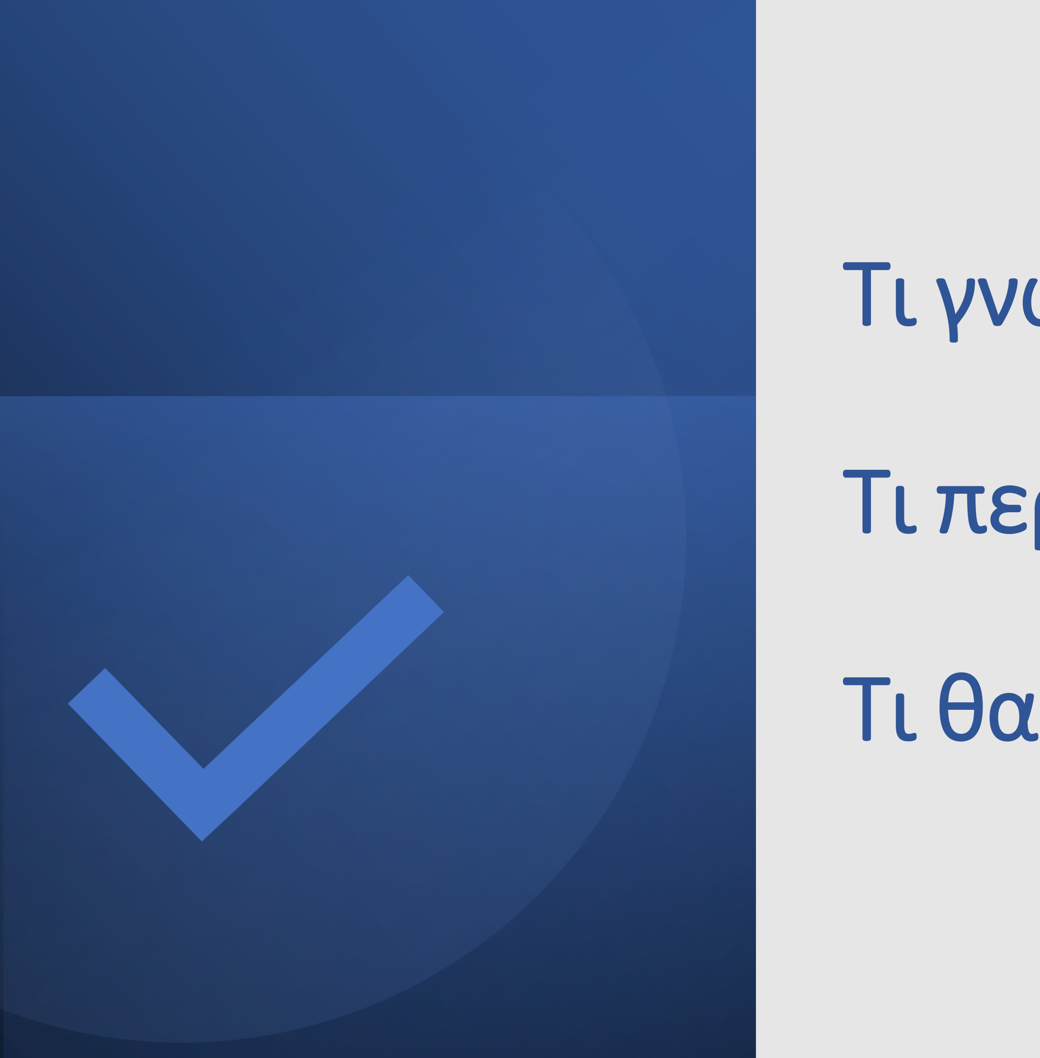
ΔΙΑΒΗΤΗΣ ΚΑΙ ΟΣΤΑ
ΒΙΒΛΙΟΓΡΑΦΙΚΗ ΕΝΗΜΕΡΩΣΗ 2023

ΦΩΤΕΙΝΗ ΑΔΑΜΙΔΟΥ
ΕΝΔΟΚΡΙΝΟΛΟΓΟΣ
ΙΠΠΟΚΡΑΤΕΙΟ ΘΕΣΣΑΛΟΝΙΚΗΣ



Τι γνωρίζουμε ήδη

Τι περισσότερο γνωρίζουμε φέτος

Τι θα θέλαμε να μάθουμε του χρόνου

"Osteoporosis is defined as a systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture"

Diabetic Bone Disease

Am J Med 1994;94:646–650
Kanis JA, Osteoporos Int (2019) 30:3–44
Ferrari SL, Osteoporosis International (2018) 29:2585–2596

Τι γνωρίζουμε

- DM 530 million 2021
- Increased risk of fracture
  - RR: all 1.9-3.2, hip 3.8, VF 2.9 (type 1)
  - RR: hip 2.3M, 1.8W (type 2)
  - 3x hip # DM1 vs DM2
  - 5x hip# DM1 vs normal-10 χρόνια νωρίτερα
  - 4% osteoporotic fracture burden
- BMD is normal/increased in DM2
  - “diabetes paradox”
- BMD underestimates fracture risk in DM1/DM2
- Trabecular bone score (TBS) and HR-pQCT

T2DM

- Pancreatic β-cell dysfunction
- Insulin resistance
- Hyperglycaemia

- Microvascular disease
- Impaired vascular–bone cell crosstalk

Senescence

AGEs

Osteocyte

SASP

↑CML

RAGE pathway → ↑NF-κB

↑MMPs

↓Bone quality

T2DM

↑AGEs

Obesity and hyperinsulinaemia

Microvascular disease (transcutaneous oxygen tension ≤40 mmHg)

