabetes	64,942	423,320	7,232	17.1	1.00	Reference
All diabetes†	32,471	229,210	5,540	24.2	1.66	1.60–1.72
Type 1	2,992	22,627	382	16.9	1.22	1.10–1.36

Fractures in diabetes can have a devastating effect on quality and length of life

- Deep wound infection OR= 1.54 (95% CI 1.06–1.71)
- Septicemia OR= 1.42 (95% CI 1.23–1.64)
- Mortality OR= 1.27 (95% CI 1.02–1.60)

Liao et al. *Diabetes Care* 2014; **37**(8): 2246-52.

Duration of T2D is associated with higher risk of hip fracture: Scottish Registry Study:

(Hothersall et al. J Bone Mineral Res, 2013)

Entire Cohort:*

Men: **RR 0.97** (0.92-1.02)
Women: **RR 1.05** (1.01-1.10)

T2D duration > 7 years:

Men: **RR 1.25** (1.08-1.45)
Women: **RR 1.55** (1.38-1.75)

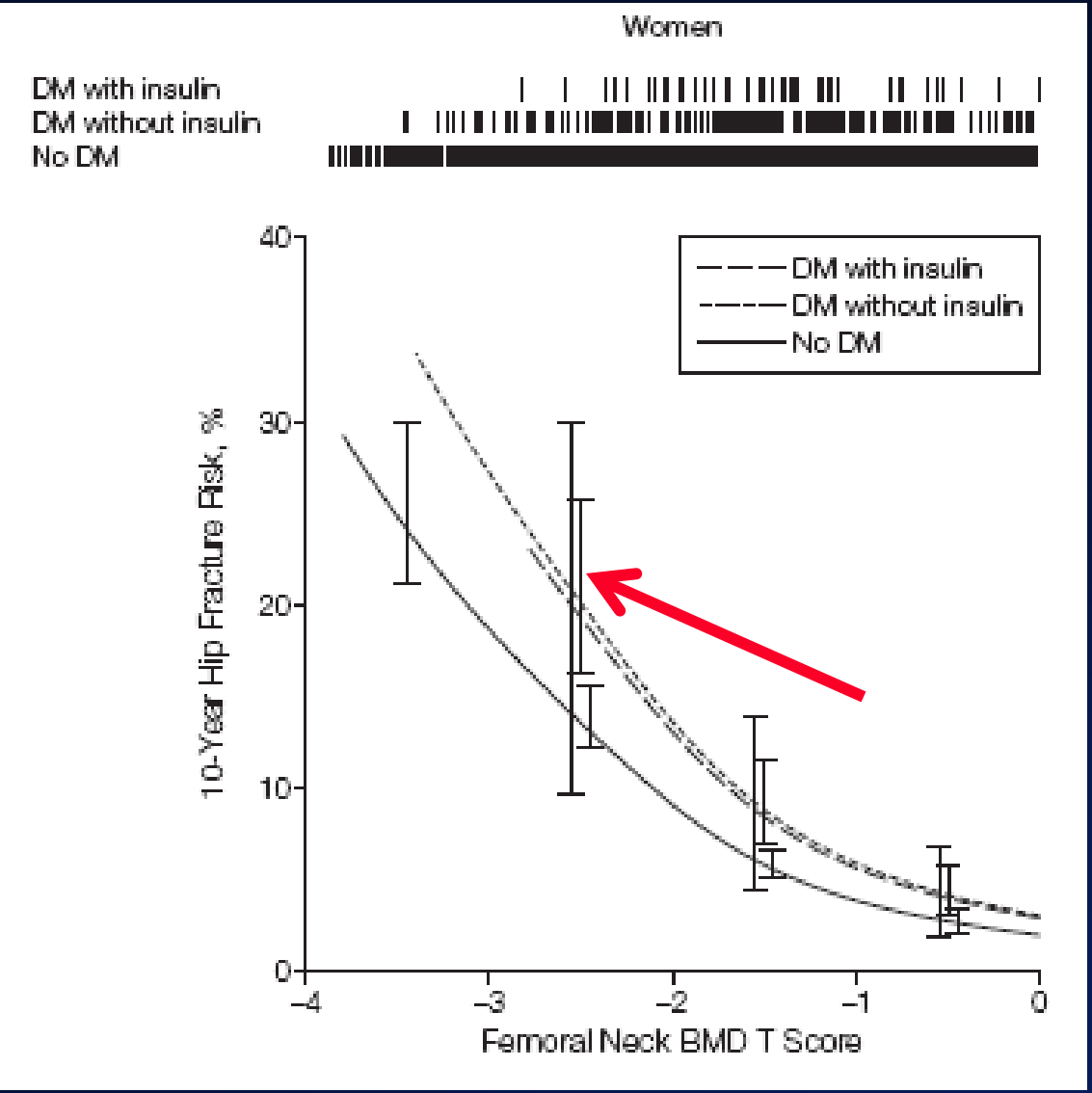
*In T1 DM: Men: RR 3.28 (2.52-4.26)
Women: RR 3.54 (2.75-4.57)

Question: If BMD is higher on average, in Diabetes, can we still use it to predict fracture ?

Answer: Yes, BMD is predictive of fracture risk in T2D, *But* the relationship is different

3 prospective cohorts:

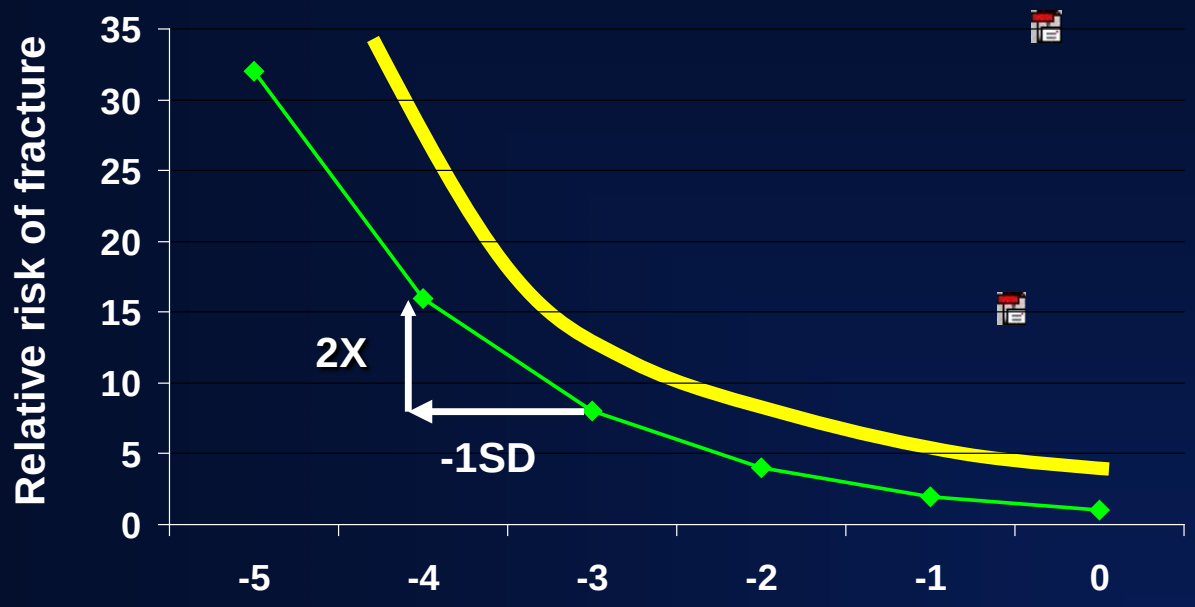
- SOF
- MrOS
- Health ABC



Schwartz JAMA 2011

BMD Can Predict Fracture in T2D

But for a given T- score,
T2D will have a higher fracture risk



T score difference of 0.6 for same fracture risk

Bone Density and Fracture Risk in Diabetes Mellitus

Patients with Diabetes mellitus fracture at a higher BMD than patients without Diabetes mellitus

Does FRAX Also Predict Fracture in T2D?

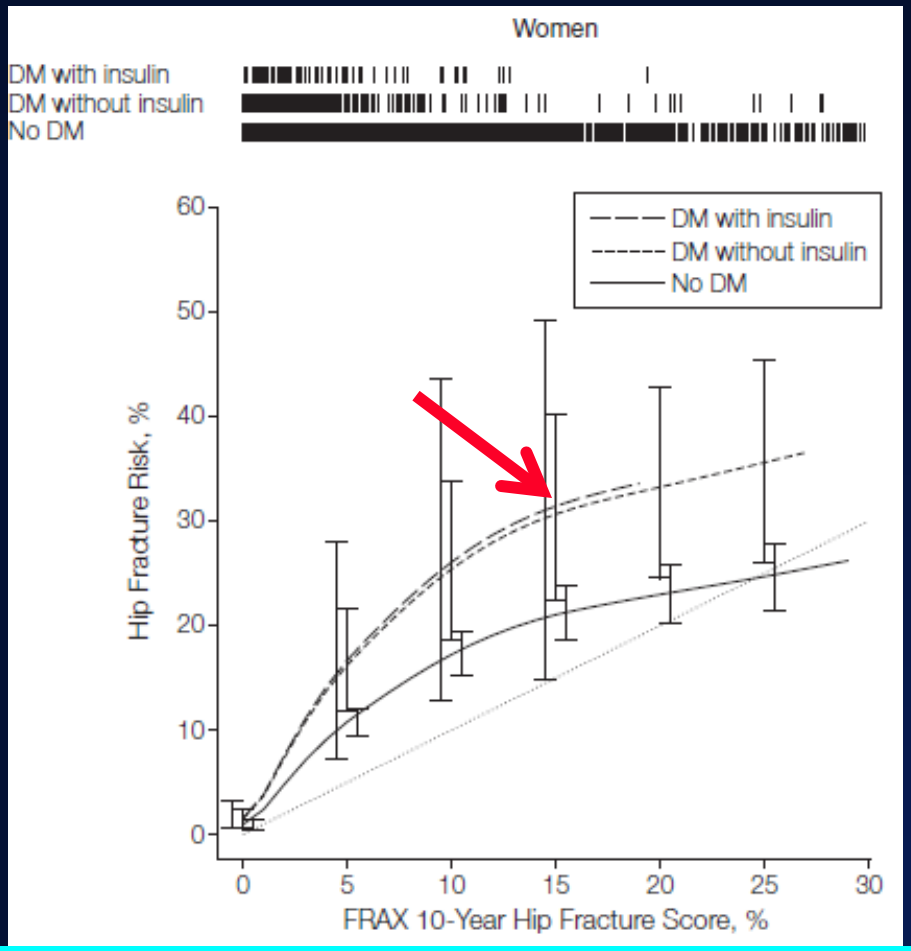
Can the FRAX Score, as currently constituted, be used reliably in T2D?*

BMD (femoral neck T-score)
Age
Gender
Race
BMI
Fracture history
Parental history of hip fracture
Current smoker
Recent corticosteroid use
Rheumatoid arthritis
3+ alcohol drinks/day

* Diabetes is not listed as a clinical risk factor!

FRAX is Predictive of Fracture Risk in T2D, But the Relationship is Different

For a given FRAX score, T2D will have a higher fracture risk



Schwartz JAMA 2011

For a given FRAX score, fracture risk is higher than predicted in T2D

Type 2 Diabetes and Fracture

- For a given BMD, fracture risk in Diabetes Mellitus is greater

- For a given FRAX score, fracture risk in Diabetes Mellitus is greater

There must be factors that account for fracture risk in T2D that are not captured by either BMD or FRAX!

Why in T2D is there an increase in fractures?

