CONGRESSO
SID AMD LAZIO 2015
IL PAZIENTE DIABETICO AL CENTRO:
RICERCA, ASSISTENZA E INNOVAZIONE

Il dr. **Andrea Palermo** dichiara di
aver ricevuto negli ultimi due anni compensi o finanziamenti
dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

AMGEN
Sanofi Aventis

RUOLO DEI NUOVI MARCATORI OSSEI IN CORSO DI DIABETE

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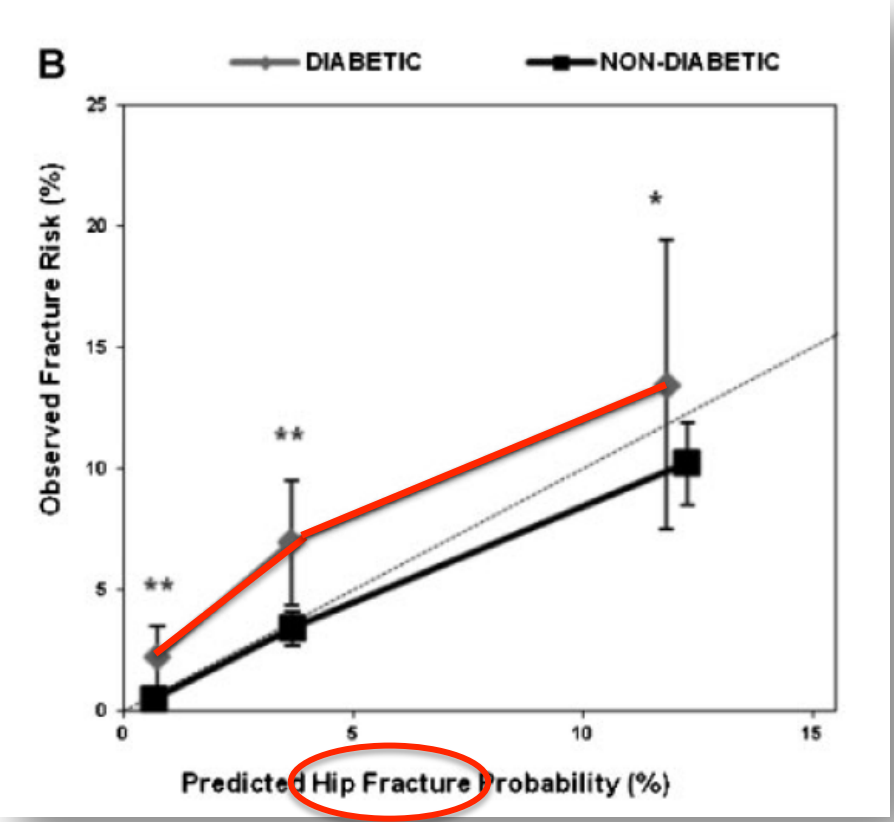
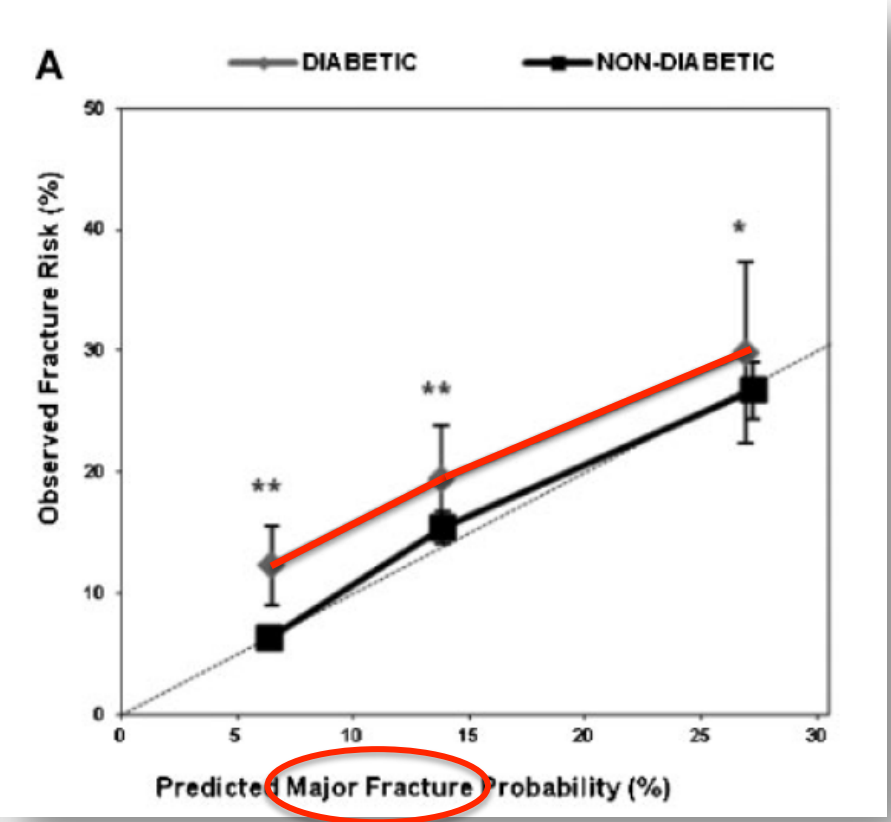
PERSPECTIVE

JBMR

Type 2 Diabetes and Bone

William D Leslie,[1] Mishaela R Rubin,[2] Ann V Schwartz,[3] and John A Kanis[4]