Normal or ↑BMD on DXA
Normal or ↑trabecular bone volume fraction

↓Bone material strength index

↑Cortical porosity

⊖

⊕

⊕

Fracture

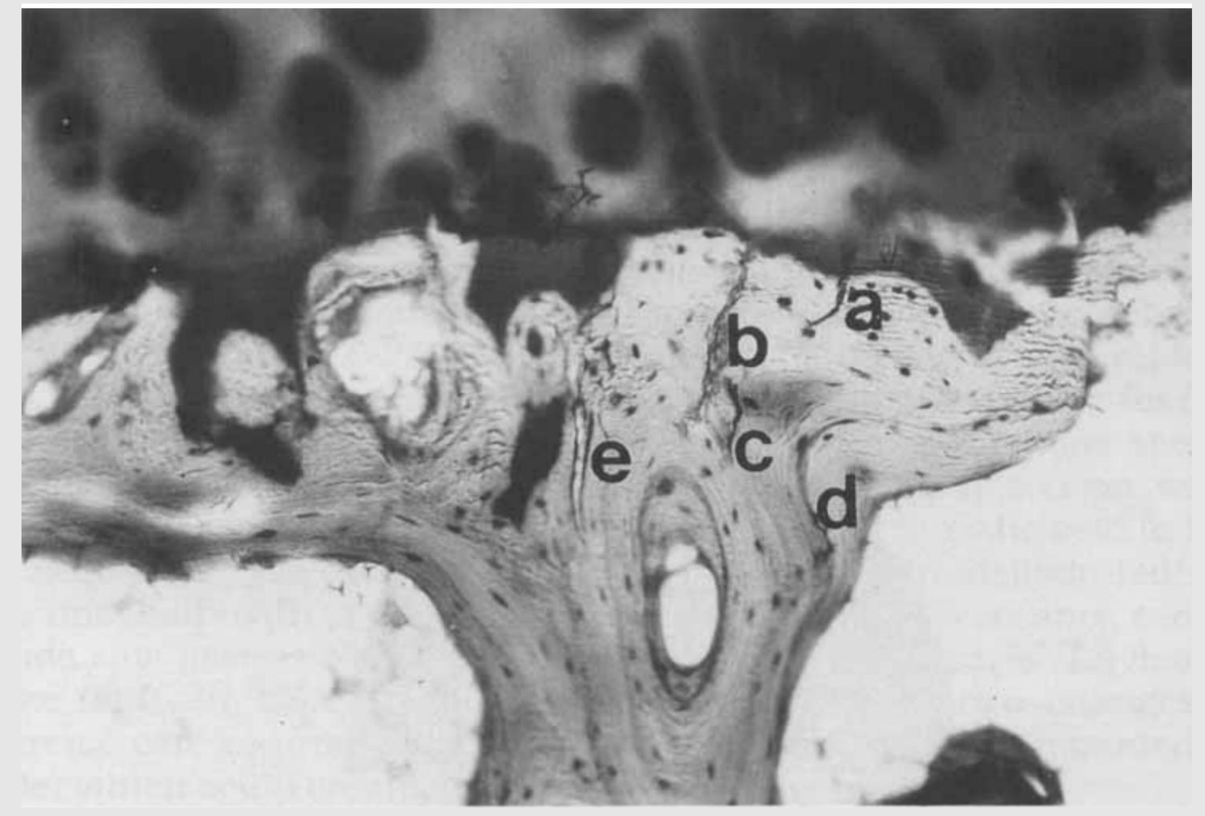
⊕

Neuropathy and other factors

Falls

Khosla S, Nat Rev Endocrinol. 2021 November ; 17(11): 685

- Expansion of bone-marrow adipose tissue
- Limitation of osteogenic differentiation
- Pro-inflammatory adipocytes in bone
- Senescence



Hofbauer LC, Lancet Diabetes Endocrinol 2022; 10: 207–20
Biotechnic and Histochemistry 1994 v69 2 p81

Panel 2: Diabetes-related risk factors for fractures

- Type 1 diabetes[3]
- Type 2 diabetes for more than 5 years[146]
- Poor glycaemic control based on HbA_{1c} >7·9% (63 mmol/mol) in type 1 diabetes[20] and >9% (75 mmol/mol) in type 2 diabetes[18]
- Diabetic microvascular complications—eg, neuropathy,[130] retinopathy, and nephropathy[129]
- Diabetes treatment with thiazolidinediones,[51] sulfonylureas,[37] and insulin[34]*

ΠΟΙΟΙ ΠΑΡΑΓΟΝΤΕΣ ΕΠΙΔΡΟΥΝ ΑΡΝΗΤΙΚΑ ΣΤΗΝ ΟΣΤΙΚΗ ΠΥΚΝΟΤΗΤΑ ΣΕ ΑΣΘΕΝΕΙΣ ΜΕ ΣΔ1?

Risk factors for lower bone mineral density in older adults with type 1 diabetes: a cross-sectional study

Ann V Schwartz, Jye-Yu C Backlund, Ian H de Boer, Mishaela R Rubin, Annette Barnie, Kaleigh Farrell, Victoria R Trapani, Naina Sinha Gregory, Amisha Wallia, Ionut Bebu, John M Lachin, Barbara H Braffett, Rose Gubitosi-Klug, and the DCCT/EDIC Research Group

ΣΧΕΔΙΑΣΜΟΣ και ΣΚΟΠΟΣ

- DCCT (1983-1989) ended 1993
- EDIC-προοπτική μελέτη παρατήρησης 1428 ενήλικες με ΣΔ1 και παρακολούθηση 30 έτη

➢ EDIC Skeletal Survey Study 2017-2019:
  - ➢ 1058 ασθενείς μέσης ηλικίας 59
  - ➢ 27 κέντρα

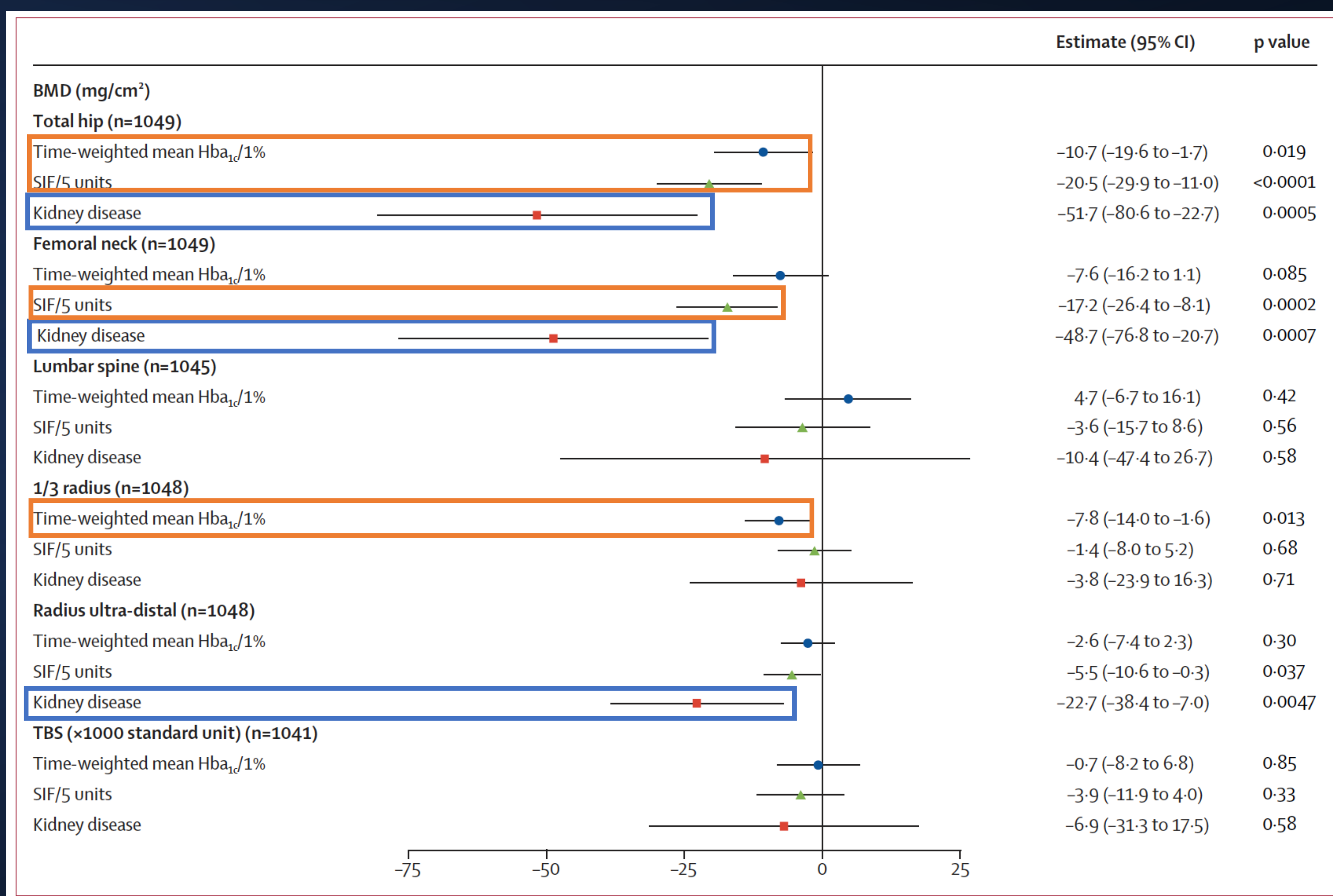
- Ποιοι παράγοντες του ΣΔ1 σχετίζονται με την οστική πυκνότητα στο ισχίο σε ασθενείς μέσης ηλικίας 59 ετών και διάρκεια νόσου 38 έτη
  - ➢ Γλυκαιμικός έλεγχος
  - ➢ Μικροαγγειακές επιπλοκές
    - ➢ Νεφροπάθεια , κ.ά
  - ➢ Συσσώρρευση AGEs
    - ➢ Αυτοφθορισμός δέρματος