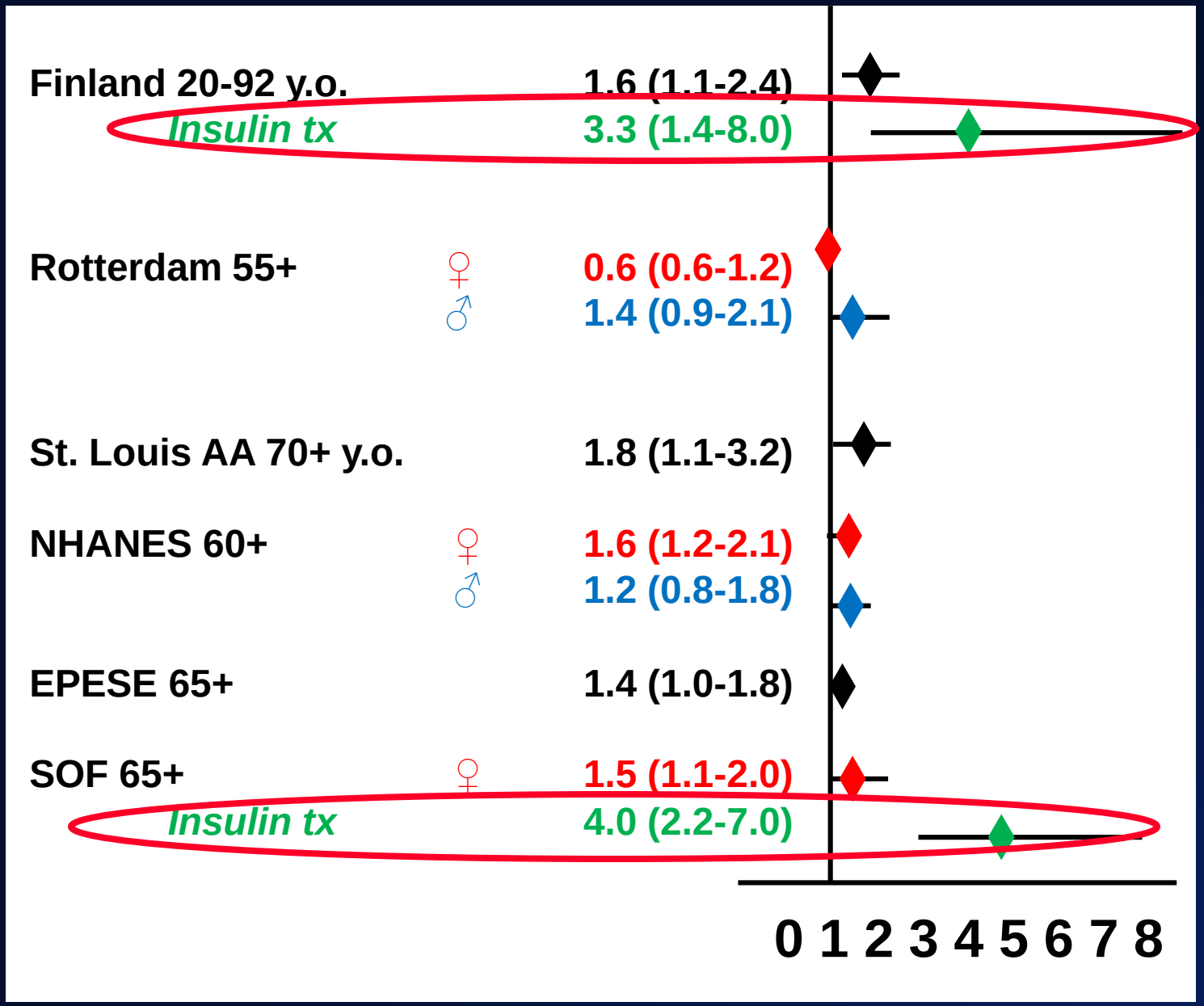
Possible contributing factors for increased fracture risk in T2 Diabetes Mellitus

- Contributing Factors:
  - Falls?
  - TZDs?
  - Skeletal abnormalities?
  - Fat?

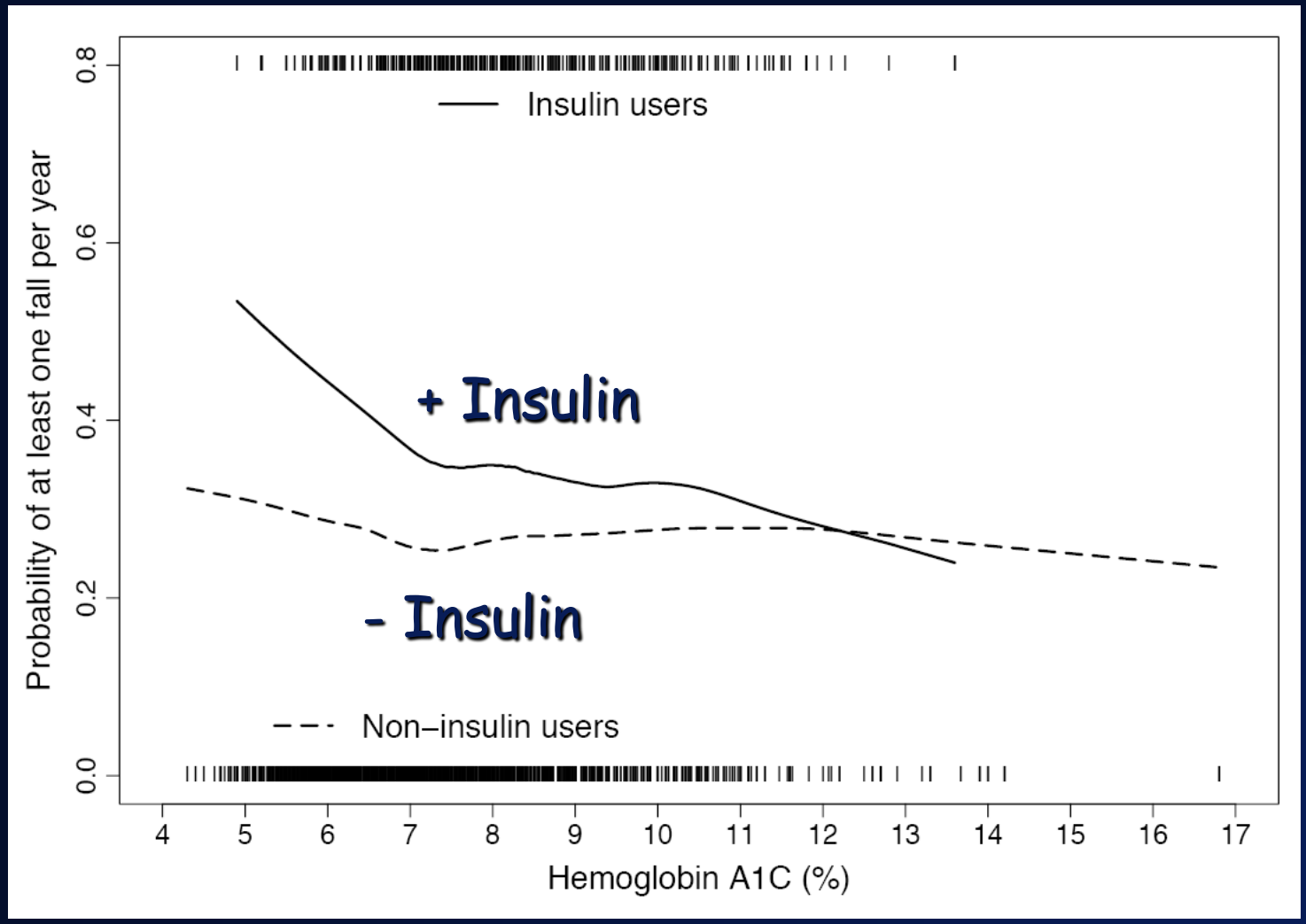
Possible reasons for increased falls in T2D

Peripheral neuropathy (impaired balance, gait)
Poorer Vision (Retinopathy)
Knee and hip osteoarthritis
Cardiovascular (CHF and arrhythmias)
History of CVA
Hypoglycemia (with insulin use)
Low vitamin D

Higher Risk of Falls in T2D



Fall Risk: A1C and Insulin Use



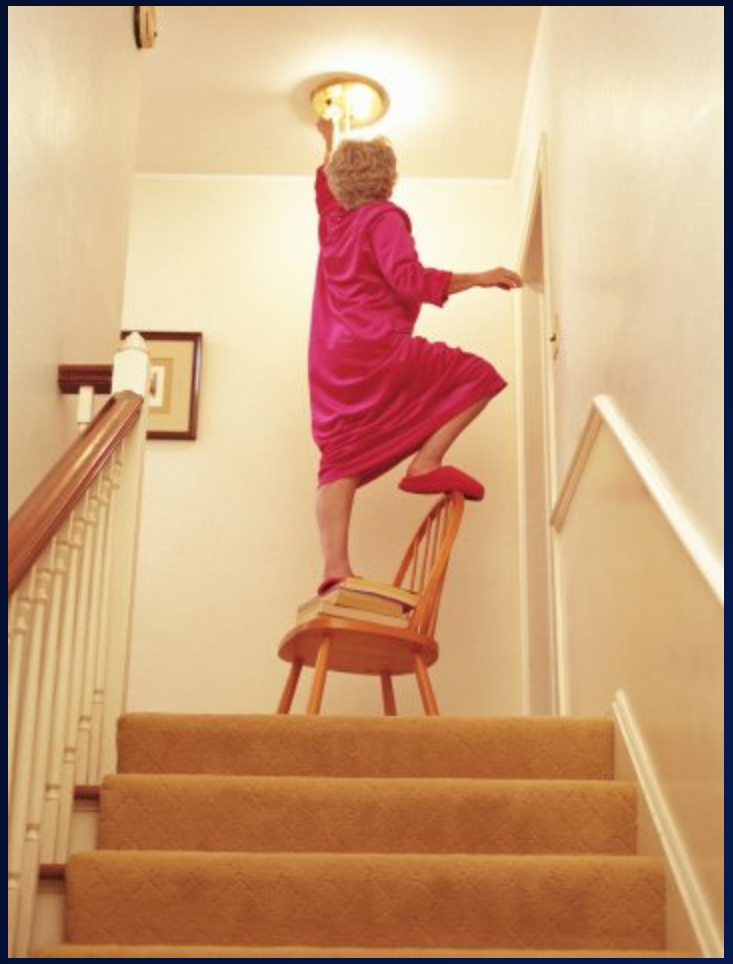
But when studies adjusted for falls,
T2D was still associated with increased fracture risk

All accounted for falls:

- -WHI Bonds 2006
- -Health ABC Strotemeyer 2005
- -SOF Schwartz 2001
- -Rotterdam study de Liefde 2005

Falls are not the whole story

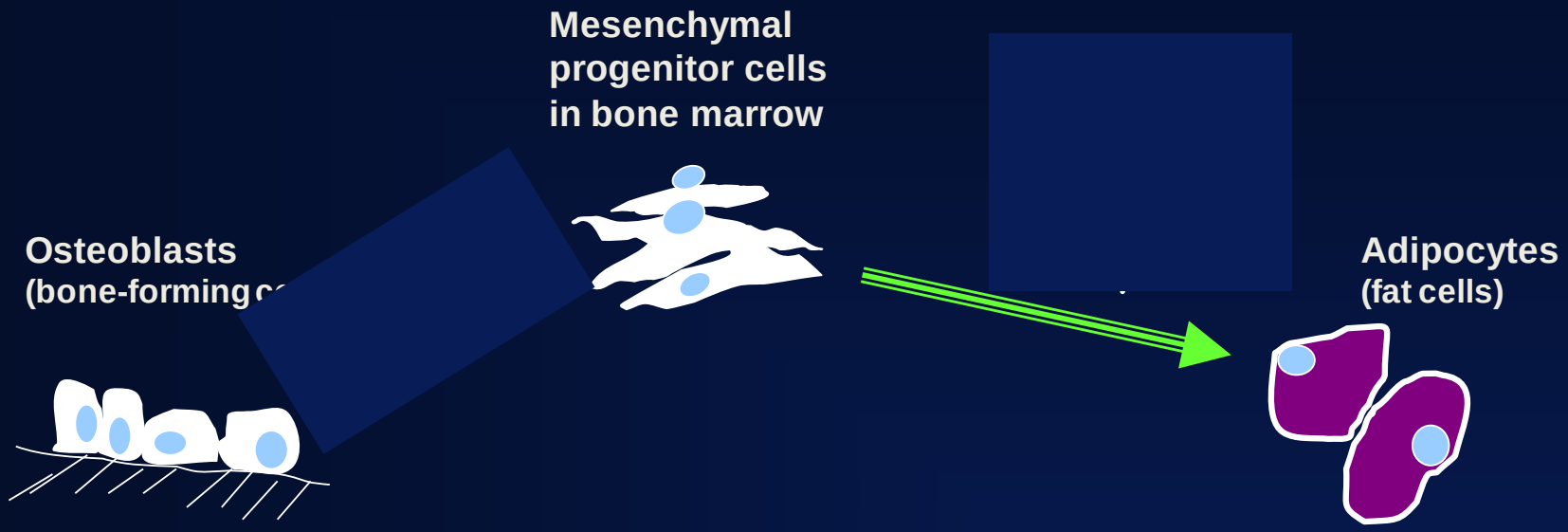
Advise against risky behavior for falls in all, especially those with Diabetes Mellitus!



Possible contributing factors for increased fracture risk in T2 Diabetes Mellitus

- Contributing Factors:
  - Falls?
  - **TZDs?**
  - Skeletal abnormalities?
  - Fat?