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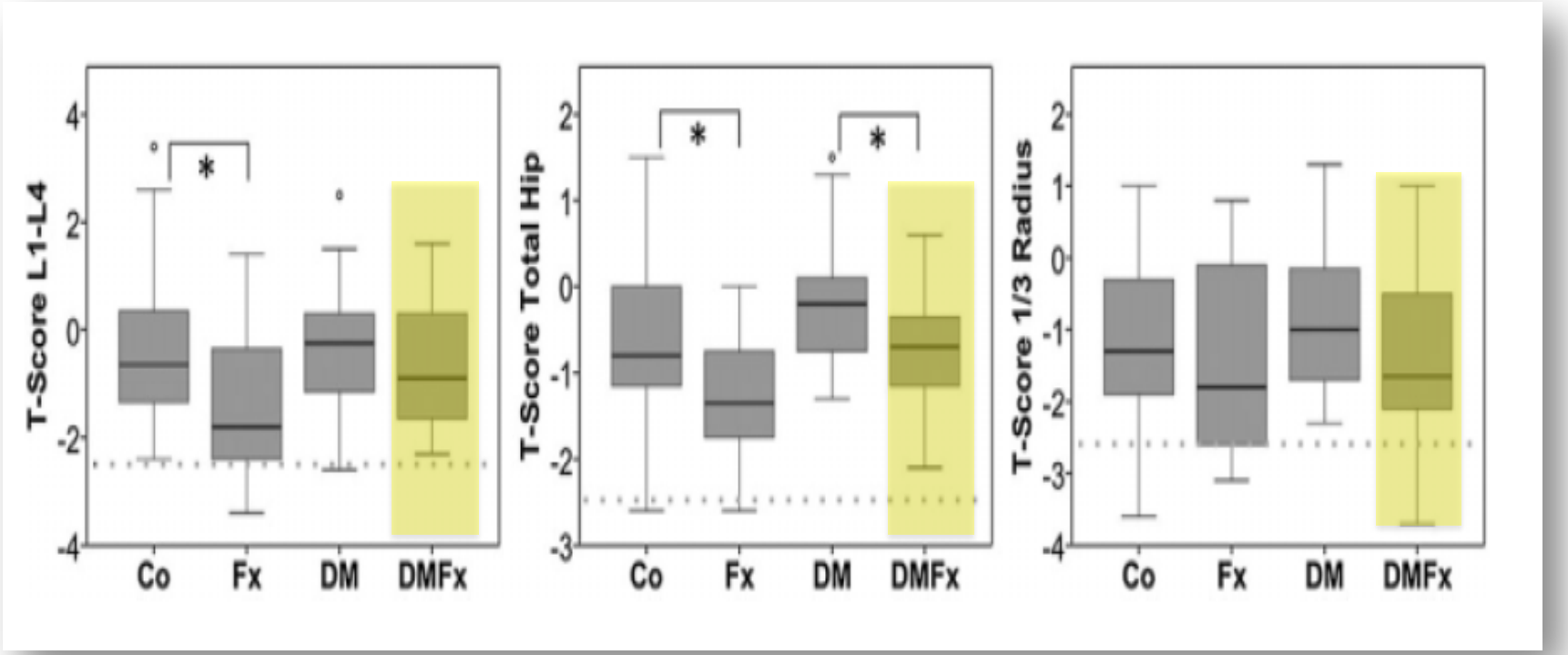
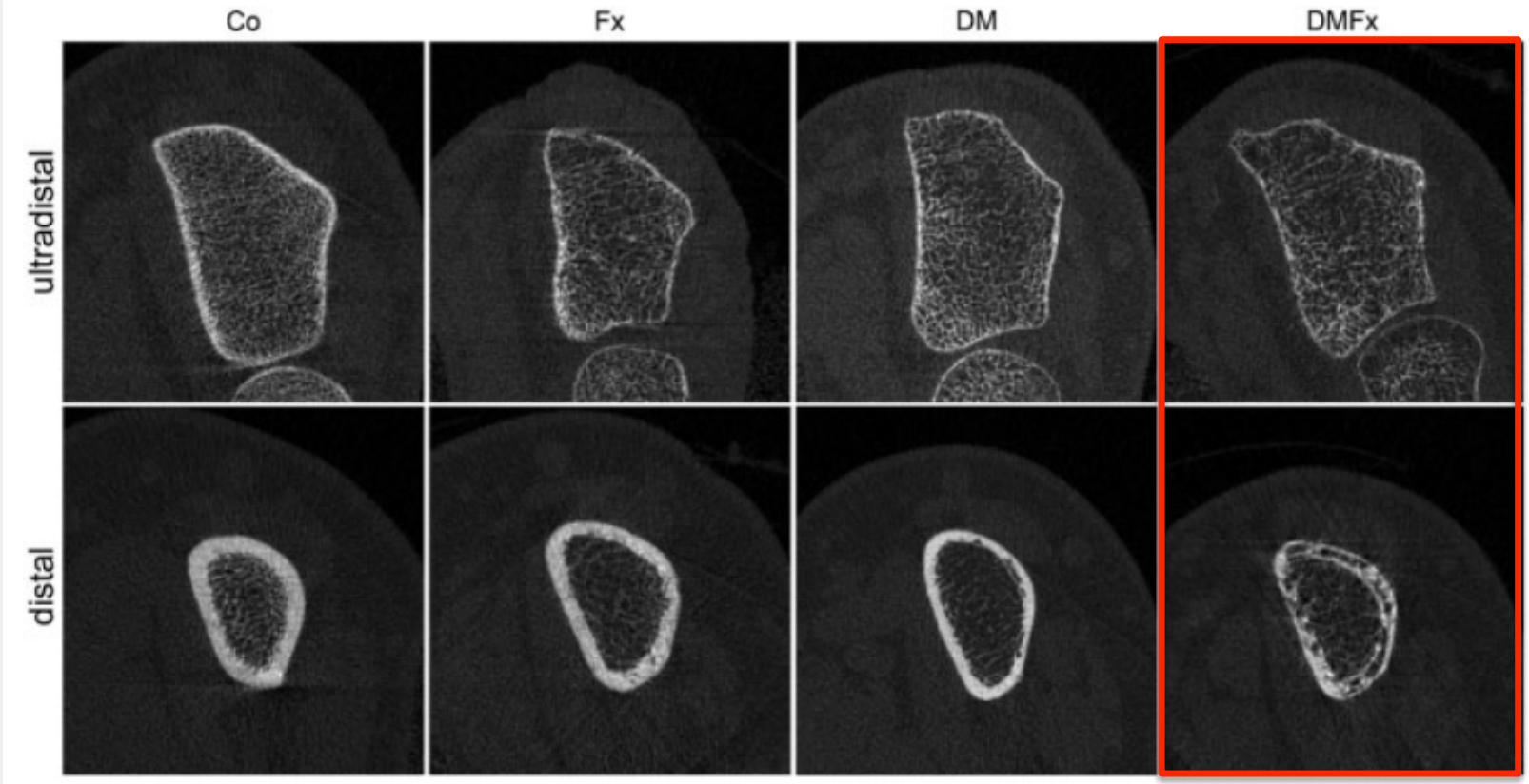


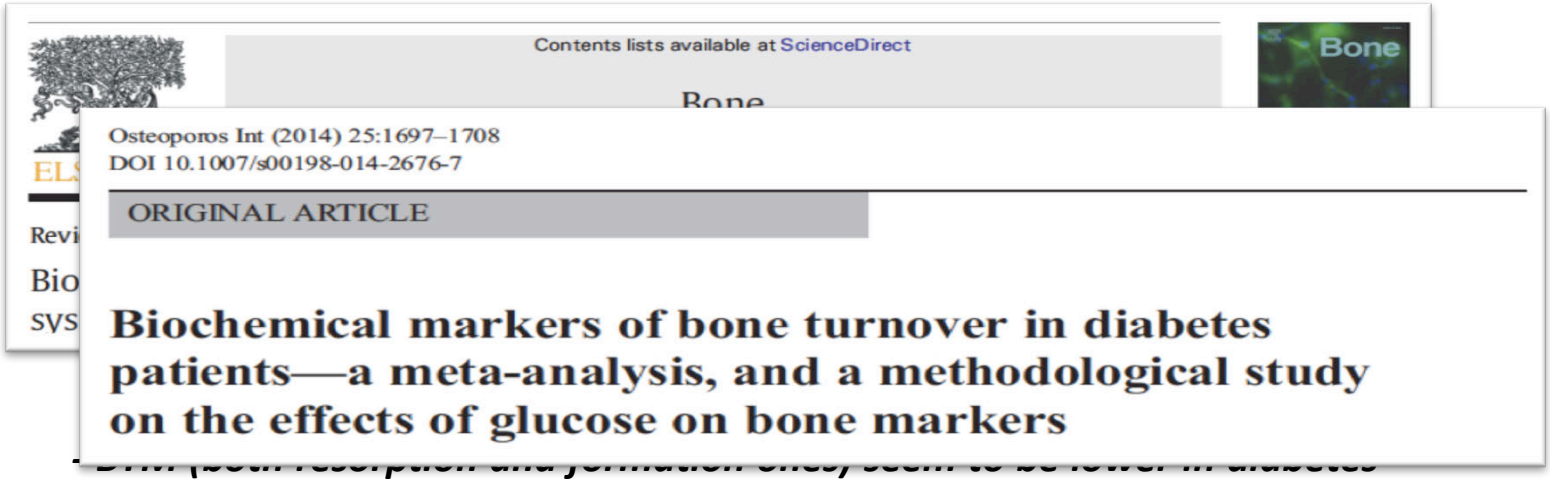
ORIGINAL ARTICLE

JBMR

Increased Cortical Porosity in Type 2 Diabetic Postmenopausal Women With Fragility Fractures

Janina M Patsch,[1*] Andrew J Burghardt,[1*] Samuel P Yap,[1] Thomas Baum,[1] Ann V Schwartz,[2] Gabby B Joseph,[1] and Thomas M Link[1]