ΑΠΟΤΕΛΕΣΜΑΤΑ

- Primary study outcome: total hip BMD

- Secondary outcomes:
  - BMD in the femoral neck, lumbar spine, distal and ultra-distal radius
  - TBS

- Exploratory outcome: Prevalence of vertebral fracture

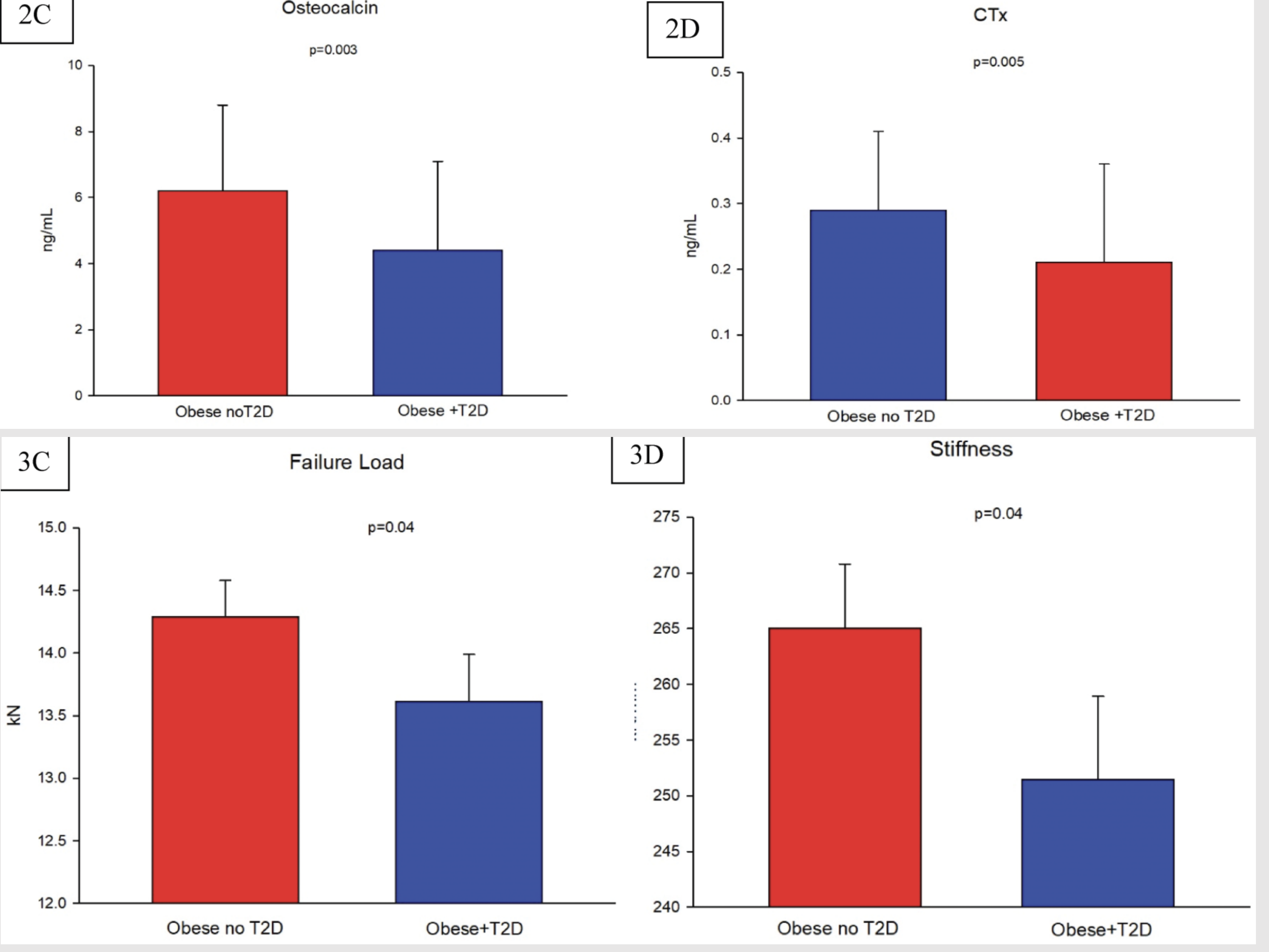


ΣΥΜΠΕΡΑΣΜΑ

ΑΝΕΞΑΡΤΗΤΟΙ ΠΑΡΑΓΟΝΤΕΣ ΚΙΝΔΥΝΟΥ ΓΙΑ ΧΑΜΗΛΗ ΟΣΤΙΚΗ ΠΥΚΝΟΤΗΤΑ ΣΤΟ ΙΣΧΙΟ ΣΕ ΑΣΘΕΝΕΙΣ ΜΕ ΣΔ1:

- Ο γλυκαιμικός έλεγχος
  - Εκτός από οσφυϊκή μοίρα και περιφ. κερκίδα
- AGEs
- Η νεφρική νόσος (GFR<60 ml/min/1.73m^2 ή νεφρική νόσος τελικού σταδίου)

ΠΟΙΑ ΕΙΝΑΙ Η ΕΠΙΔΡΑΣΗ ΤΗΣ ΠΑΧΥΣΑΡΚΙΑΣ ΣΤΗΝ ΟΣΤΙΚΗ ΠΥΚΝΟΤΗΤΑ?



The Journal of Clinical Endocrinology & Metabolism 2021 106(5):1362

ΠΟΙΑ ΕΙΝΑΙ Η ΕΠΙΔΡΑΣΗ ΤΗΣ ΠΑΧΥΣΑΡΚΙΑΣ ΣΤΗΝ ΟΣΤΙΚΗ ΠΥΚΝΟΤΗΤΑ?

The Journal of Clinical Endocrinology & Metabolism, 2022, **107**, e2545–e2552
https://doi.org/10.1210/clinem/dgac040
Advance access publication 10 February 2022

Clinical Research Article

Fat Mass Has Negative Effects on Bone, Especially in Men: A Cross-sectional Analysis of NHANES 2011-2018

Rajesh K. Jain[1], and Tamara Vokes[1]

[1]Department of Endocrinology, Diabetes, and Metabolism, University of Chicago Medicine, Chicago, IL 60637, USA

Fat Mass Has Negative Effects on Bone, Especially in Men: A Cross-Sectional Analysis of NHANES 2011-2018

THE UNIVERSITY OF CHICAGO
UChicago Medicine
Department of Medicine

Presenting Author: Rajesh Jain
Co-Authors: Tamara Vokes

Introduction

There is a strong positive correlation between BMD and body weight [1], but it is not clear whether this is true at high levels of obesity or which components of body composition are most responsible for this correlation. NHANES recently released body composition data from years 2011-2018, comprising over 10,000 subjects representative of the U.S. population. We have shown that total body BMD (tbBMD) is strongly correlated with total hip BMD and is an appropriate surrogate for overall bone mass. Thus, the NHANES data may help clarify the association of BMD (using tbBMD) and body composition across the wide range of body weight, which has not been accomplished in studies performed to date.

Methods

We analyzed 10,814 subjects (5,373 men) at least 20 years old from NHANES 2011-2018. Lean mass and fat mass were normalized for body size by dividing by height squared to create lean mass index (LMI) and fat mass index (FMI). Linear regression models were created with total body BMD T-score (tbBMD T-score) as the outcome, while examining LMI and FMI and controlling for age, race/ethnicity, height, and smoking status. Weight was not included due to strong collinearities with LMI/FMI. Stata 16 was used for analysis and for the generation of figure. Microsoft Excel was also used for the generation of figures.