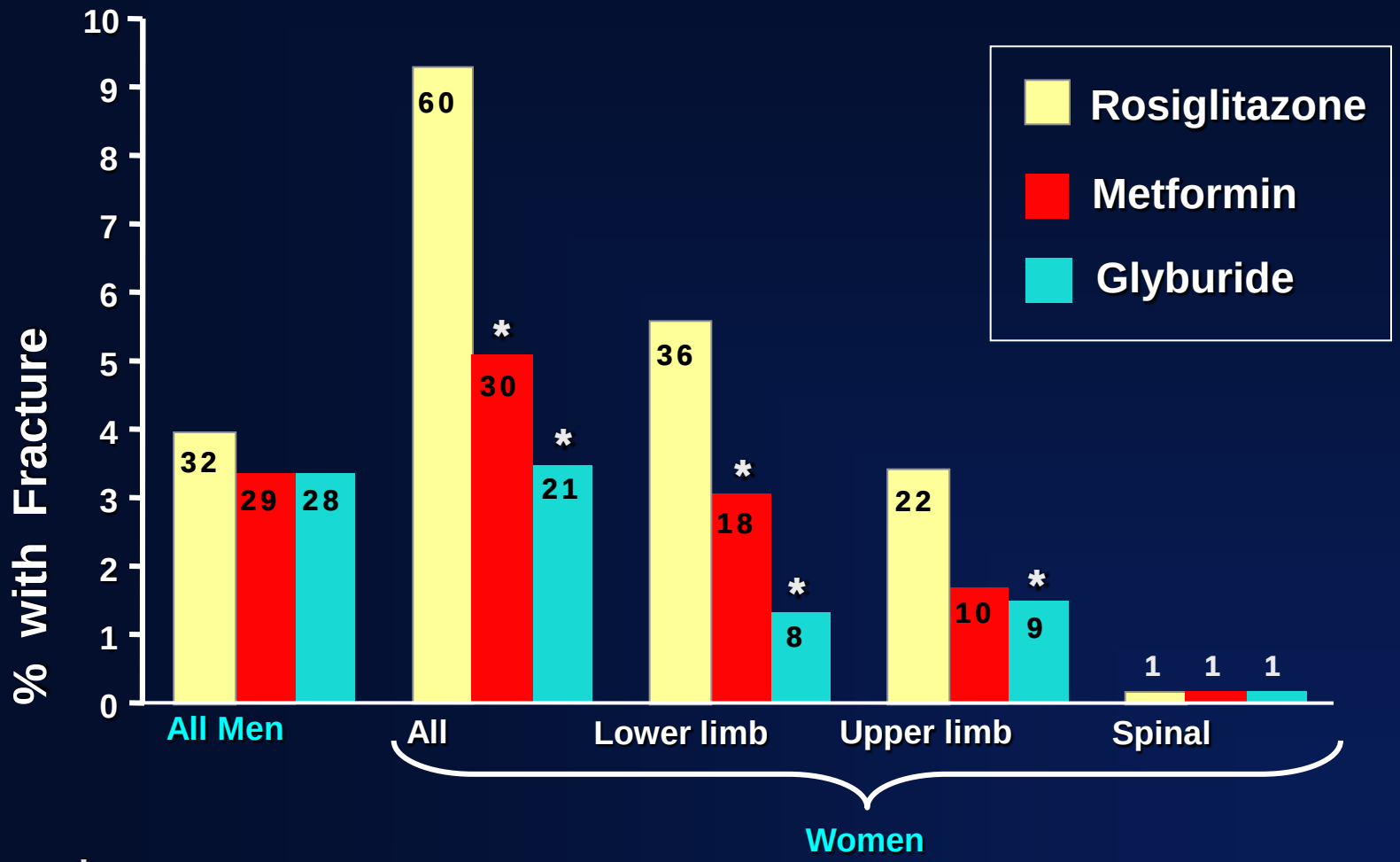
TZDs influence the lineage pathway of marrow mesencymal progenitors



TZDs are likely to shift bipotential bone marrow precursor cells from the osteoblast lineage tract to the adipocyte lineage tract

ADOPT Trial: RPCT

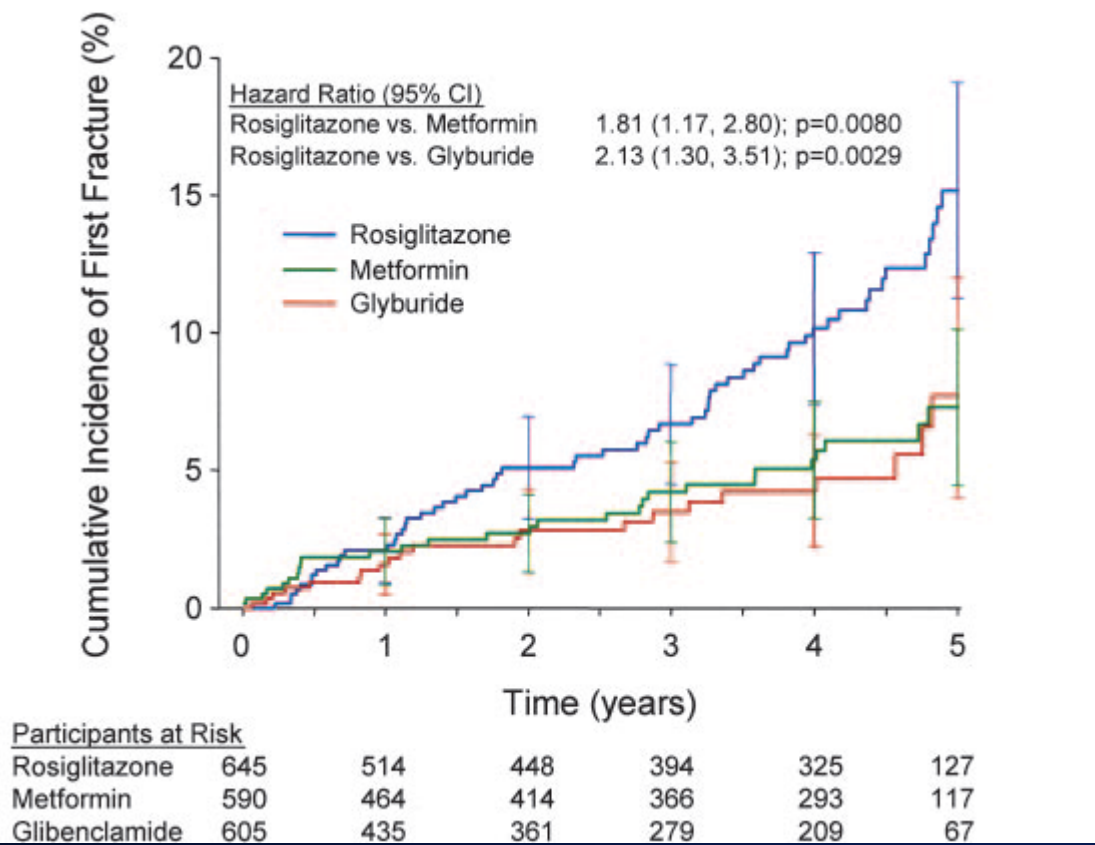
Rosiglitazone increased fracture risk in women



*P<0.05 for the comparison with rosiglitazone (unadjusted, contingency chi-square test).

Kahn Diabetes Care 2008

TZDs and Fracture



TZDs should not be used in women at higher risk of fracture

Kahn Diabetes Care 2008

TZDs increase fracture risk

But, TZDs cannot account for fracture risk in Diabetes because they are used sparingly in this population

TZDs are not the whole story

Diabetics Have Multiple Risk Factors for Poor Skeletal Health

- Contributing Factors:
  - Falls
  - TZDs
  - **Abnormal Skeletal Properties**
    - **Reduced Turnover?**
    - **Abnormal Biomechanics?**
    - **Reduced Bone Quality?**

Reduced Bone Formation in T2D

The circulating bone formation marker, osteocalcin, is reduced

Gerdhem OI 2005, Dobnig JCEM 2006,
Yamamoto JCEM 2012

By bone biopsy, bone formation rate is low

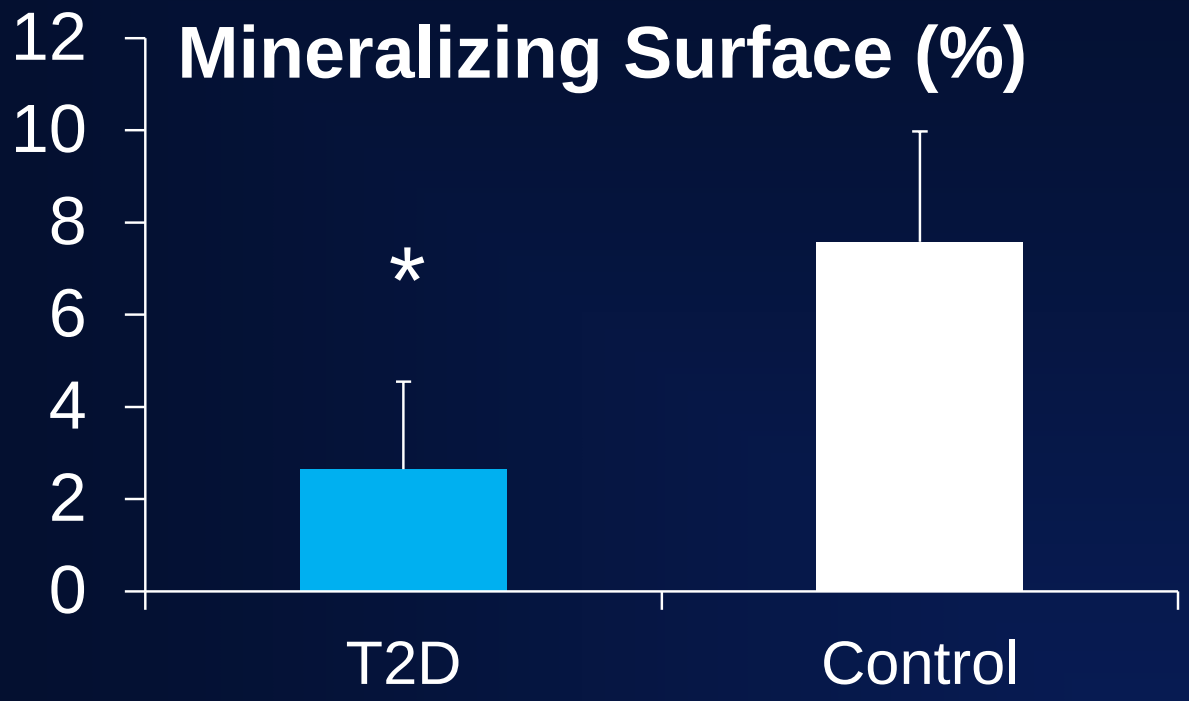
T2D (n=6) compared with premenopausal women