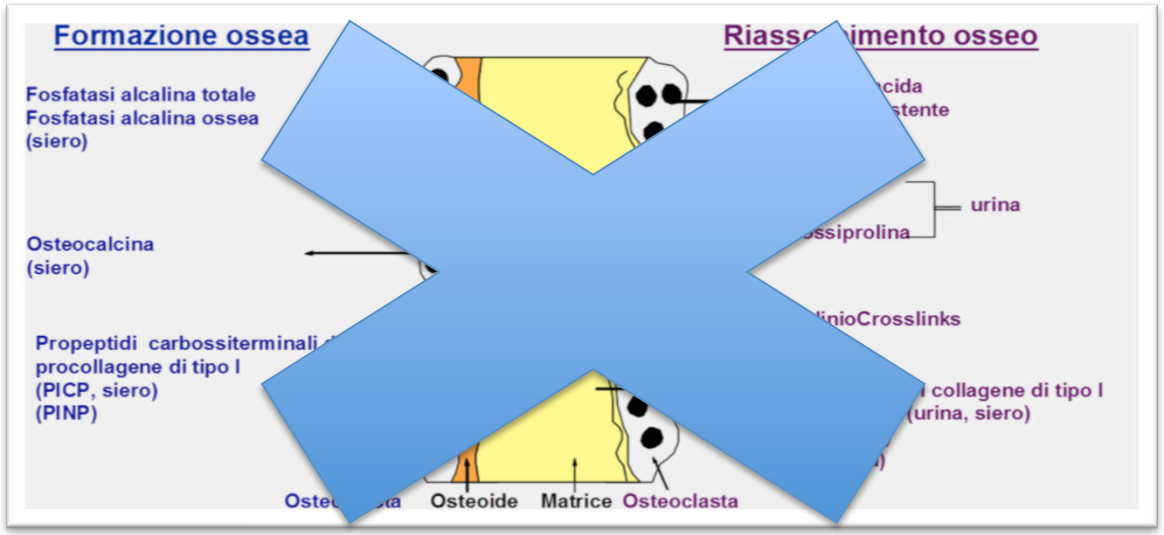
patients.

- BALP is normal or increased, which suggests that the matrix becomes hypermineralized in diabetes patients.

- ***… Osteocalcin and Beta CTX are lower in diabetes patients compared to healthy subjects";***

- ***"… Hyperglycaemia or addition of glucose do not significantly affect BTM";***

- ***"…Other factors related to diabetes could explain these results".***



- ***Esistono nuovi marcatori di danno osseo in corso di diabete?***

- ***Esistono marcatori ossei con significativo ruolo metabolico in corso di diabete?***

CROSS-LINK FORMATION IN BONE COLLAGEN

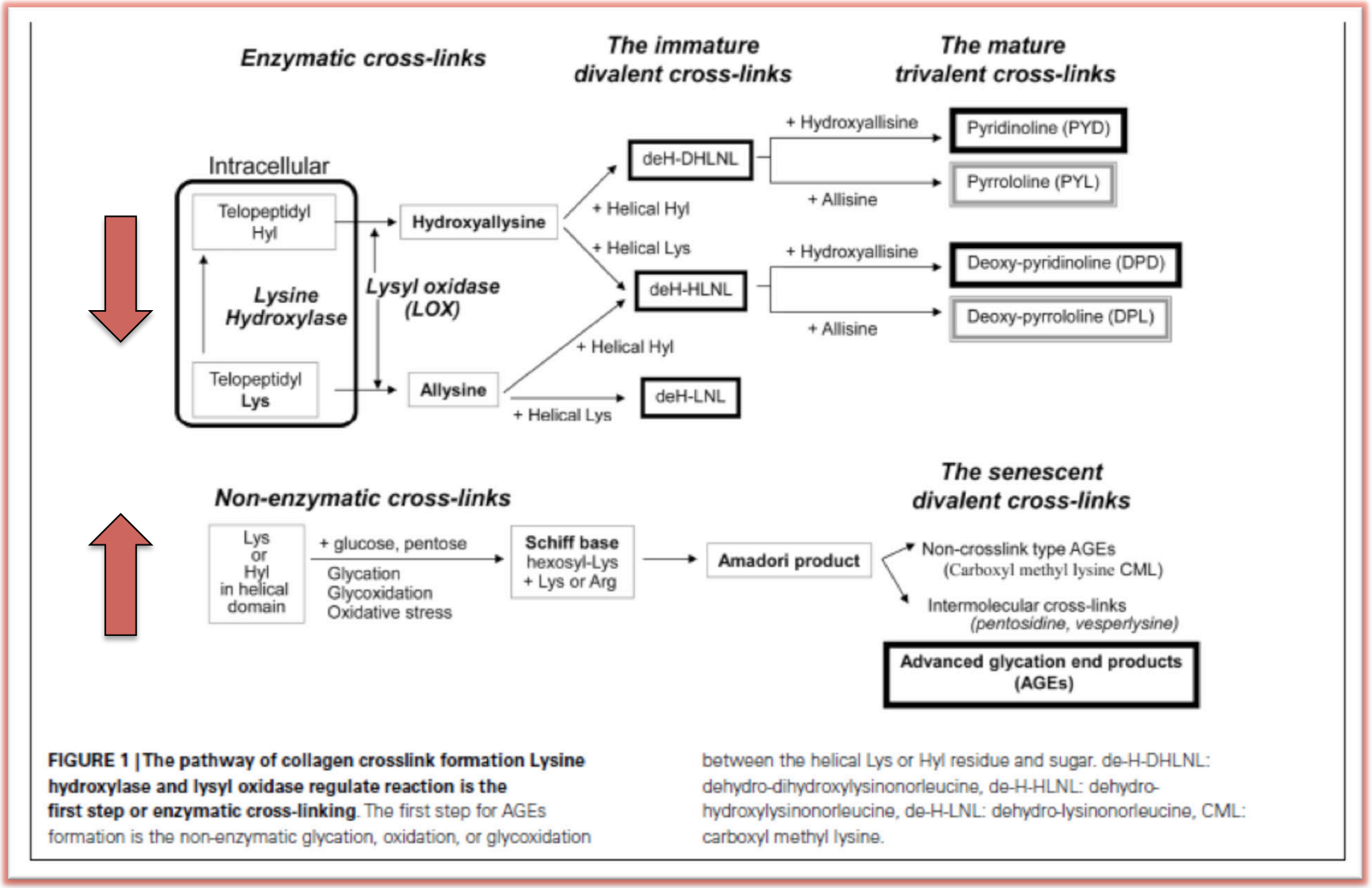


FIGURE 1 | The pathway of collagen crosslink formation Lysine hydroxylase and lysyl oxidase regulate reaction is the first step or enzymatic cross-linking. The first step for AGEs formation is the non-enzymatic glycation, oxidation, or glycoxidation between the helical Lys or Hyl residue and sugar. de-H-DHLNL: dehydro-dihydroxylysinonorleucine, de-H-HLNL: dehydro-hydroxylysinonorleucine, de-H-LNL: dehydro-lysinonorleucine, CML: carboxyl methyl lysine.