References

1) Felson et al. Effects of weight and body mass index on bone mineral

Results

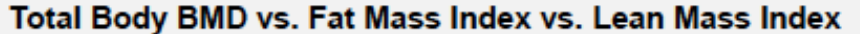
Table 1: Demographics

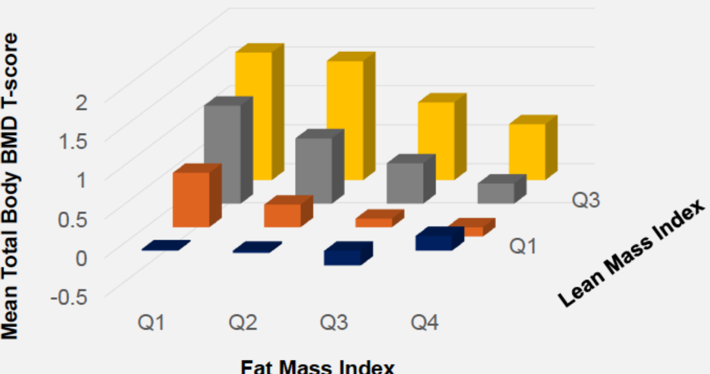
Bold italics indicate significant differences as compared to other groups

	BMI <30 (6795)	BMI 30-40 (3248)	BMI ≥ 40 (771)
Age	***38.7 ± 0.3***	40.8 ± 0.3	40.4 ± 0.6
BMI	***24.8 ± 0.1***	***33.7 ± 0.1***	***44.8 ± 0.2***
Male	51.4% ± 0.8%	51.5% ± 1.0%	33.6% ± 2.6%
Race	***63.0% White*** ***9.5% Black*** ***8.7% MA*** 7.2% HIS ***8.3% Asian*** 3.3% Other	58.3% White ***13.0% Black*** 13.6% MA ***8.4% HIS*** ***2.7% Asian*** 4.0% Other	58.6% White ***18.6% Black*** 12.2% MA 6.2% HIS ***0.6% Asian*** 3.7% Other
Total Body BMD (tbBMD)	***1.105 ± 0.003***	1.128 ± 0.004	1.130 ± 0.005
Lean Mass (kg)	***48.1 ± 0.2***	***58.7 ± 0.3***	***68.1 ± 0.6***
Lean Mass Index (range) [kg/m²]	***16.6 ± 0.04 (8.6-24.0)***	***20.4 ± 0.06 (14.2-28.7)***	***24.2 ± 0.14 (18.6-35.1)***
Fat Mass (kg)	***21.4 ± 0.1***	***35.2 ± 0.2***	***54.9 ± 0.4***
Fat Mass Index (range) [kg/m²]	***7.6 ± 0.05 (2.1-14.3)***	***12.5 ± 0.07 (5.5-20.1)***	***19.8 ± 0.20 (10.1-35.4)***

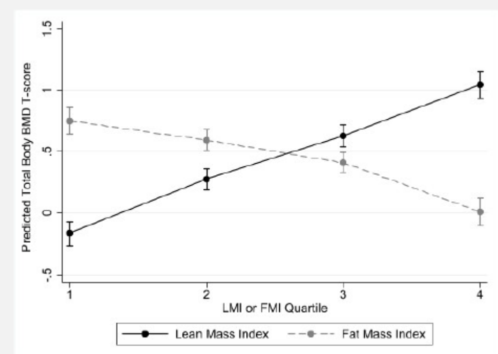
Mean ± SE

When holding lean mass constant, tbBMD T-score generally decreased with increasing fat mass index

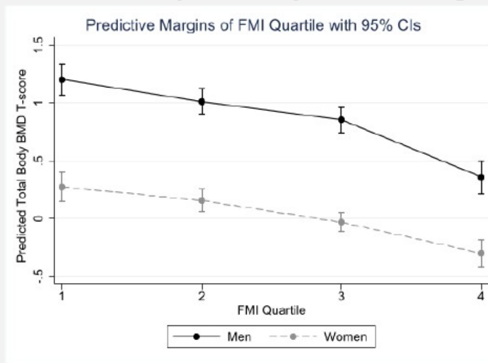




In multivariable modeling, lean mass index (LMI) had a positive association with tbBMD even at high levels of lean mass, while fat mass index (FMI) had a negative association with tbBMD.



The negative association of FMI and BMD was more prominent in men than women and was particularly notable at high levels of fat.



Conclusion

Obesity may exert negative effects on bone density, which may explain the increased fracture risk associated with obesity in at least some studies.

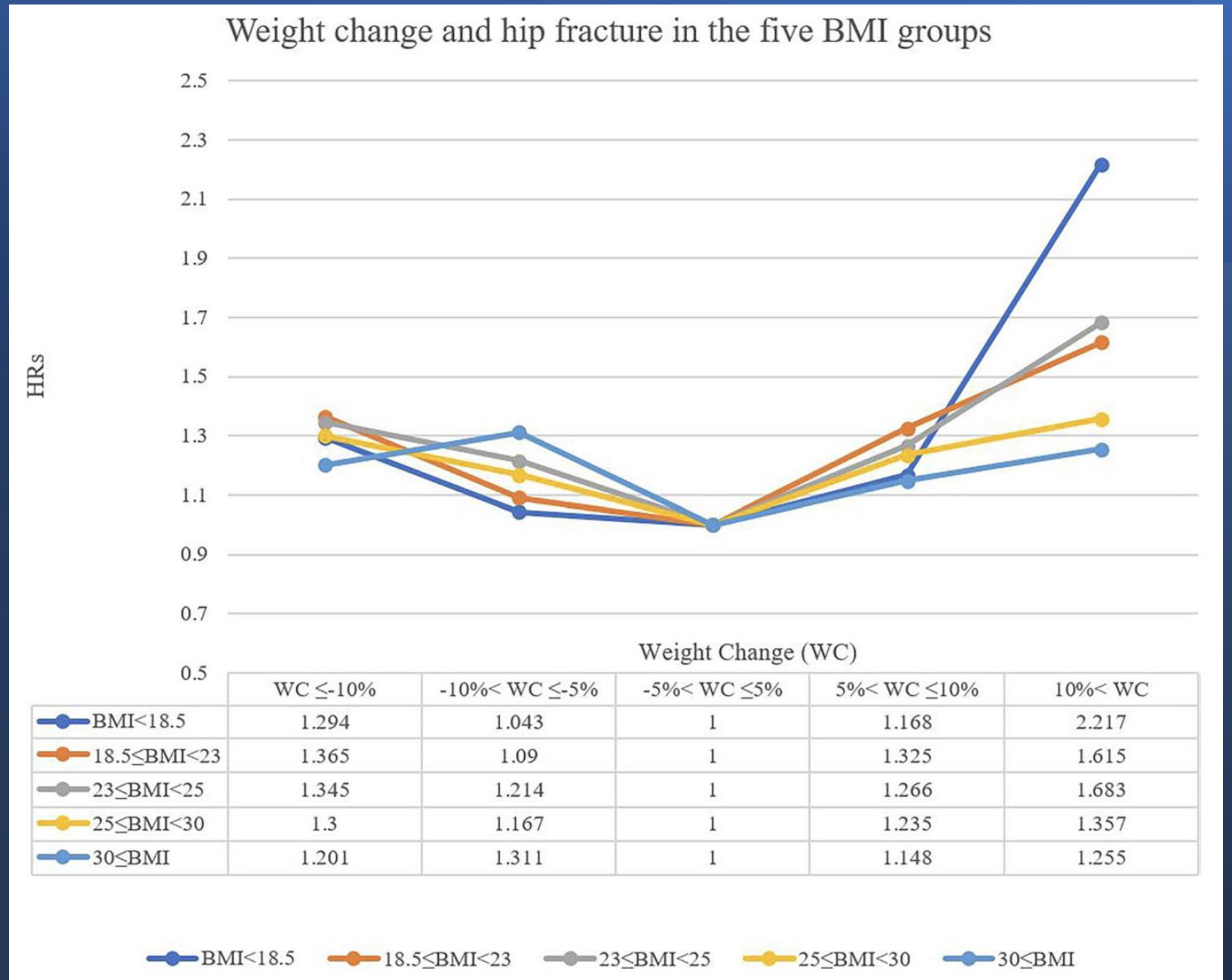
ΠΟΙΑ ΕΙΝΑΙ Η ΕΠΙΔΡΑΣΗ ΑΠΩΛΕΙΑΣ ΒΑΡΟΥΣ ΣΤΟΝ ΚΙΝΔΥΝΟ ΚΑΤΑΓΜΑΤΟΣ ΙΣΧΙΟΥ ΣΤΟΝ ΣΔ2?