Krakauer et al 1995

T2D (n=5) compared with controls
(n=5), postmenopausal women

Manavalan et al 2012

Histomorphometric Bone Formation is Low in T2D

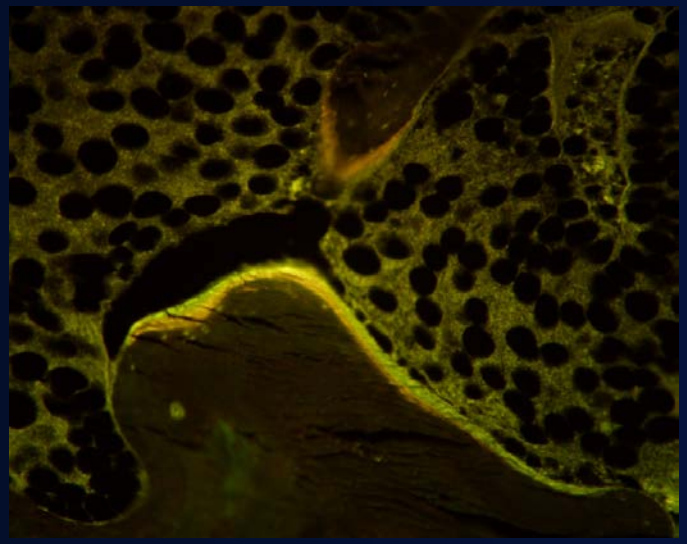


Manavalan JCEM 2012

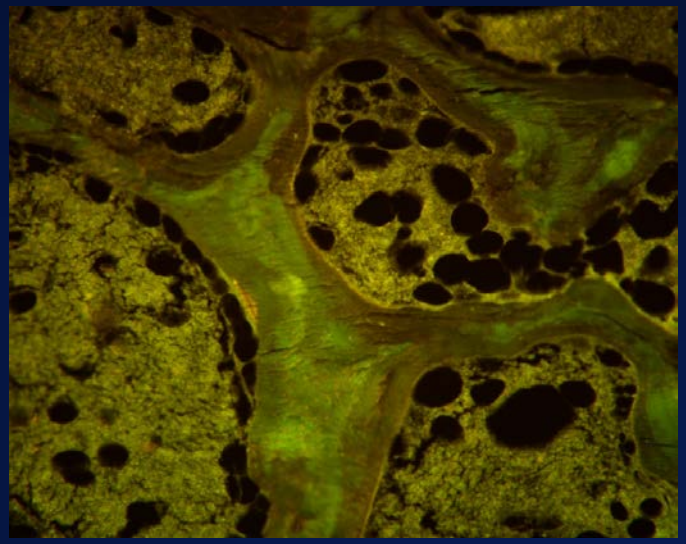
Low Bone Formation in T2D

Osteocalcin is decreased

Gerdhem OI 2005, Dobnig JCEM 2006, Yamamoto JCEM 2012



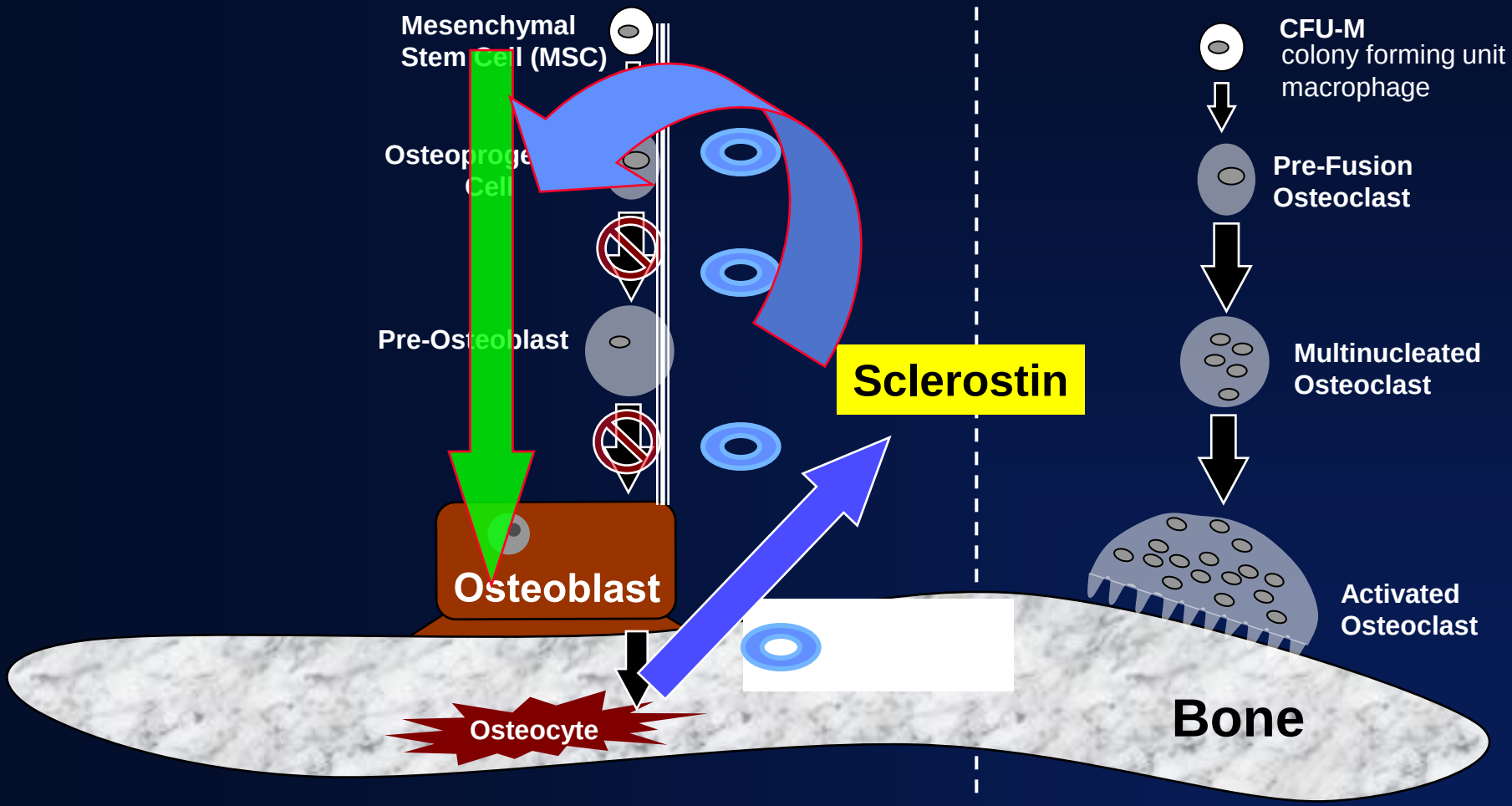
Control



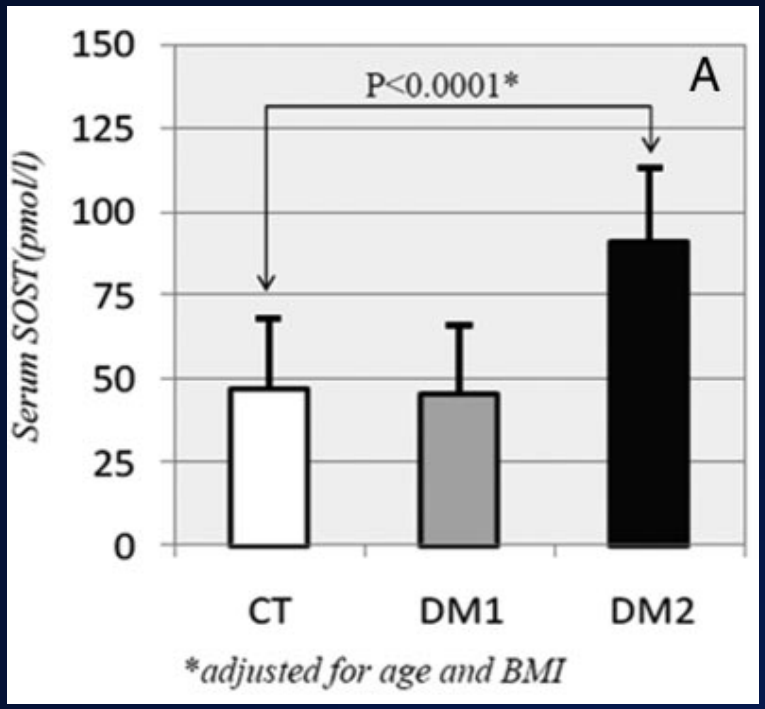
T2D

Krakauer Diabetes 1995, Manavalan JCEM 2012

Sclerostin, a product of the osteocyte, inhibits bone formation



Sclerostin is Increased in T2D



Sclerostin may suppress bone formation in T2D

Gennari JCEM 2012

Diabetics Have Multiple Risk Factors for Poor Skeletal Health

- Contributing Factors:
  - Falls
  - TZDs
  - **Abnormal Skeletal Properties**
    - **Reduced Turnover**
    - **Abnormal Biomechanics?**
    - **Reduced Bone Quality?**

Skeletal Geometry is Worse in T2D

- By BMD: femoral neck aBMD is higher, but femoral neck strength is lower relative to load

Ishii J Clin Endocrinol Metab 2012

- By QCT: Trabecular BMD is higher but load to strength ratio for hip fracture is not enhanced

Melton J Clin Endocrinol Metab 2008

- By pQCT: Cross sectional area and bone bending strength at cortical sites are lower

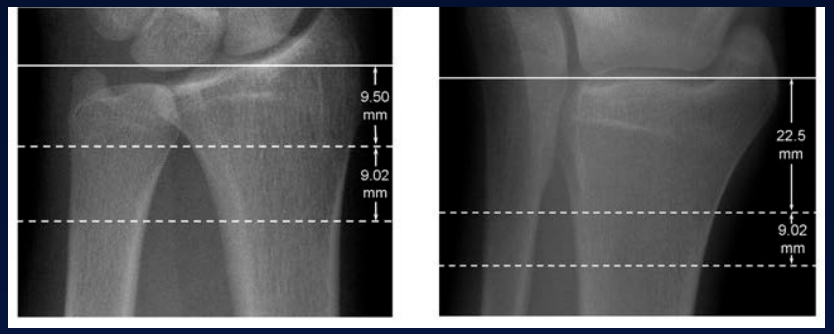
Petit J Bone Miner Res 2010

Despite higher areal BMD, biomechanical indices are worse

Skeletal Abnormalities in T2 Diabetics Mellitus

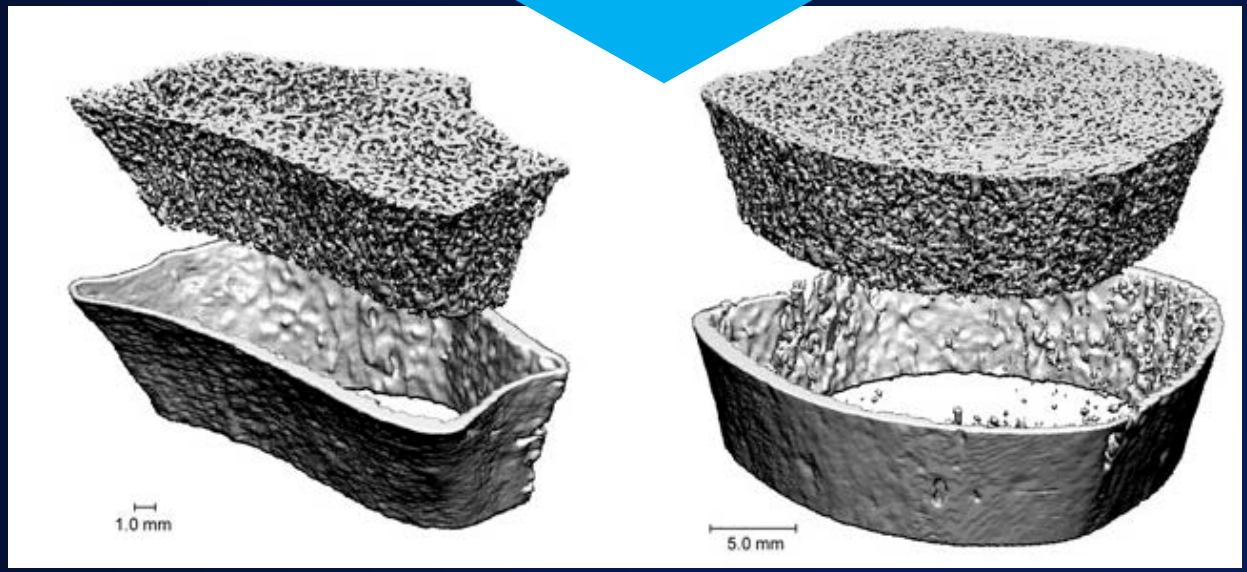
- Reduced Turnover
- Abnormal Biomechanics
- Reduced Bone Quality?
  - Cortical
  - Trabecular
  - Matrix (AGEs)
  - Marrow fat

Extreme CT:
Is Microarchitecture Abnormal in T2D?



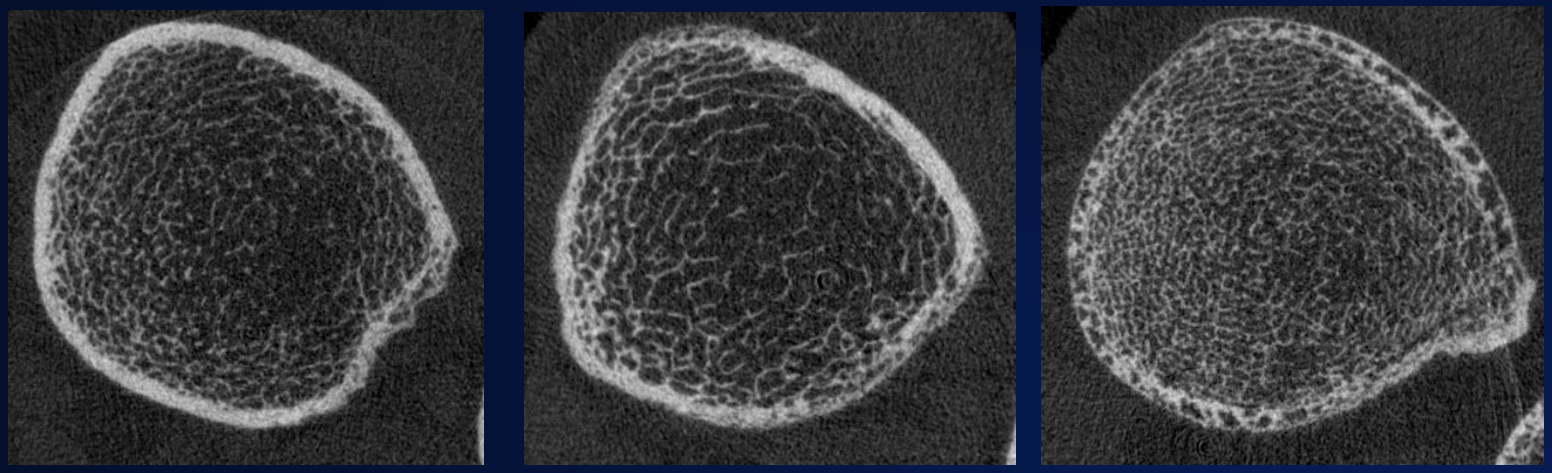
82
microns

High Resolution Peripheral Quantitative Computed Tomography



Cortical Porosity May be Increased in T2D

- 19 T2D women vs 19 controls
- Cortical porosity was 124% higher in T2D at radius



Control | Diabetes | Diabetes + fracture

Burghardt JCEM 2010

Cortical Porosity: Higher in T2D with fracture

Postmenopausal women

	No diabetes		T2 diabetes	
	No fracture	**History of fracture**	**No fracture**	**History of fracture**
N	20	20	20	20
Distal radius	1.2%	2.5%	0.8%	**3.9%***
Distal tibia	4.3%	4.8%	3.0%	**5.7%***

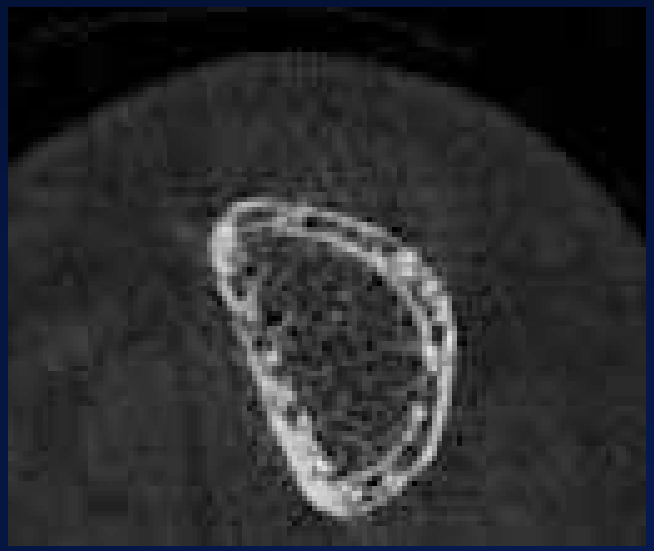
*p<0.05 compared to T2D without fracture
Standard HRpQCT variables did not differ by diabetes or fracture status

Patsch JBMR 2013

Cortical Porosity May be Increased in T2D With Fragility Fractures

Distal Radius

Diabetic



Diabetic with Fracture

Changes in cortical bone are captured by HRpQCT in T2D with fractures

Patsch JBMR 2013

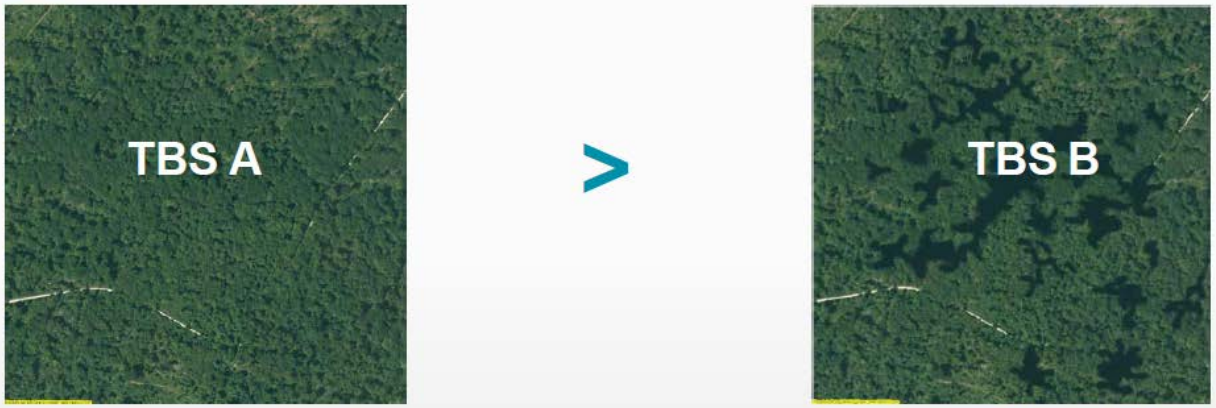
Skeletal Abnormalities in T2 Diabetes Mellitus

- Reduced Turnover
- Abnormal Biomechanics
- Reduced Bone Quality
  - Cortical
  - Trabecular?
  - Matrix (AGEs)?
  - Marrow fat?