Saito and Marumo. Frontiers in Endocrinology, 2013

AGEs: Reduce material properties of bone (*in vitro* studies)

- Advanced glycation endproducts (AGEs) formed by **non-enzymatic** reaction between glucose and protein
- Accumulate in collagen, including bone collagen, with **older age** and **diabetes**
- Form cross-links that increase **stiffness of bone collagen**
- AGEs reduce **bone strength**
- **Lower bone turnover** may allow greater accumulation

Vashishth et al 2001; Wang X et al 2002; Willett et al 2013

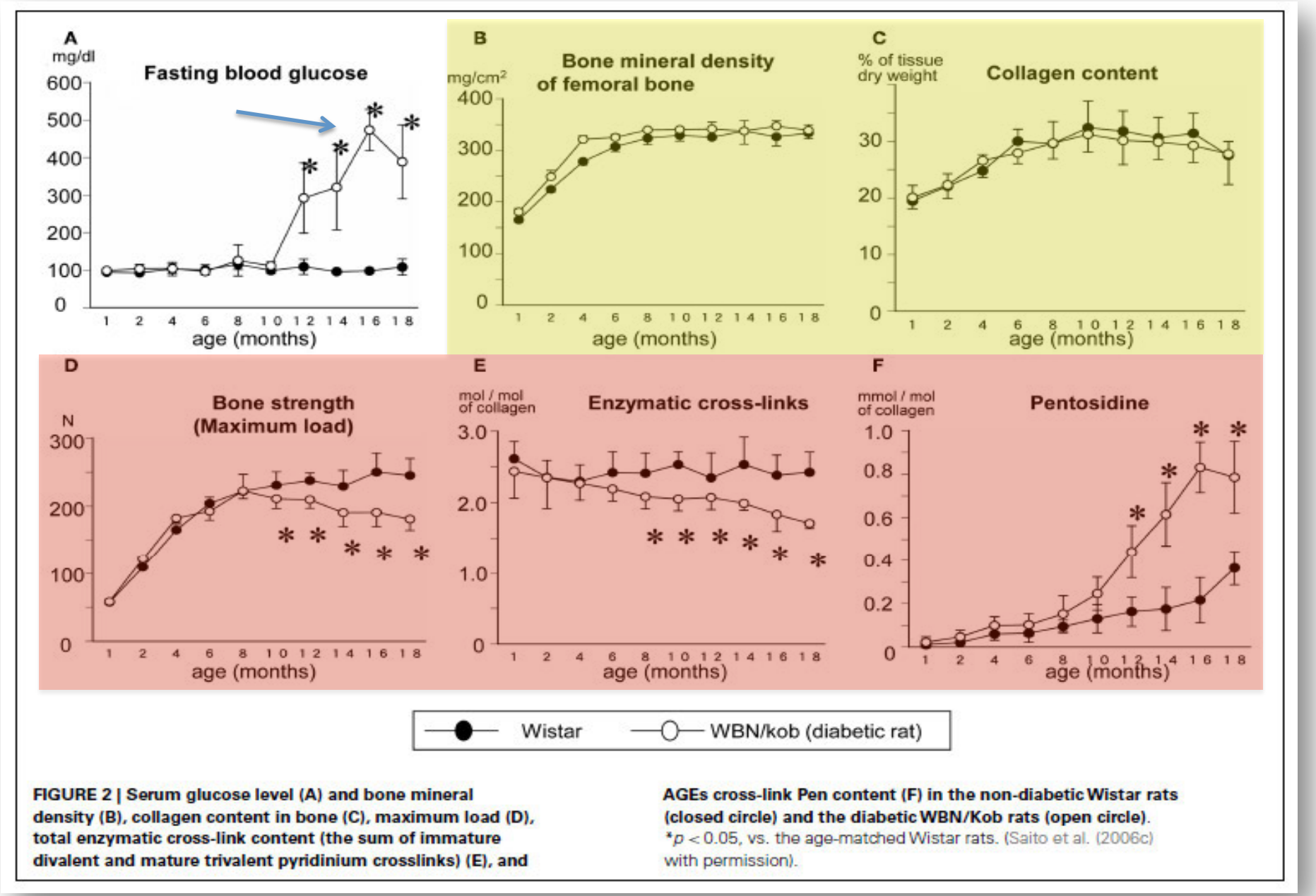
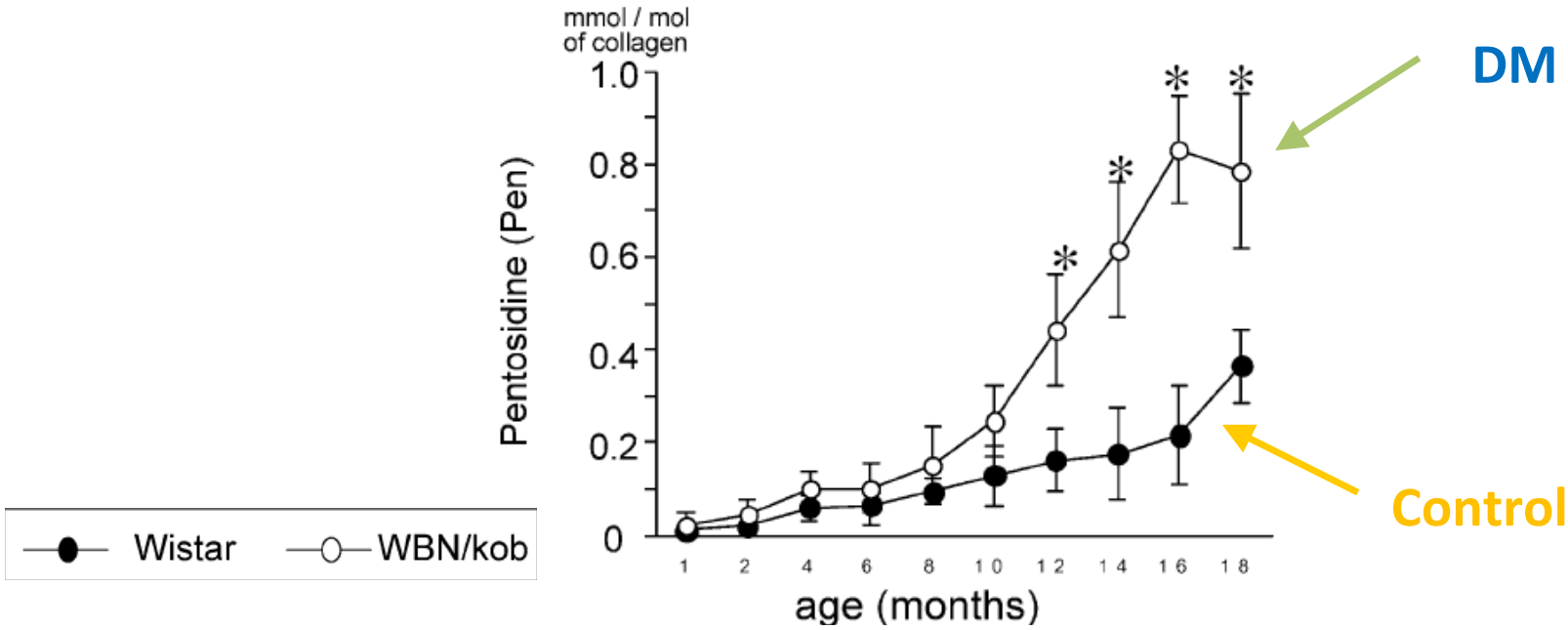


FIGURE 2 | Serum glucose level (A) and bone mineral density (B), collagen content in bone (C), maximum load (D), total enzymatic cross-link content (the sum of immature divalent and mature trivalent pyridinium crosslinks) (E), and AGEs cross-link Pen content (F) in the non-diabetic Wistar rats (closed circle) and the diabetic WBN/Kob rats (open circle). *$p < 0.05$, vs. the age-matched Wistar rats. (Saito et al. (2006c) with permission).