Osteoporosis International (2022) 33:1755–1767
https://doi.org/10.1007/s00198-022-06398-8

ORIGINAL ARTICLE

Weight change and the risk of hip fractures in patients with type 2 diabetes: a nationwide cohort study

S.-W. Lee[1,2] · K. Han[3] · H.-S. Kwon[4,5]



	WC ≤-10%	-10%< WC ≤-5%	-5%< WC ≤5%	5%< WC ≤10%	10%< WC
BMI<18.5	1.294	1.043	1	1.168	2.217
18.5≤BMI<23	1.365	1.09	1	1.325	1.615
23≤BMI<25	1.345	1.214	1	1.266	1.683
25≤BMI<30	1.3	1.167	1	1.235	1.357
30≤BMI	1.201	1.311	1	1.148	1.255

ΠΩΣ ΒΟΗΘΑΕΙ ΤΟ HR-pQCT ΣΤΗΝ ΚΑΤΑΝΟΗΣΗ ΤΗΣ ΜΙΚΡΟΑΡΧΙΤΕΚΤΟΝΙΚΗΣ ΣΤΟΝ ΣΔ?

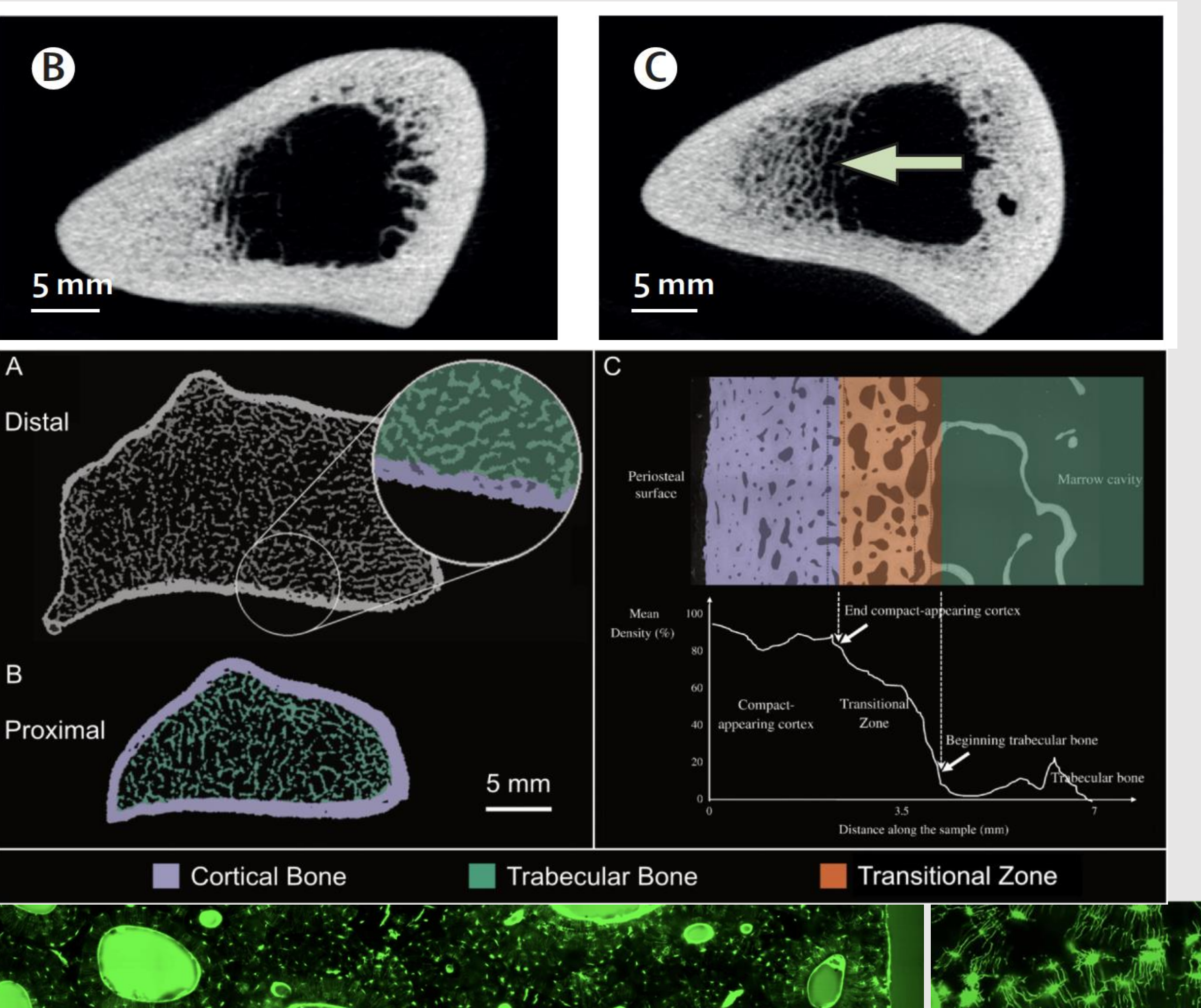
Current Osteoporosis Reports (2022) 20:398–409
https://doi.org/10.1007/s11914-022-00755-6

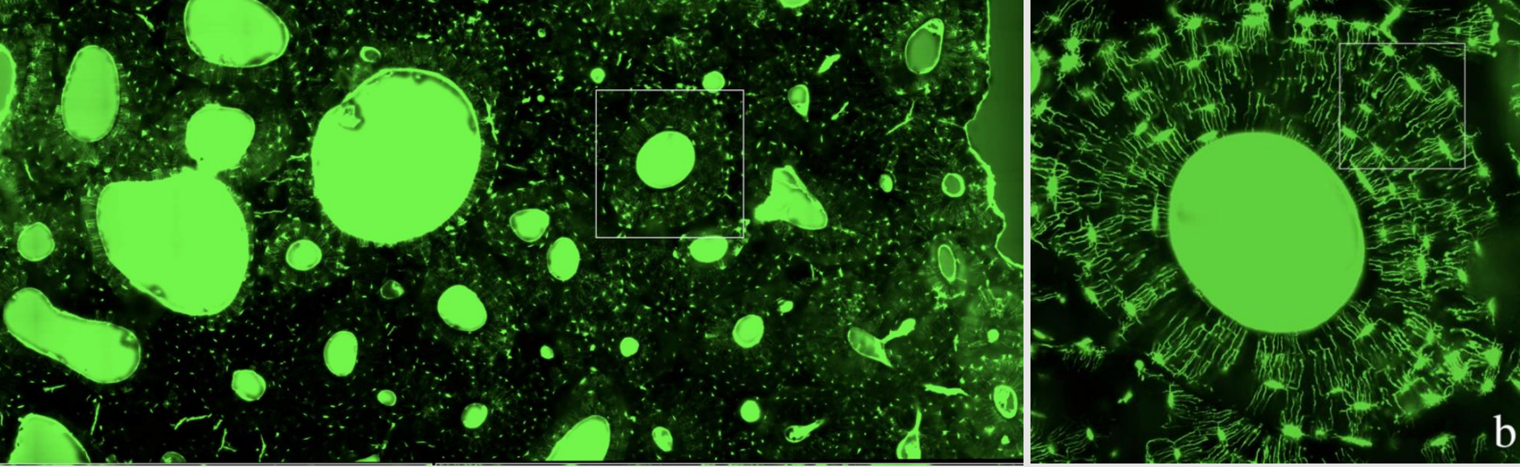
IMAGING (H ISAKSSON AND S BOYD, SECTION EDITORS)