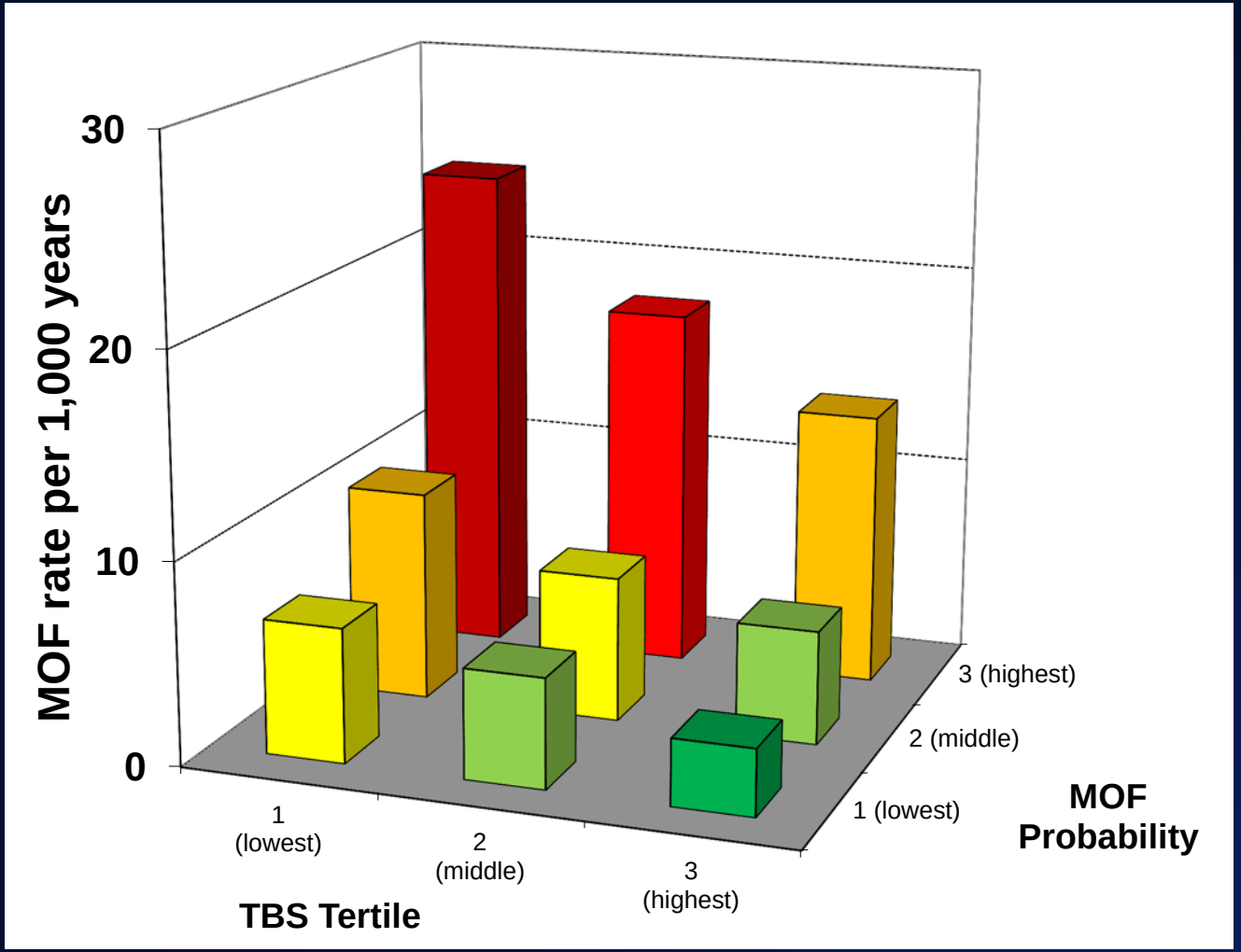
IMAGING AND BIOMECHANICS

TRABECULAR BONE SCORE (TBS)

TBS Simplified Principle



Fracture rates per 1,000 woman-years according to FRAX and TBS tertiles



Adapted from WD. Leslie et al. Osteoporos Int. 2014 Jun 21

TBS Predicts Osteoporotic Fractures in Diabetes

In Diabetes:

- **Higher BMD but lower TBS**
- **TBS predicted fracture, independent of BMD: adjusted hazard ratio of 1.27 (1.10-1.46)**

TBS captures a larger portion of the diabetes-associated fracture risk than BMD

Leslie et al JCEM, 2013

Skeletal Abnormalities in T2 Diabetics Mellitus

- Reduced Turnover
- Abnormal Biomechanics
- Reduced Bone Quality
  - Cortical
  - Trabecular
  - Matrix (AGEs)?
  - Marrow fat?

Advanced Glycation Endproducts (AGEs)

"Browning" meat

Glucose + amino acid protein

Schiff's base

Amadori product

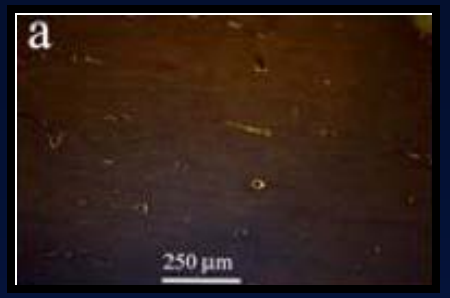
Oxidative pathway

Non-oxidative pathway

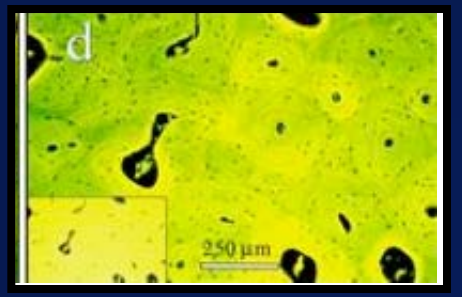
CML

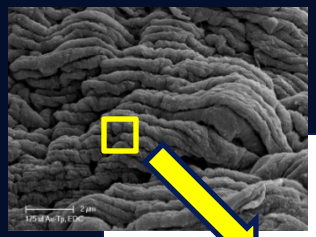
Pentosidine

pyrraline

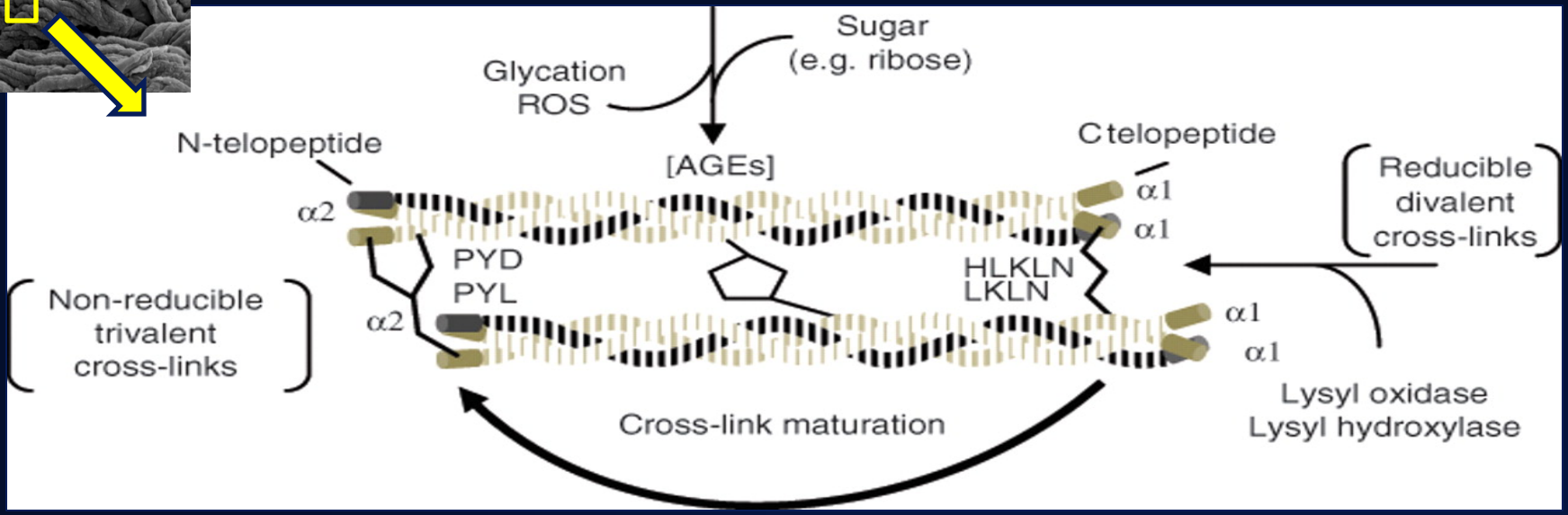


"Browning" bone





AGEs Alter Bone Material



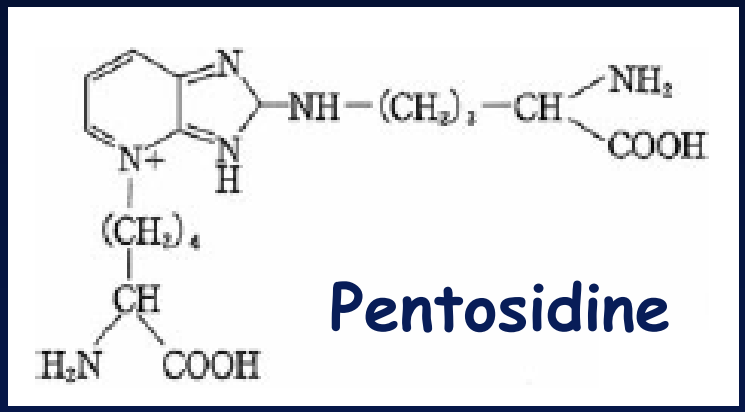
- Type 1 collagen: scaffolding and toughness
- Enzymatic cross-linking: stiffness
- *Non-enzymatic cross-linking (AGE):*
  - *-accumulate with age and glucose*
  - *-slow bone turnover*
  - *-brittleness*
  - ***-decrease bone strength independent of BMD***

AGEs are associated with fractures

- 765 postmenopausal women followed for 5 years; *HR for 1 SD increase in urinary pentosidine 1.18 for vertebral fracture and 1.20 for long bone and vertebral fracture.* Tanaka J Bone Miner Res 2011

- 76 T2D women had *higher serum pentosidine levels if they had vertebral fracture (OR 2.50, CI: 1.09-5.73).* Yamamoto J Clin Endocrinol Metab 2008

- Health ABC: 1,000 patients followed for 7.5 years, *urinary pentosidine was associated with increased clinical fracture incidence in T2D (RH 1.42, 1.10-1.83).* Schwartz J Clin Endocrinol Metab 2009



Findings were independent of BMD

Possible contributing factors for increased fracture risk in T2 Diabetes Mellitus

- Contributing Factors:
  - Falls
  - TZDs
  - Skeletal abnormalities
  - Obesity?

A Link Among Osteoporosis, Diabetes, and Obesity?