Saito and Marumo. Frontiers in Endocrinology, 2013

Pentosidine in bone increases with age and DM

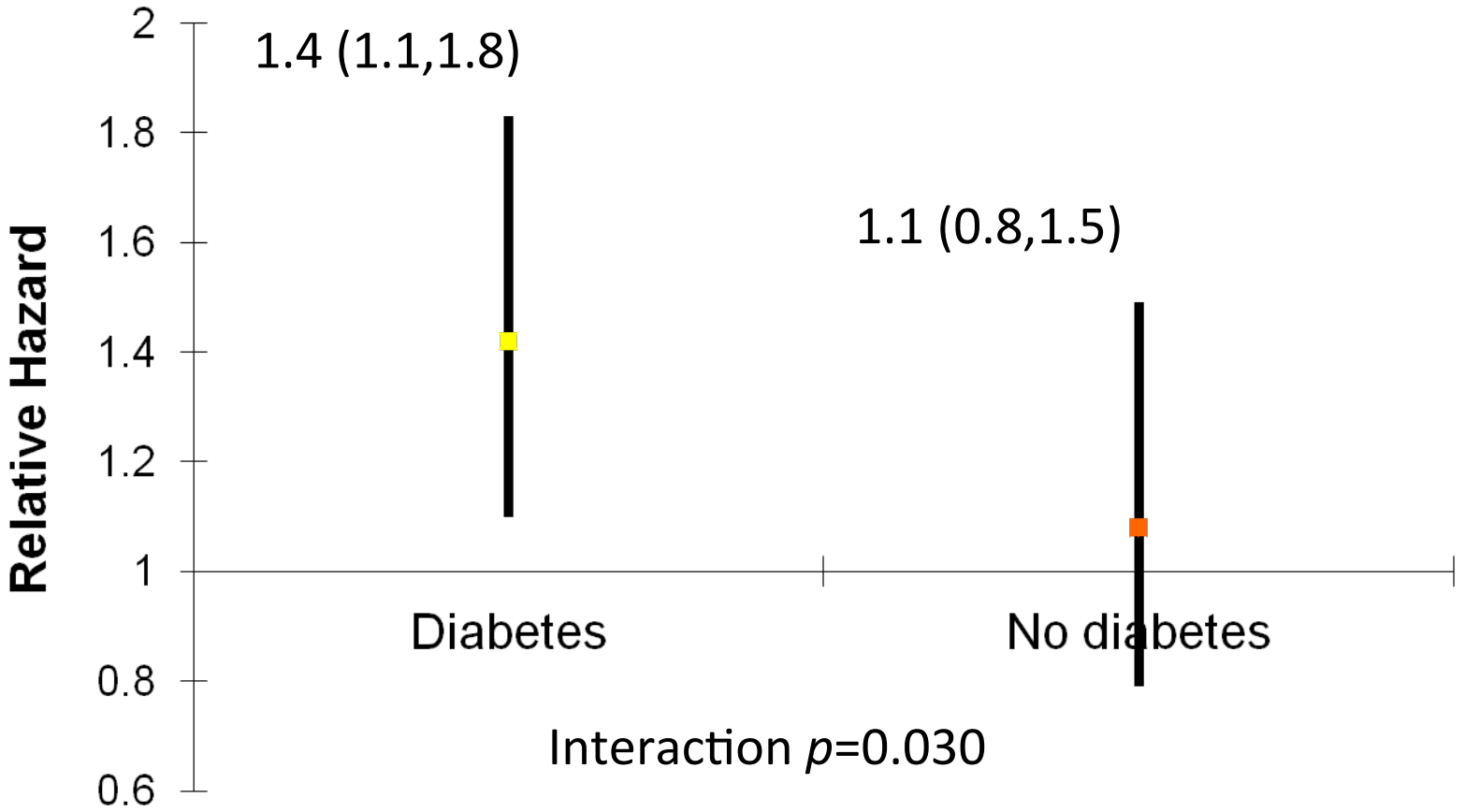


	Elastic modulus	Energy absorption	Stiffness	Maximum load
Pentosidine	**-0.579***	**-0.312***	**0.677***	**-0.448***

Saito et al. 2006

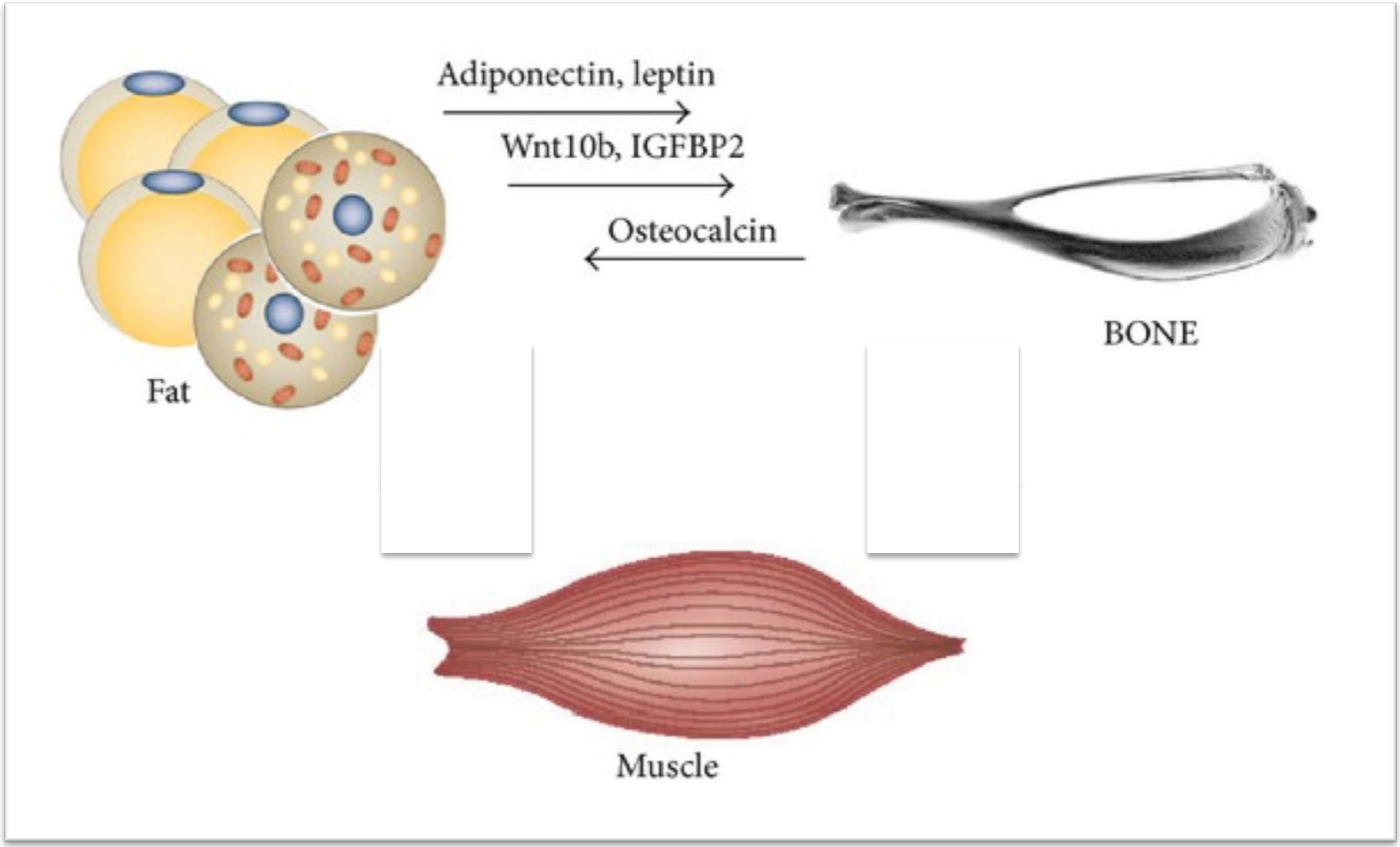
Urine pentosidine predicts incident clinical fractures in T2D