Meta-analysis of Diabetes Mellitus-Associated Differences in Bone Structure Assessed by High-Resolution Peripheral Quantitative Computed Tomography

Matthias Walle[1] · Danielle E. Whittier[1] · Morten Frost[2] · Ralph Müller[1] · Caitlyn J. Collins[1,3]

- Resolution 82µm
- Image processing
- Computational analysis
- Trabecular architecture
- Trabecular heterogeneity
- Cortical architecture
- Calculate load failure
- Bending strength
- Cortical porosity- “trabecularization”





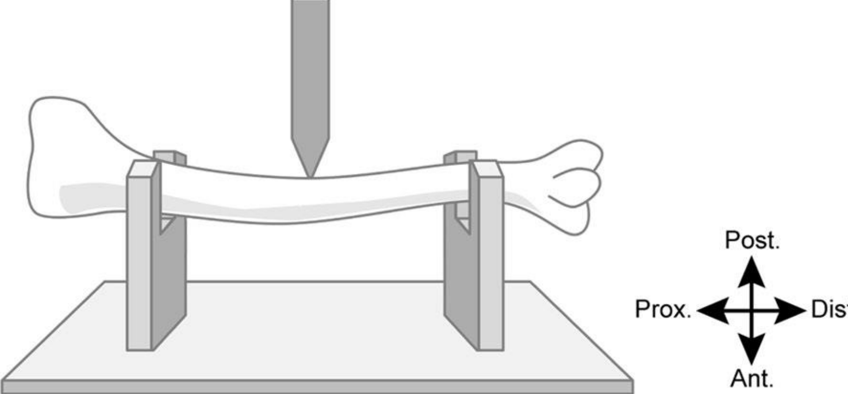


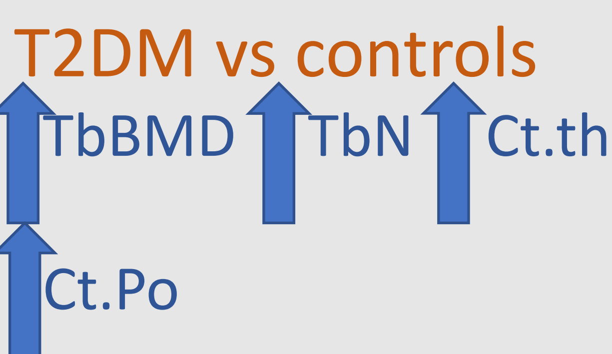
Table 1 Primary HR-pQCT parameters included in the meta-analysis

Parameter (abbreviation)	Description	Units
Areal (Ar) bone measures		
Total (Tt.Ar)	Total bone area	mm^2
Volumetric bone mineral density (BMD) measures		
Total (Tt.BMD)	Total volumetric density	mg HA/cm^3
Cortical (Ct.BMD)	Cortical volumetric density	mg HA/cm^3
Trabecular (Tb.BMD)	Trabecular volumetric density	mg HA/cm^3
Cortical (Ct.) measures		
Cortical thickness (Ct.Th)	Mean cortical thickness, calculated directly	mm
Cortical porosity (Ct.Po)	Cortical porosity, calculated using a density-based method [33]	%
Trabecular (Tb.) measures		
Trabecular number (Tb.N)	Mean number of trabeculae per unit length	mm^{-1}
Inhomogeneity of trabecular network (Tb.1/N.SD)	Deviation of the distance between trabeculae	mm
Finite element analysis (FEA) measures		
Failure Load (FL)	Estimated maximum load using the Pistoia criterion [34]	N

T1DM vs controls

↓ T.bBMD ↓ TbN ↑ heterogeneity

T2DM vs controls



- T1DM adverse trabecular characteristics
- T2DM adverse cortical characteristics
- Radius worse than tibia
- Site-specific loading conditions

Distal Radius

Type 1 Diabetes | Type 2 Diabetes | Healthy

Distal Tibia

Type 1 Diabetes | Type 2 Diabetes | Healthy

F_{body}

Anabolic | Catabolic

1. Impaired trabecular homogeneity
2. Impaired trabecular bone structure
3. Impaired cortical porosity
4. Enhanced cortical thickness
5. Enhanced trabecular bone structure
6. Loading may reduce negative effects

ΠΟΙΑ ΕΙΝΑΙ Η ΕΠΙΔΡΑΣΗ ΤΗΣ ΜΕΤΦΟΡΜΙΝΗΣ ΣΕ ΜΟΝΤΕΛΟ ΔΙΑΒΗΤΙΚΗΣ ΟΣΤΕΟΠΟΡΩΣΗΣ?

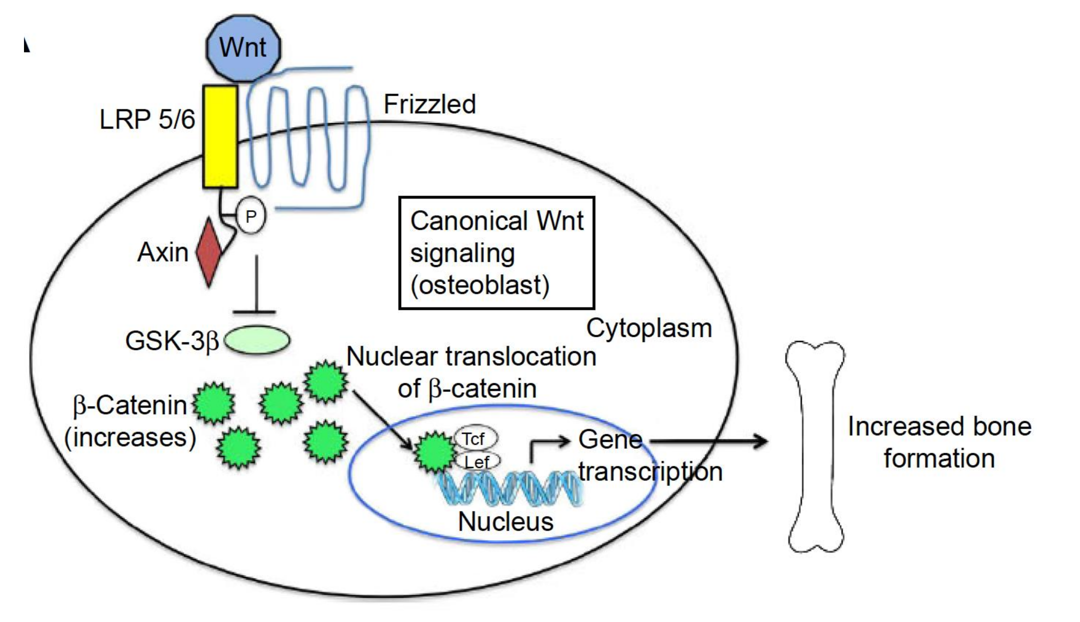
Huang *et al. BMC Endocrine Disorders* *(2022) 22:189*
https://doi.org/10.1186/s12902-022-01103-6