Obesity: Shared Problem

Obesity Rates (BMI ≥30)	U.S. (2009-2010)[1]	Armenia (2010)[2]
Men	35.5%	40%
Women	35.8%	30%
Boys (ages 2-19)	18.6%	
Girls (ages 2-19)	15.0%	
Children (under age 5)		15.0%

1. Data from the National Health and Nutrition Examination Survey, 2009–2010 http://www.cdc.gov/nchs/data/databriefs/db82.htm
2. Armenia Demographic and Health survey, 2010 http://www.measuredhs.com/pubs/pdf/FR252/FR252.pdf

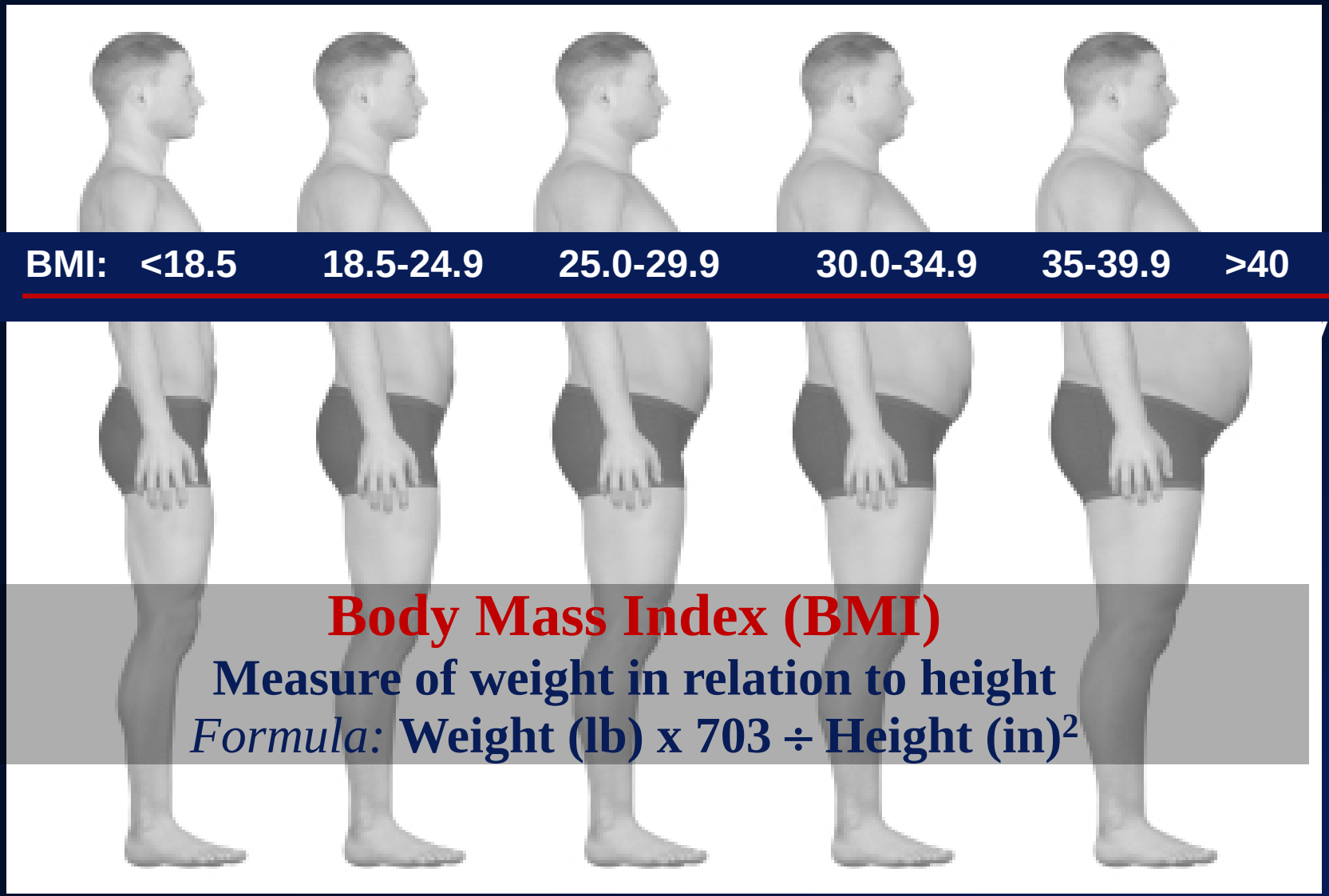
45-52%
of American WOMEN
will be obese by 2030

Wang YC, et al. Lancet. 2011 Aug 27;378(9793):815-25.

50% of American MEN
will be obese by 2030

Wang YC, et al. Lancet. 2011 Aug 27;378(9793):815-25.

Weight Classification



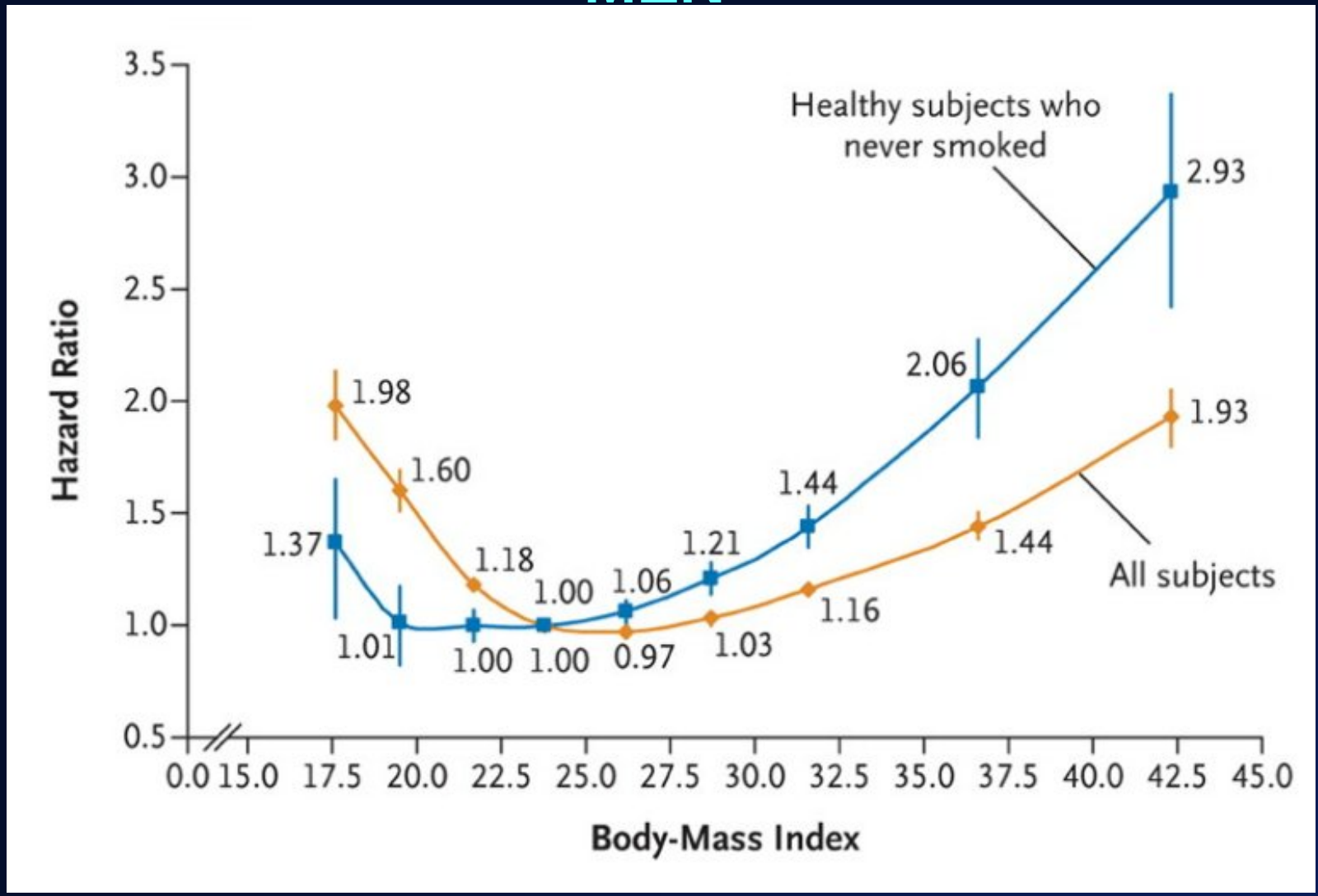
Body Mass Index (BMI)

Measure of weight in relation to height

Formula: **Weight (lb) x 703 ÷ Height (in)^2**

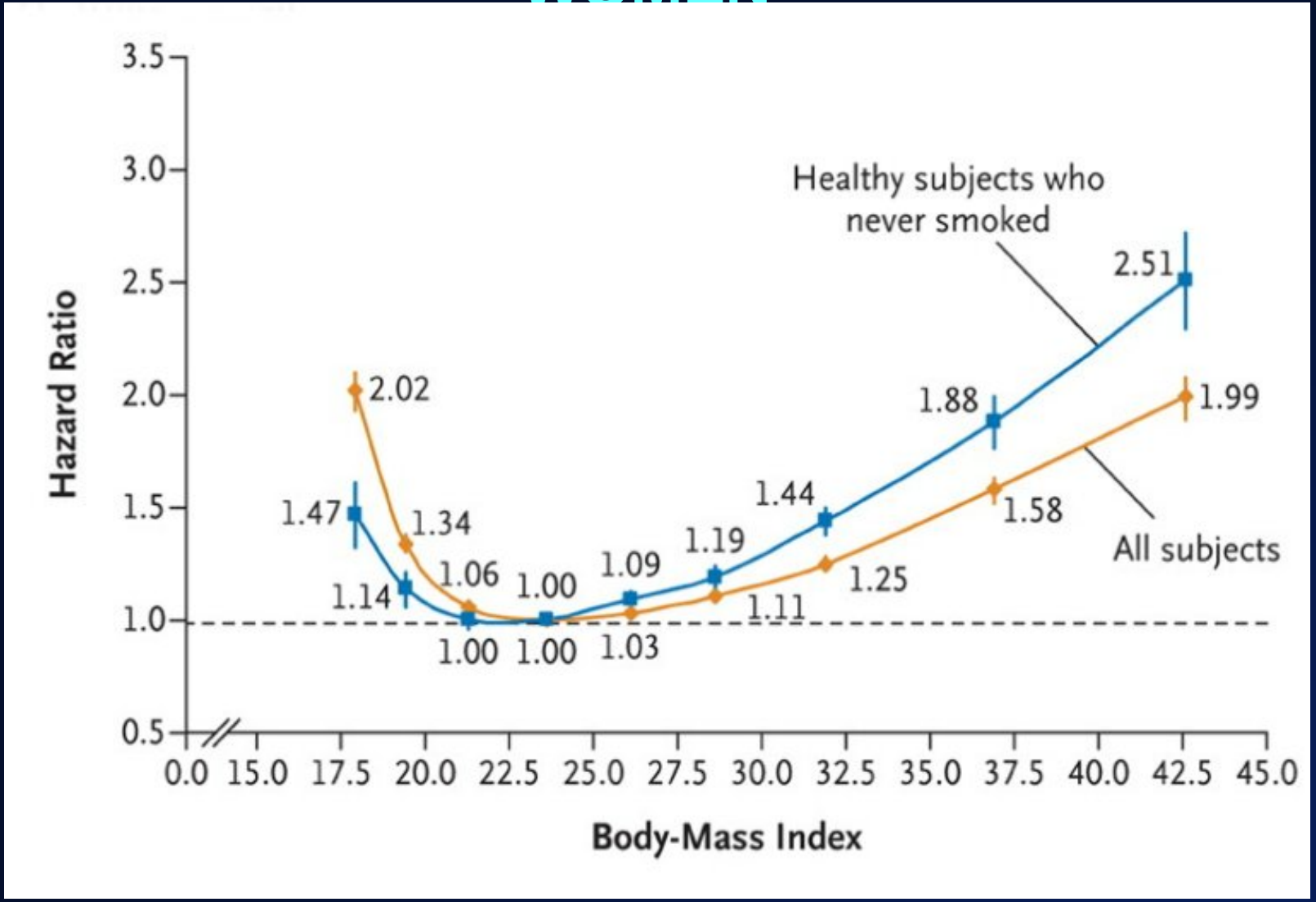
www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/

Underweight, Overweight and Obesity Associated with Increased All-cause Mortality: MEN



Berrington de Gonzalez et al. NEJM. 2010;363: 2211-9.

Underweight, Overweight and Obesity Associated with Increased All-cause Mortality: WOMEN



Berrington de Gonzalez et al. NEJM. 2010;363: 2211-9.