RR* of fracture for 1 SD increase in log PEN



Schwartz et al. 2009

MUSCLE-FAT-BONE AXIS

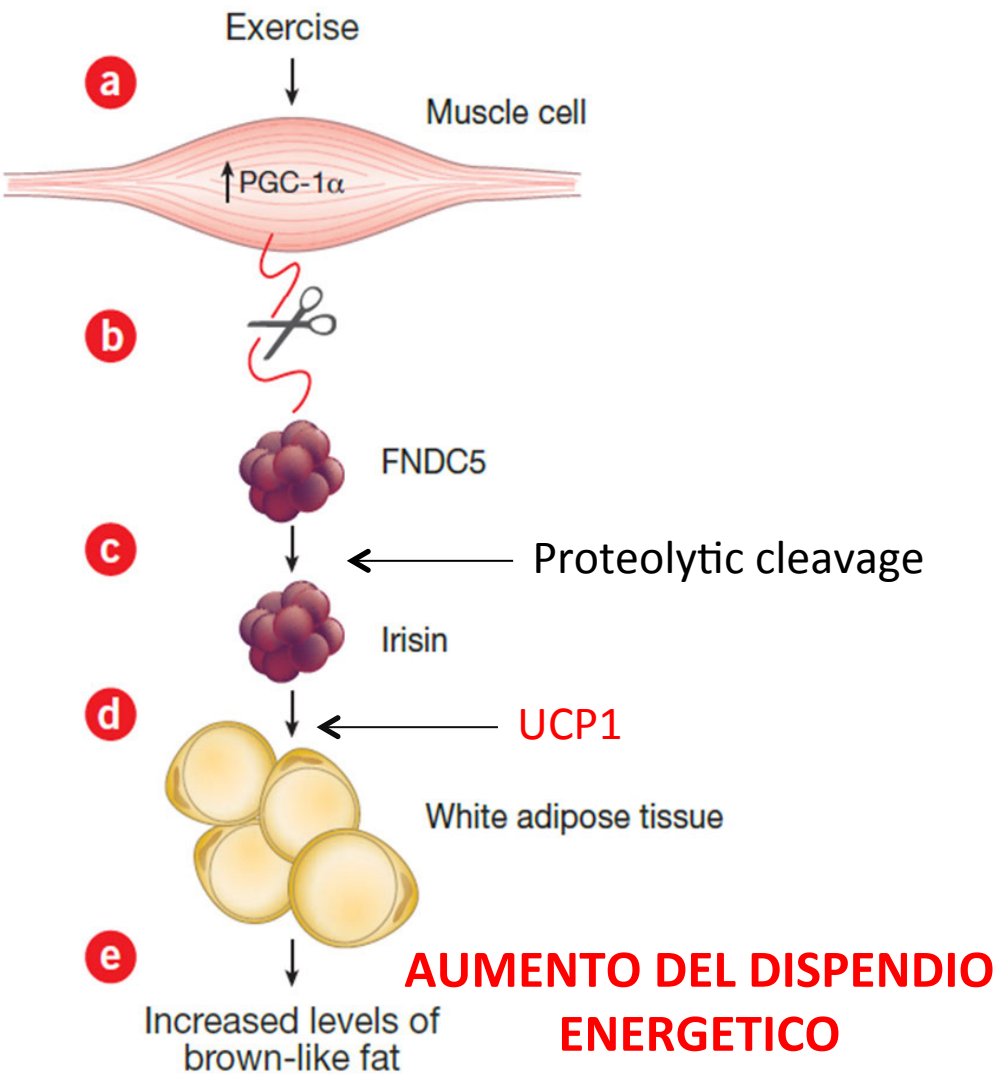


Colaianni G et al. *Irisin Enhances Osteoblast Differentiation In Vitro*, Int J Endocrinol. 2012

UN NUOVO ORMONE: L'IRISINA

Nel 2012 Boström et al.: scoperta dell'**IRISINA.**

- Polipeptide (12kDa) secreto dal muscolo scheletrico in risposta all'**esercizio fisico.**
- Stimola la **termoregolazione** con aumento del **dispendio energetico** (EE) tramite l'espressione di UCP1.
- Promozione **browning,** conversione del tessuto adiposo bianco (WAT) in tessuto adiposo bruno (BAT) in vitro e in vivo.



AUMENTO DEL DISPENDIO ENERGETICO

Kotz, J. Feb. 2 2012 Browning fat, SciBX 5(5);doi:10.1038/scibx.2012.114

IRISINA - OBESITA' - DIABETE

- ✓ Serum ***irisin levels*** were decreased in T2D patients and inversely associated with newly diagnosed T2D.

Diabetes Res Clin Pract. 2013 Apr;100(1):96-101.

- ✓ ***Lower circulating irisin*** is associated with obesity and type 2 diabetes mellitus.

J Diabetes Complications. 2013 Jul-Aug;27(4):303-4.

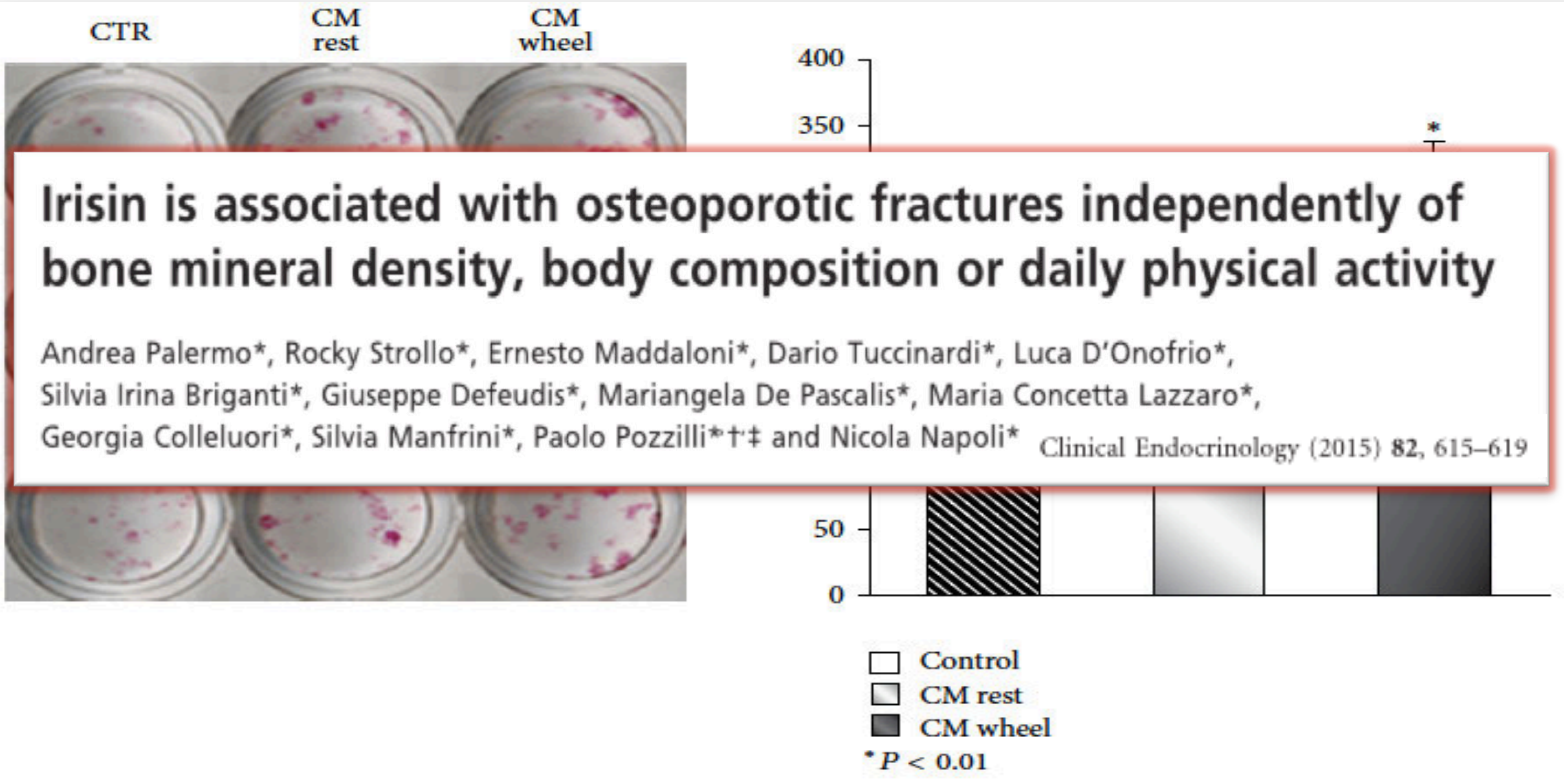
- ✓ ***Decreased circulating irisin*** concentration and ***FNDC5 gene expression*** in **adipose tissue** and **muscle** from obese and type 2 diabetic subjects suggests a loss of brown-like characteristics and a potential target for therapy.