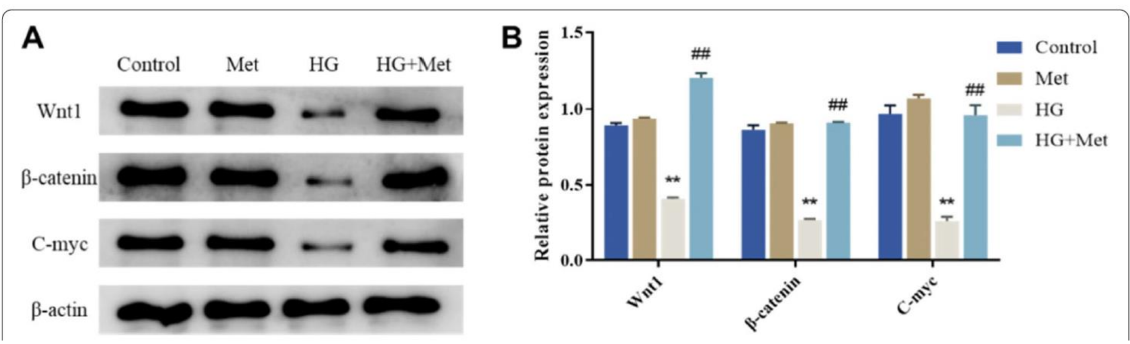
BMC Endocrine Disorders

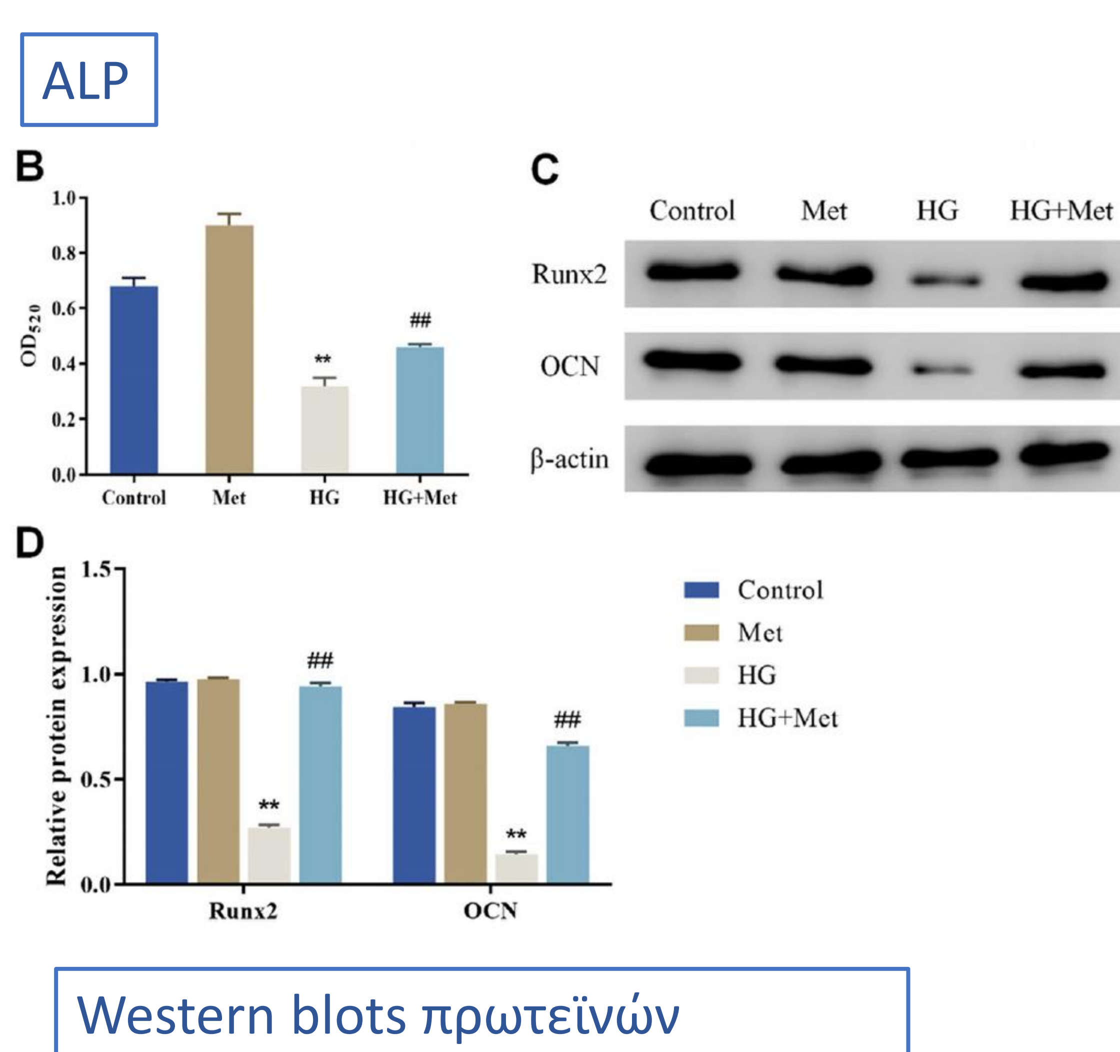
RESEARCH **Open Access**

Metformin activates Wnt/β-catenin for the treatment of diabetic osteoporosis

Xiaopeng Huang, Siyun Li, Wenjie Lu and Longjiang Xiong*







Western blots πρωτεϊνών οστεοβλαστικής διαφοροποίησης

ΕΙΝΑΙ ΑΠΟΤΕΛΕΣΜΑΤΙΚΑ ΤΑ ΔΙΦΩΣΦΟΝΙΚΑ ΣΤΗΝ ΠΡΟΛΗΨΗ ΚΑΤΑΓΜΑΤΩΝ ΣΤΟΝ ΔΙΑΒΗΤΗ?

RESEARCH ARTICLE

Diabetes Mellitus and the Benefit of Antiresorptive Therapy on Fracture Risk

Richard Eastell,[1] Eric Vittinghoff,[2] Li-Yung Lui,[3] Susan K. Ewing,[2] Ann V. Schwartz,[2] Douglas C. Bauer,[2,4] Dennis M. Black,[2] and Mary L. Bouxsein[5]

Table 1. DM Status by Trial in SABRE Study

Trial	Drug class	Study drug	*N* in non-DM	*N* in T2D
FIT I Black 1996[9]	Bisphosphonate	Alendronate	1955	72
FIT II[10]	Bisphosphonate	Alendronate	4286	146
BONE[11]	Bisphosphonate	Ibandronate	2831	98
IBAN IV[12]	Bisphosphonate	Ibandronate (intravenous)	2835	25
HIP[13]	Bisphosphonate	Risedronate	8816	515
VERT-MN[14]	Bisphosphonate	Risedronate	791	23
VERT-NA[15]	Bisphosphonate	Risedronate	1568	60
HORIZON PFT[16]	Bisphosphonate	Zoledronic acid (intravenous)	7234	502
HORIZON RFT Lyles 2007[17]	Bisphosphonate	Zoledronic acid (intravenous)	2092	35
LOFT[18]	Odanacatib	Odanacatib	14,302	1769
WHI-E[19]	Hormone therapy	Hormone therapy	9682	1054
WHI-EP[20]	Hormone therapy	Hormone therapy	15,626	971
FREEDOM[21]	Denosumab	Denosumab (subcutaneous)	7192	596
PEARL[22]	SERMs	Lasofoxifene	8051	505
MORE[23]	SERMs	Raloxifene	2585	168

ΟΛΕΣ ΟΙ ΘΕΡΑΠΕΙΕΣ

Table 3. Pooled Analyses of Anti-Fracture Treatment Efficacy in Non-DM and T2D in 15 Trials of Anti-Resorptive Medications

	Non-DM		T2D			
Fracture type	Treatment effect HR or OR (95% CI)	% with fracture (*n*/*N*)	Treatment effect HR or OR (95% CI)	% with fracture (*n*/*N*)	Interaction HR or OR (95% CI)	Interaction p^a
Vertebral	0.52 (0.49–0.56)	7.3 (3947/54,193)	0.48 (0.36–0.63)	5.7 (215/3787)	0.91 (0.68–1.22)	0.53
Nonvertebral	0.82 (0.78–0.85)	9.6 (8647/89,846)	0.86 (0.74–1.00)	10.2 (666/6539)	1.05 (0.89–1.22)	0.58
All	0.72 (0.69–0.74)	13.9 (12,478/89,846)	0.74 (0.64–0.84)	13.5 (880/6539)	1.02 (0.89–1.17)	0.80
Hip	0.68 (0.61–0.77)	1.3 (1202/89,846)	0.82 (0.57–1.16)	1.9 (125/6539)	1.20 (0.83–1.74)	0.33

All results are adjusted for trial.
[a]Two-way interaction: Treatment * Diabetes status.