Armenia 2012

Nutritional "Double Burden"

Obesity in Armenian Children
11% in 2005
15% in 2010

- After the Soviet Union fell, healthy school food canteens were transformed into school cafes
  - Offerings were: chips, burgers, hot dogs, buns, popcorns, soft drinks, crackers and candy bars

1. Armenia Demographic and Health survey, 2010 http://www.measuredhs.com/pubs/pdf/FR252/FR252.pdf
2. http://www.armenianow.com/society/health/41791/armenian_children_obesity_schools_canteens_healty_life_style

Armenian Children: Obesity

Study of Renata Markosyan (Supervised by Dr. Elena Aghajanova):

202 school children, ages 12-15

- 117 boys: 14.5 % are overweight and 2.5% % were obese
- 85 girls: 12% were overweight and 2.1% were obese

Adult Obesity Rates: Armenia

Percent of Adults, ≥ age 15,
Body Mass Index >= 30 in 2010

- 40% Men
- 30% Women

Armenia Demographic and Health survey, 2010
http://www.measuredhs.com/pubs/pdf/FR252/FR252.pdf

2010 ADHS interviewed 5,922 women, ages 15-49, and 1,584 men, ages 15-49, in over 7,000 Armenian households

Armine Pashinyan, a chief specialist at the Bormental Center, told that 57% of the country's population turns out to be overweight[3]

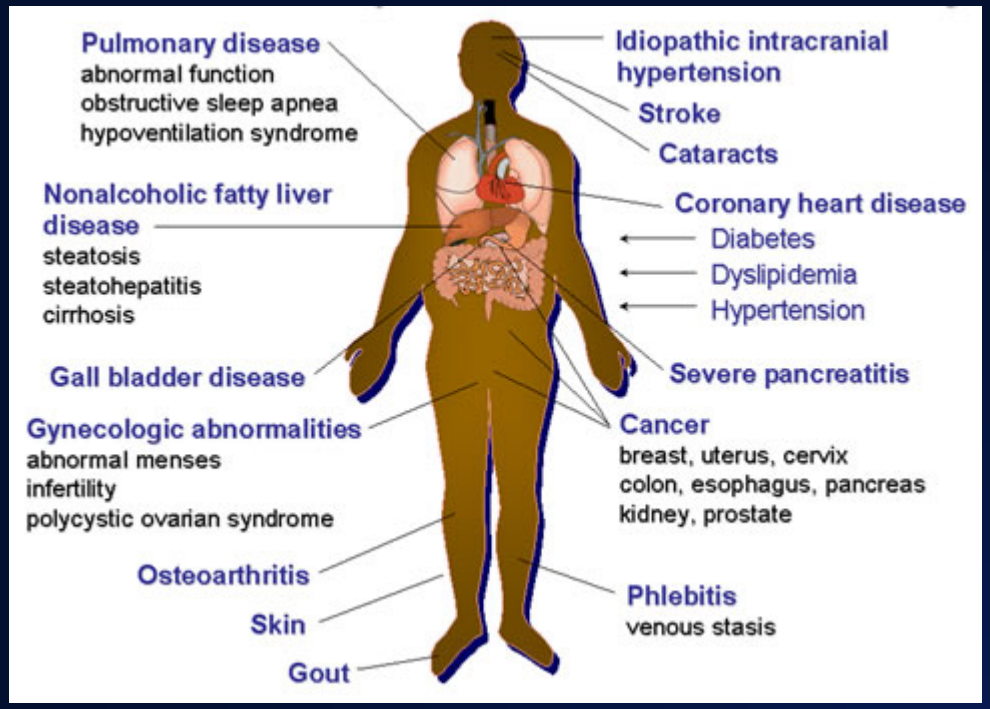
- **Problem more widespread in the regions, target group is middle-aged individuals, particularly women, May 2012**

http://www.tert.am/en/news/2012/05/21/obessity/

Health Fair in October 2013 at YSMU
Mariam Manoukian, MD, PhD, Director

70% of 250 people screened during the fair were obese with a BMI of above 30 kg/m^2

Medical Consequences of Obesity



Diabetes

Fractures?

FAT and BONE

- Dogma: **Fat is good for bone**
  - Low weight is a risk factor for osteoporosis/fractures
  - Higher weight has been associated with higher BMD and lower fracture rates
  - Fat is a source of estrogens (good for bones)
  - Higher insulin levels may be a positive skeletal factor
  - The extra padding of fat helps to lessen the impact of a fall!

Albala 1996, Reid 1992, De Laet & Kanis 2005

FAT and BONE

- A challenge to the dogma: **Fat is bad for bone***
  - Fat can induce an artifact of the DXA measurement giving a falsely elevated BMD
  - Co-morbidities such as diabetes and vitamin D deficiency are often present
  - In women, an earlier menopause; in men lower testosterone levels
  - Marrow has more fat; fewer osteoblasts
  - Increased incidence of falls!

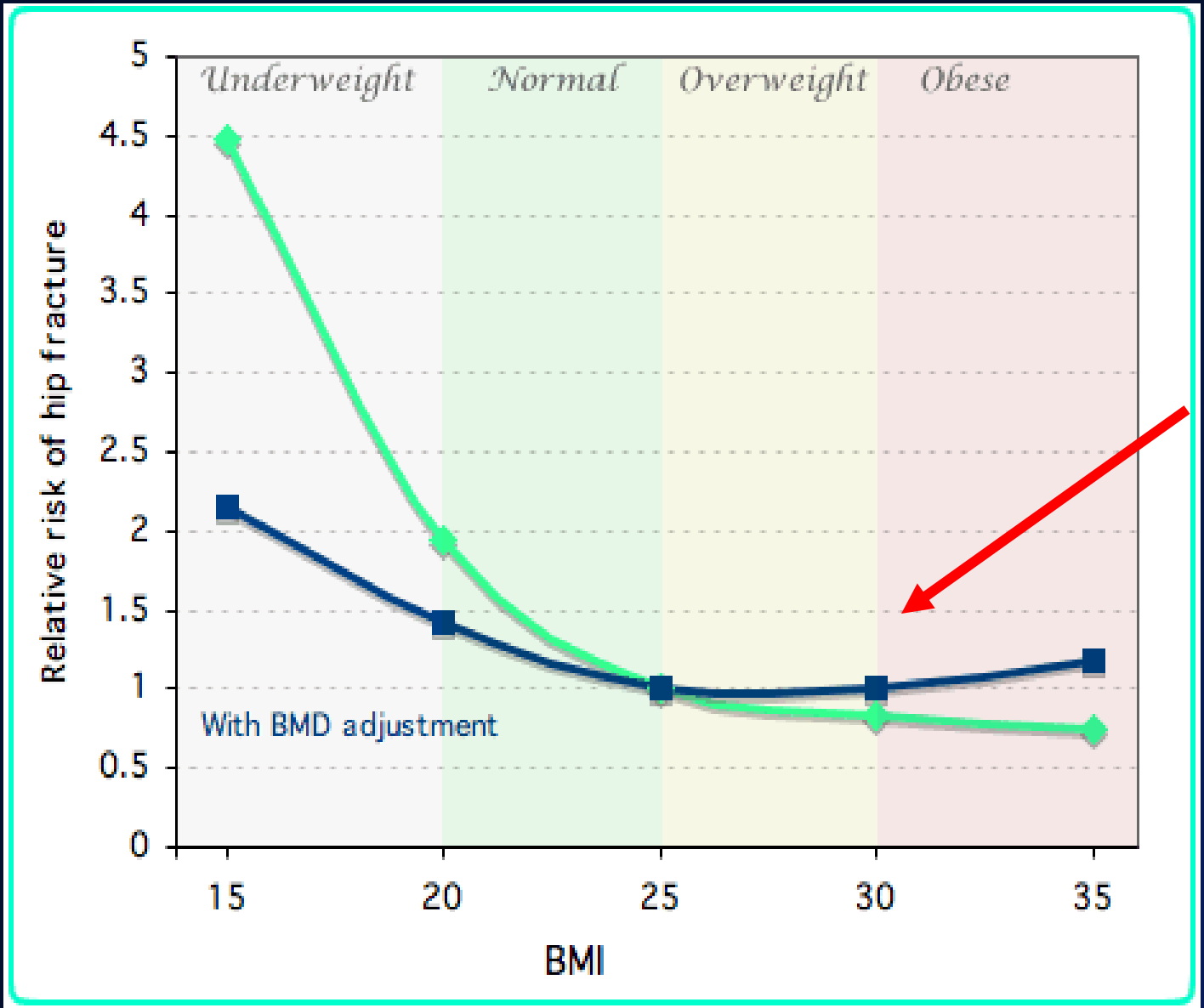
Nielson, CM et al. J Bone Miner Res 2012; 27:1-10; Nielson CM et al. J Bone Miner Res 2011; 26:496-502
Compston JE et al. Am J Med 2011; 124:1043-50

FAT and BONE; A bad combination!

- More challenges to the dogma:
  - *By fracture incidence*: higher rates of fractures at all ages when compared to non-obese subjects
  - *By body composition*:
    - Lean/muscle mass associated with higher BMD
    - Fat mass associated with lower BMD

Nielson 2011, Hsu 2006, Compston 2011, Laslett 2012, Goulding 2005, Bredella 2011, Gilsanz 2009, Janicka 2007, Pollock 2011, Zhao 2007, Sheu 2011

Low body weight and high body weight may both be risk factors for fracture!



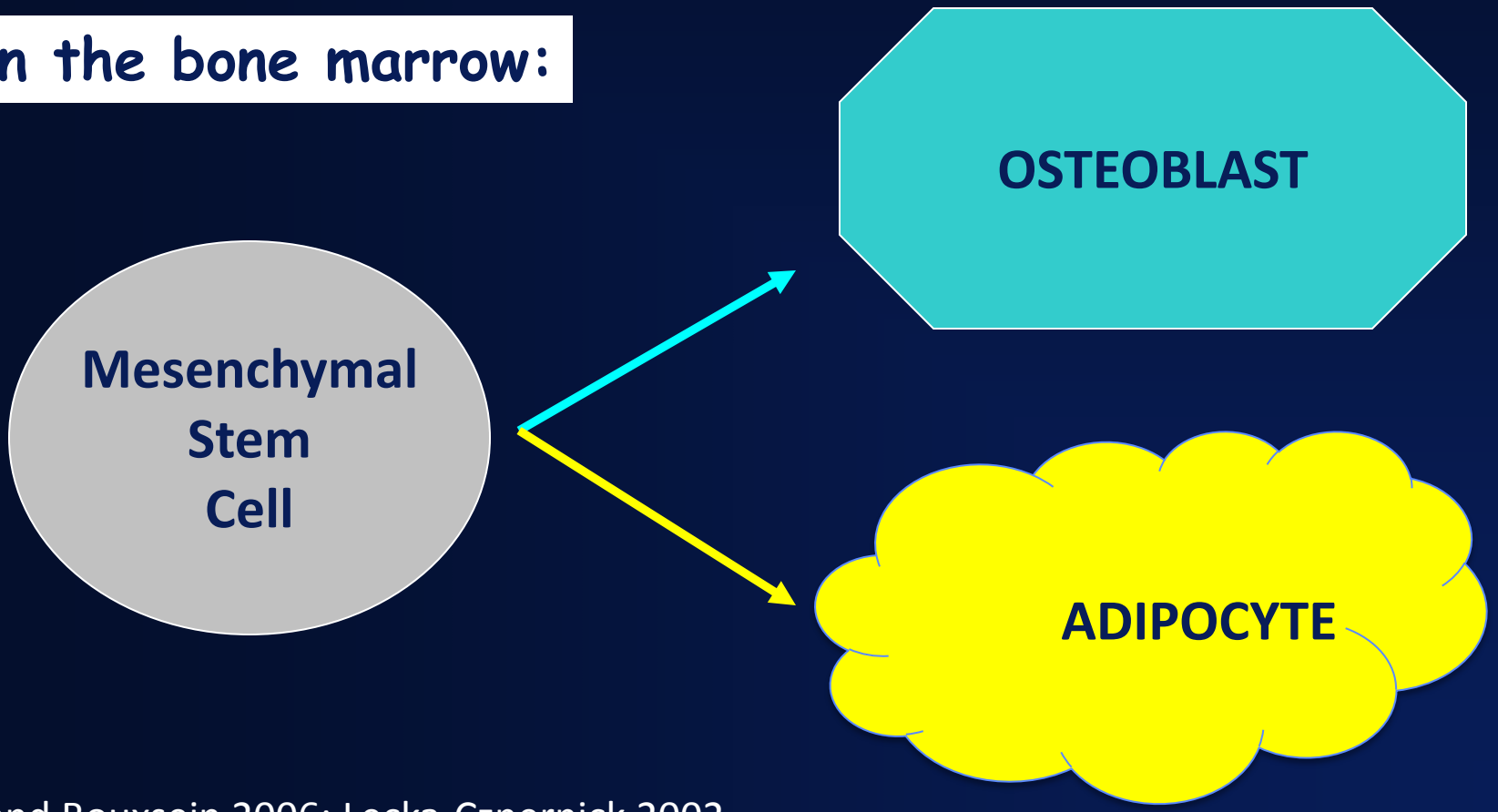
FAT IS NOT FAT IS NOT FAT!

- Where is the fat?
  - Marrow
  - Visceral vs peripheral

Evidence of a bone formation defect

The Osteoblast

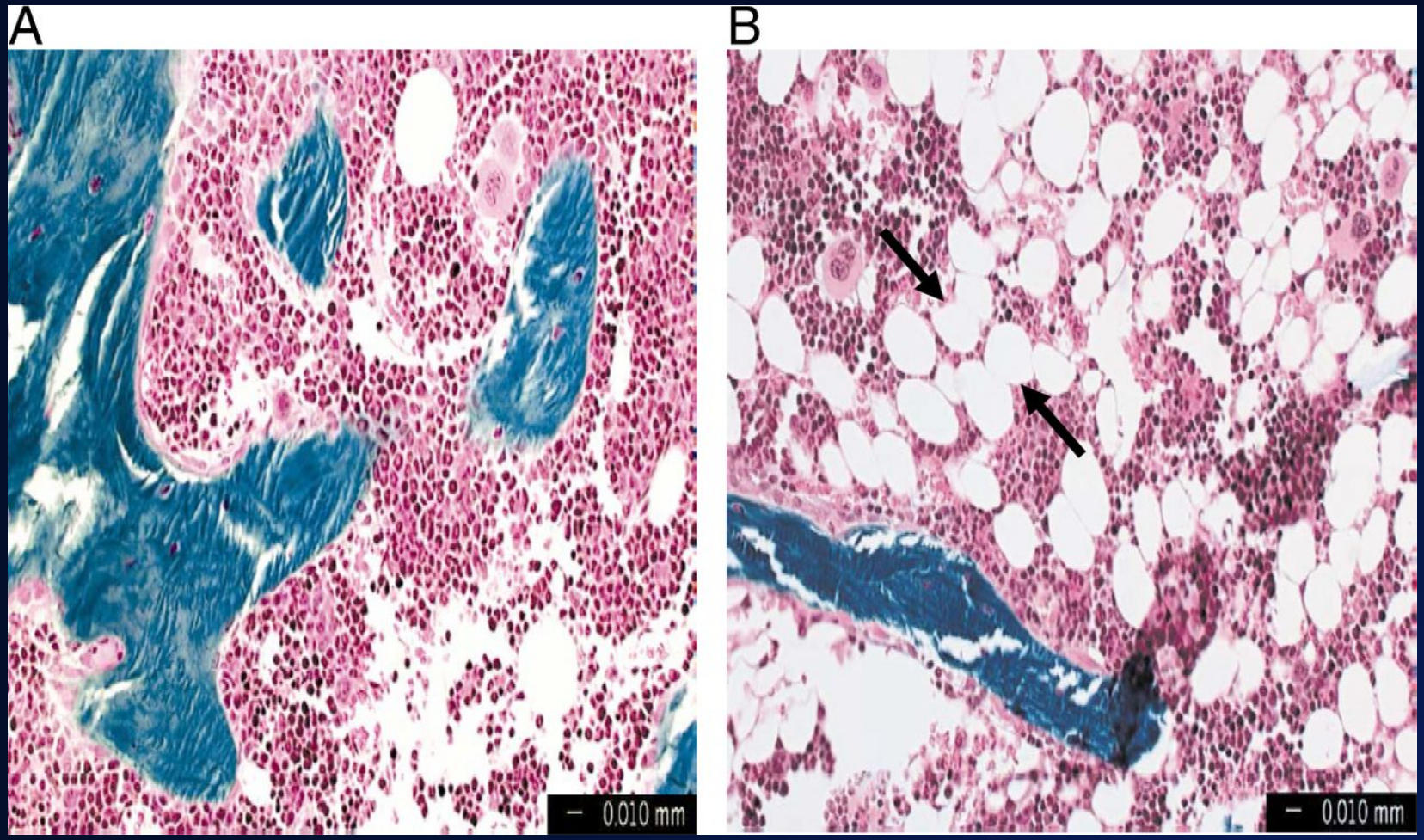
In the bone marrow:



Rosen and Bouxsein 2006; Lecka-Cznernick 2002

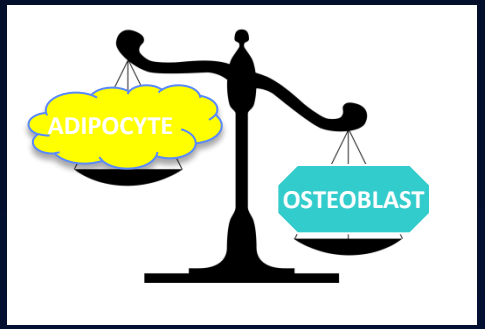
Marrow fat increases with aging

Fazeli P K et al. JCEM 2013;98:935-945



Human marrow from the iliac crest of an 18 year old (A) and an 80 year old (B), demonstrating the age-related increase in marrow adipocyte “ghosts” (arrows) in human marrow.

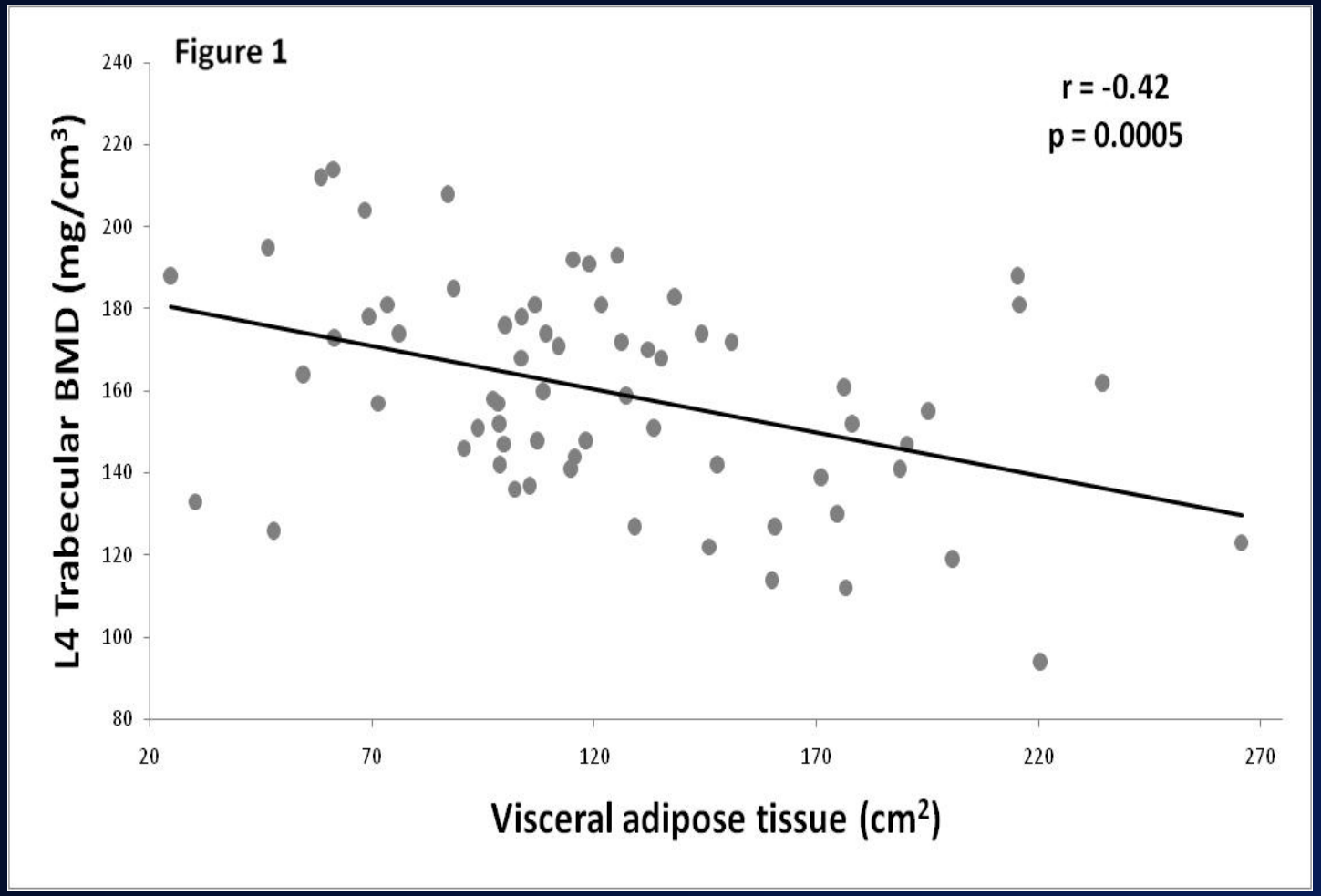
Marrow Fat and Osteoporosis



- Reciprocal relationship between adipocytes and osteoblasts has been implicated in osteoporosis related to
  - Aging
  - Diabetes (T1 and T2)
  - Menopause
  - Anorexia nervosa
  - Glucocorticoids
  - Thiazolidinediones

Justesen 2001, Syed 2008, Bredella 2009, Schellinger 2001 and 2004, Griffith 2006, Canalis 2007

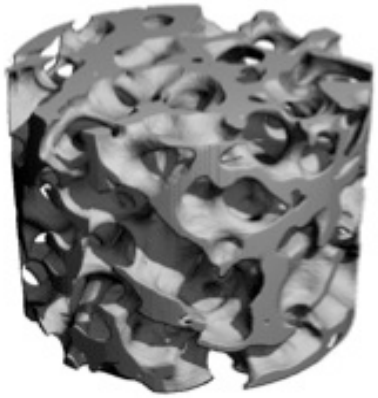
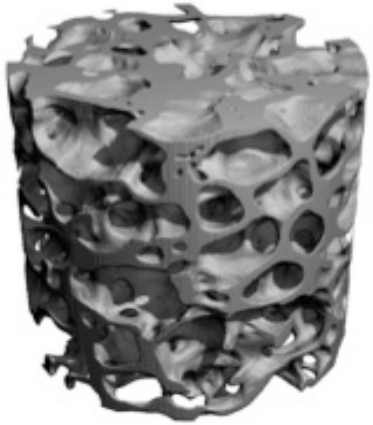
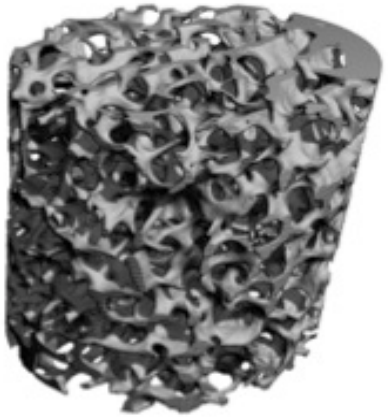
Visceral Fat is bad for bones: Negative association with trabecular BMD by QCT



Bredella, 2011 Bone

TERTILES based on %Trunk Fat BONE STRUCTURE (Cohen, et al, 2013)

Bone volume fraction by µCT in premenopausal women from each tertile of trunk fat by DXA

Lowest Tertile	Middle Tertile	Highest Tertile
		
BMI: 22.2 kg/m2 Trunk Fat: 16.8% LS Z score: -0.5 BV/TV: 30.8%	BMI:28.3 kg/m2 Trunk Fat: 36.2% LS Z score: +1.4 BV/TV:22.5%	BMI: 36.9 kg/m2 Trunk Fat: 42.0% LS Z score: +3.6 BV/TV:19.6%

High Abdominal Fat group has substantially:

- ↓Bone volume
- ↓Trabecular number
- ↓Trabecular thickness
- ↓Estimated bone stiffness (FEA)

Summary:
Skeletal health in Type 2 Diabetes Mellitus

- Fracture risk is greater after accounting for BMD and known clinical risk factors

- Contributing factors include falls and TZDs

- More important contributing factors include abnormalities in bone quality (bone formation, geometry, cortical porosity, trabecular structure, accumulation of AGEs, bone marrow fat)

- Obesity

Summary -2-
Skeletal health in Type 2 Diabetes Mellitus

- T- score and FRAX predict fracture but underestimate risk

- Intensive glycemic control does not increase fractures. Poor control may increase fracture risk.

- Apply standard guidelines for fracture prevention:
fall prevention, nutritional adequacy (calcium and vitamin D), lifestyle modification

- If fracture has occurred or if fracture risk is high, pharmacological treatment is appropriate, but current therapies have not been well-studied

Adding to the growing list of risk factors for Osteoporosis

- Age
- Family (genetics)
- The menopause
- Certain medications like glucocorticoids
- Other diseases (rheumatoid arthritis, COPD, Type 1 Diabetes mellitus)
- Nutrition (anorexia, vitamin D deficiency)
- Lifestyle issues (smoking, excessive alcohol, lack of exercise)
- **Diabetes Mellitus**
- **Obesity**

Bottom Lines

- Diabetes is bad for bones!
- Obesity is bad for bones!
- Diabetes AND obesity are doubly bad for bones!

Diabetes and bone:
a not very sweet
problem!
and….
Obesity makes it worse

Diabetic Foot, circa 1700

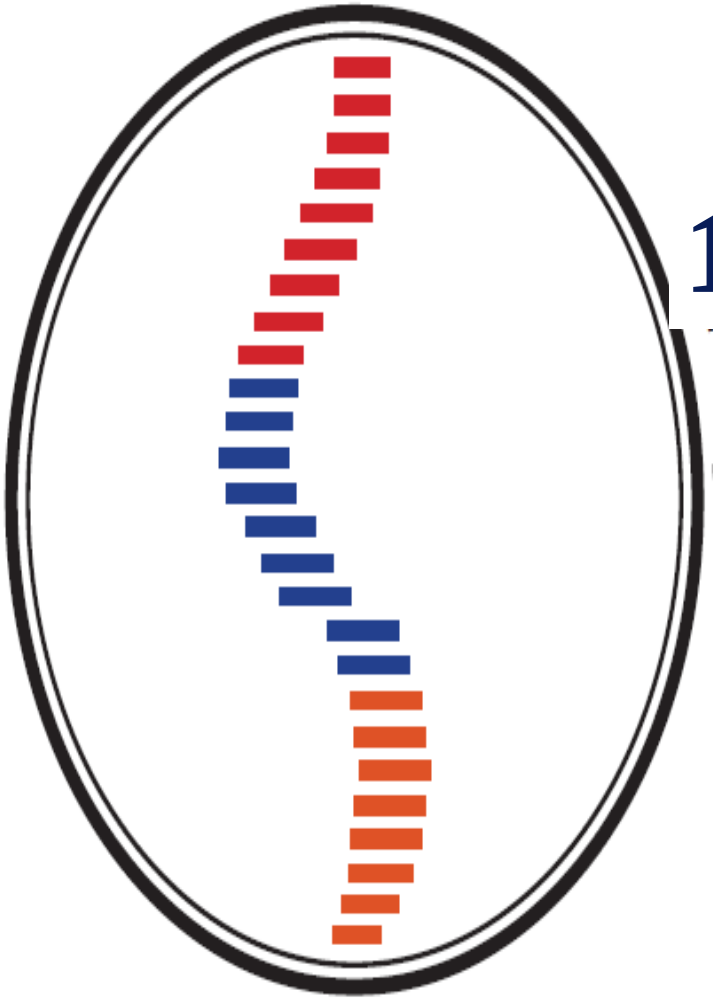
COMING THIS FALL TO YEREVAN

Two important events!

An International Summit on Osteoporosis

15 Eastern European and Central Asian Countries will meet in Yerevan for the first such conference to be held outside Russia!

Tuesday, 4 October 2016



10th International Osteoporosis Symposium

Yerevan, Armenia

6 October 2016

Thank You!