J Clin Endocrinol Metab. 2013 Apr;98(4):E769-78

Research Article

Irisin Enhances Osteoblast Differentiation *In Vitro*

Graziana Colaianni,[1] Concetta Cuscito,[1] Teresa Mongelli,[1] Angela Oranger,[1]
Giorgio Mori,[2] Giacomina Brunetti,[1] Silvia Colucci,[1] Saverio Cinti,[3] and Maria Grano[1]



Irisin is associated with osteoporotic fractures independently of bone mineral density, body composition or daily physical activity

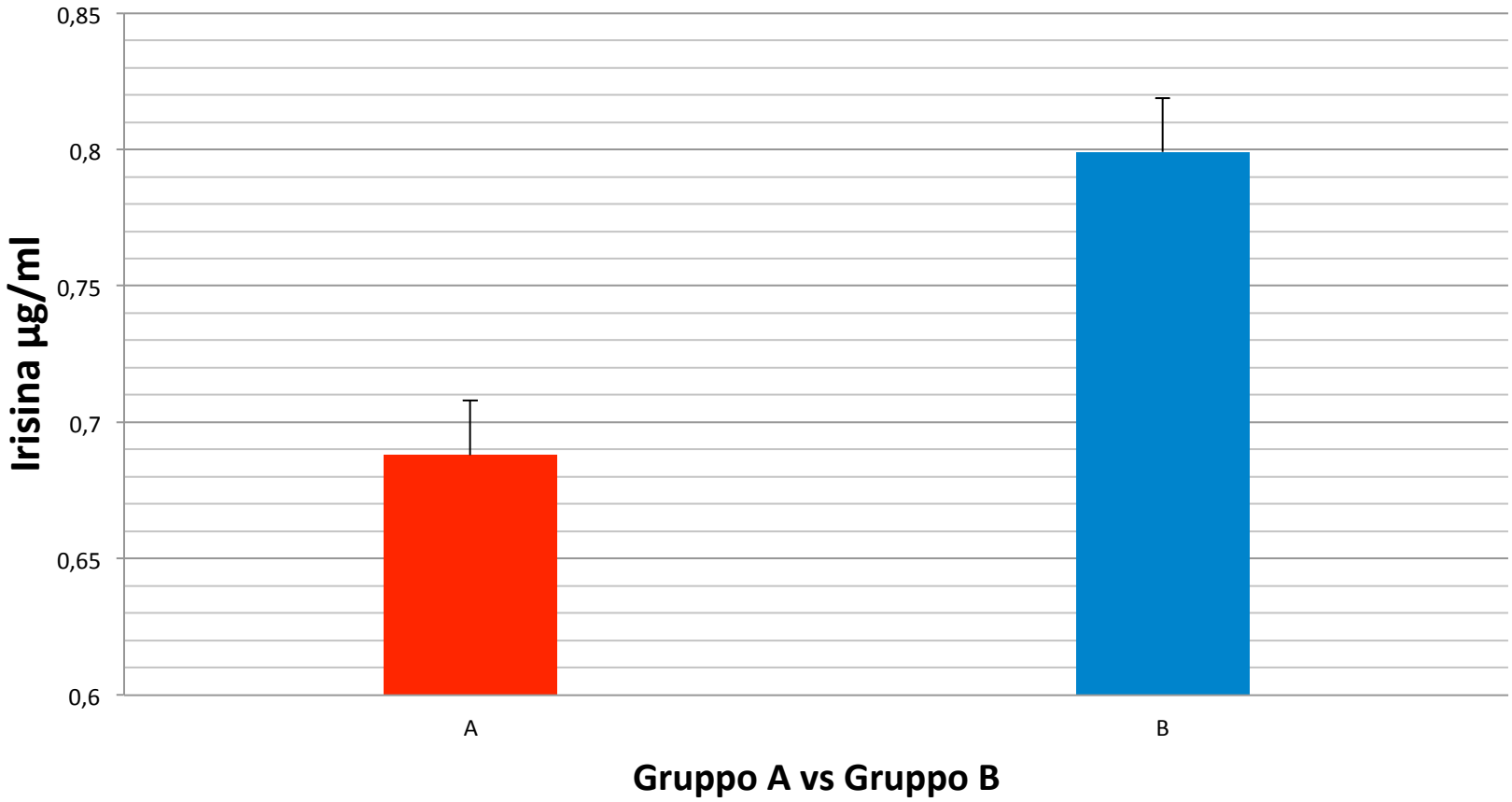
Andrea Palermo*, Rocky Strollo*, Ernesto Maddaloni*, Dario Tuccinardi*, Luca D'Onofrio*,
Silvia Irina Briganti*, Giuseppe Defeudis*, Mariangela De Pascalis*, Maria Concetta Lazzaro*,
Georgia Colleluori*, Silvia Manfrini*, Paolo Pozzilli*†‡ and Nicola Napoli*

Clinical Endocrinology (2015) **82**, 615–619

	Gruppo con frattura (A) (n=36)	Gruppo controlli (B) (n=36)	P value
Età, media ± SD (anni)	65.6 ± 6.7	62.9 ± 5.1	ns
Indice di Massa Corporea, Media ± SD (Kg/m²)	25.7 ± 2.8	26.6 ± 3.0	ns
Irisina, (µg/mL)	0.688 ± 0.224	0.799 ± 0.204	**0.032***
BMD Vertebrale (g/cm²)	0.725 ± 0.166	0.948 ± 0.110	**<0.001**
BMD totale del femore (g/cm²)	0.692 ± 0.138	0.858 ± 0.086	**<0.001**
BMD collo del femore (g/cm²)	0.603 ± 0.102	0.750 ± 0.080	**<0.001**
Massa magra subtotale (g)	29753.29 ± 2865.99	33328.09 ± 3898.15	**<0.001**
Massa grassa totale (g)	24848 ± 5564.25	26847.58 ± 5807.99	ns
METs	1.314 ± 0.193	1.361 ± 0.222	ns