Table 4. Pooled Analyses of Anti-Fracture Treatment Efficacy in non-DM and T2D in Nine Bisphosphonate Trials

	Non-DM		T2D			
Fracture type	Treatment effect HR or OR (95% CI)	% with fracture (*n*/*N*)	Treatment effect HR or OR (95% CI)	% with fracture (*n*/*N*)	Interaction HR or OR (95% CI)	Interaction p^a
Vertebral	0.56 (0.51–0.61)	8.4 (2089/24,910)	0.38 (0.23–0.64)	7.0 (74/1060)	0.73 (0.44–1.20)	0.21
Nonvertebral	0.88 (0.82–0.94)	9.6 (3094/32,408)	0.77 (0.56–1.06)	10.3 (152/1476)	0.90 (0.65–1.24)	0.51
All	0.74 (0.70–0.79)	15.4 (4982/32,408)	0.64 (0.49–0.83)	14.7 (217/1476)	0.87 (0.67–1.15)	0.32
Hip	0.69 (0.58–0.83)	1.6 (517/32,408)	1.13 (0.58–2.20)	2.5 (37/1476)	1.69 (0.85–3.35)	0.14

All results are adjusted for trial.
[a]2-way interaction: Treatment * Diabetes status.

ΔΙΦΩΣΦΩΝΙΚΑ

ΑΠΟΤΕΛΕΣΜΑΤΑ

- Η αποτελεσματικότητα των αντι-οστεοαπορροφητικών φαρμάκων δεν επηρεάζεται από τον ΣΔ
- Τα φάρμακα αυτά μειώνουν τα κατάγματα, αυξάνουν την οστική πυκνότητα και μεώνουν τους δείκτες οστικής ανακατασκευής στους ασθενείς με ΣΔ όσο στους μη διαβητικούς

ΠΟΙΑ ΑΝΤΙΔΙΑΒΗΤΙΚΗ ΘΕΡΑΠΕΙΑ ΠΡΩΤΗΣ ΓΡΑΜΜΗΣ ΕΙΝΑΙ ΠΡΟΤΙΜΟΤΕΡΗ ΣΕ ΣΧΕΣΗ ΜΕ ΤΗΝ ΟΣΤΙΚΗ ΥΓΕΙΑ ΣΤΟΝ ΣΔ2 ?

SGLT2 inhibitor treatment is not associated with an increased risk of osteoporotic fractures when compared to GLP-1 receptor agonists: A nationwide cohort study

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Τι θα θέλαμε να μάθουμε του χρόνου

- Ποιος είναι ο ρόλος των AGEs στην παθογένεση της διαβητικής οστικής νόσου?
  - Πώς τα μετρούμε
- Πώς θα αξιολογούμε τη μέτρηση DXA στη διάγνωση και παρακολούθηση της διαβητικής οστικής νόσου?
- Πώς εκδηλώνεται η διαβητική οστική νόσος στους άντρες και στις γυναίκες και γιατί?
- Πώς επηρεάζει η παχυσαρκία τον καταγματικό κίνδυνο?
- Πως μπορούμε να εκτιμήσουμε καλύτερα τον καταγματικό κίνδυνο στον διαβητικό ασθενή στην κλινική πράξη? Σε ποιες ανατομικές θέσεις?
- Ποια θεραπεία είναι καταλληλότερη? αντι-οστεοκλαστική ή οστεοαναβολική?
- Ποιες φαρμακευτικές επιλογές γλυκαιμικού ελέγχου προλαμβάνουν τη διαβητική οστική νόσο?

THE NEW FRAX

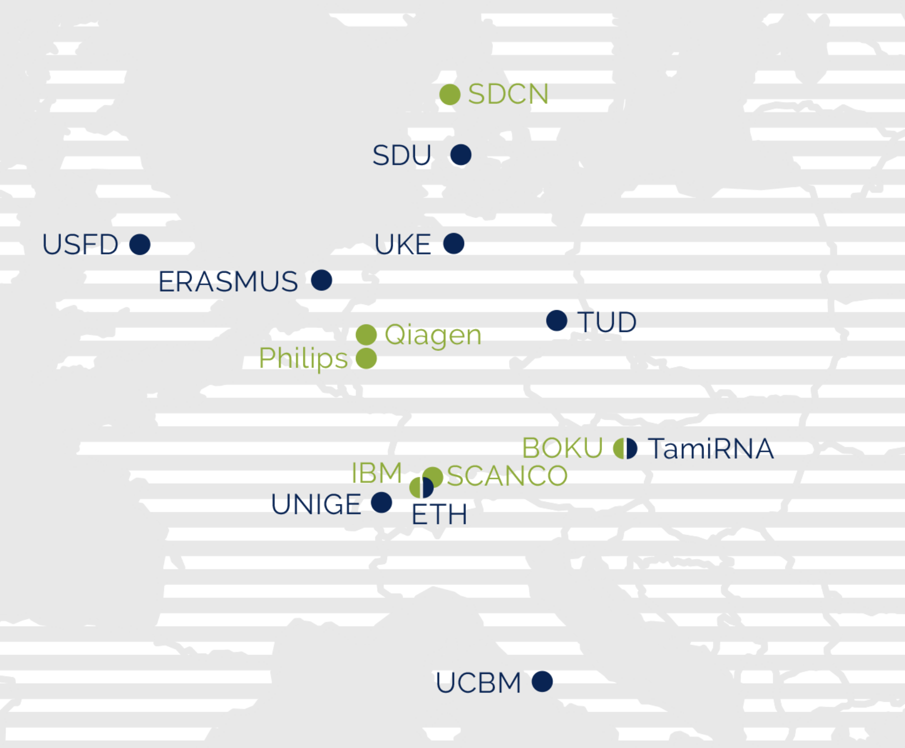
REVIEW

Update of the fracture risk prediction tool FRAX:

a systematic review of potential cohorts and analysis plan

Osteoporosis International https://doi.org/10.1007/s00198-022-06435-6

- 53 προοπτικές μελέτες με κλινικούς παράγοντες κινδύνου και incident fractures
- 4 νέες κοόρτες και 60 ήδη υπάρχουσες
- 2.138.428 άτομα με παρακολούθηση 20 εκ. person-years
- 116.117 μείζονα οστεοπορωτικά κατάγματα
- Θα υπολογιστούν μοντέλα 10ετούς πιθανότητας μείζονος κατάγματος και ισχίου
  - Με ή χωρίς την BMD



Participants

Associated Partners

The research programme will address different aspects of diabetic bone disease:

It will utilise advanced imaging and computational approaches, diabetes mouse models and access to clinical cohorts and registry data to obtain a comprehensive overview how diabetes increases fracture risk.