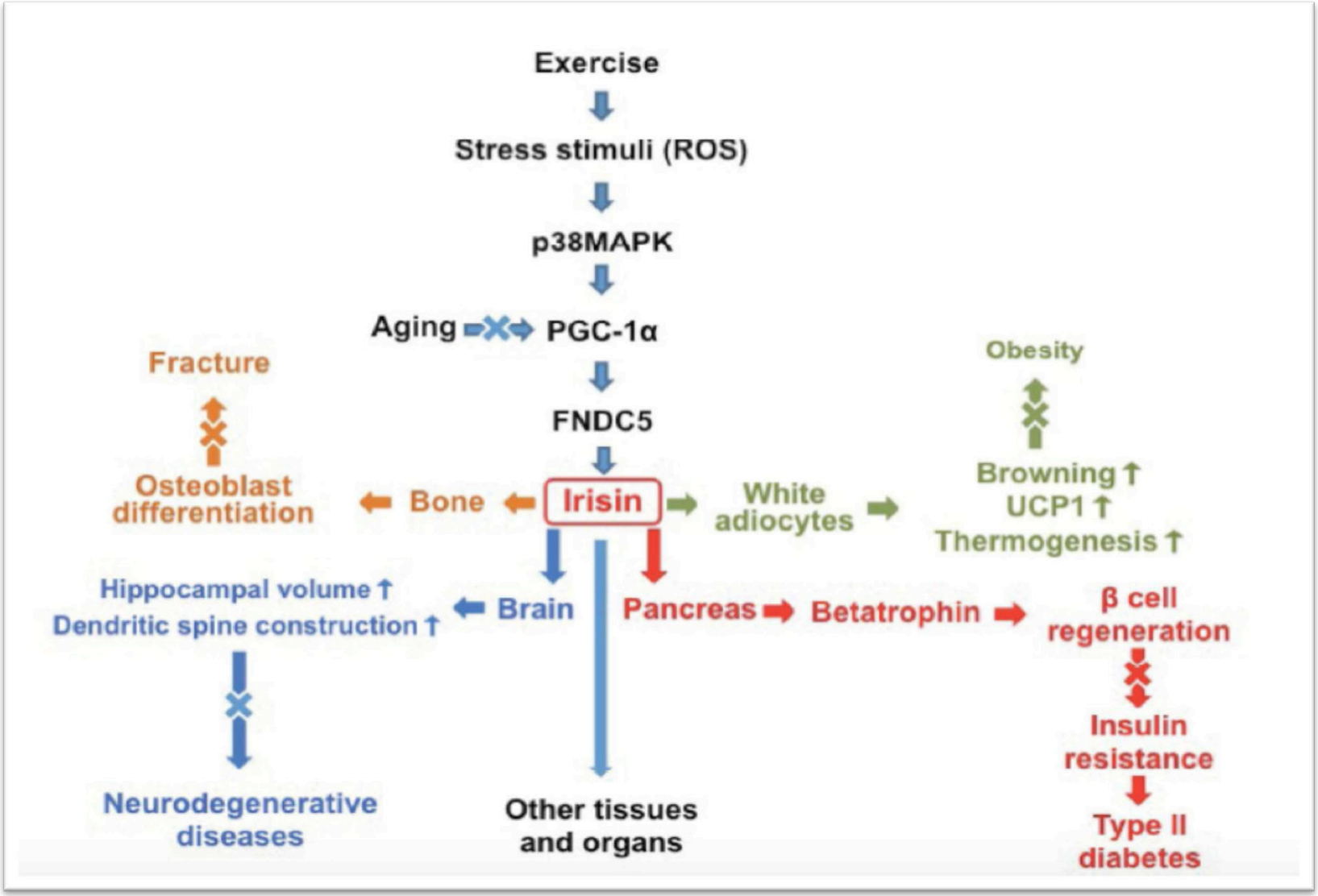
Results

RISULTATI



* Adjusted for: massa magra (p=0.02), BMD lombare (0.023), BMD femore totale (0.032).

IRISINA
ORMONE MULTI-TARGET



Ning Chen et al, DMRR 2015 *"in press"*

Clinical Endocrinology (2013) 78, 489–496 doi: 10.1111/cen.12095

REVIEW ARTICLE

Fibroblast Growth Factor 21 as an emerging metabolic regulator: clinical perspectives

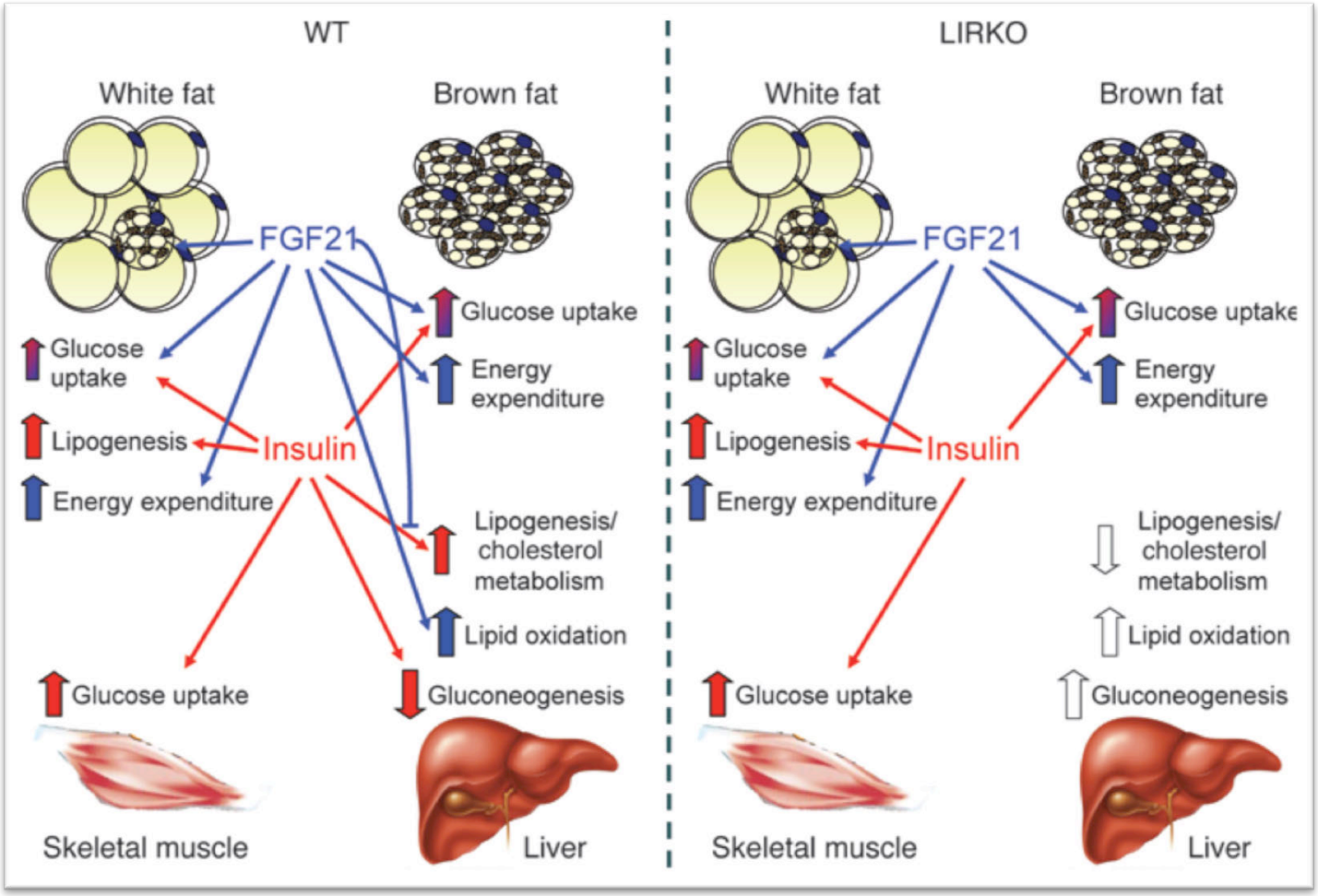
Y. C. Woo*, Aimin Xu*,†,‡, Yu Wang†,‡ and Karen S. L. Lam*,‡

Summary

Fibroblast growth factor 21 (FGF21), a metabolic hormone predominantly produced by the liver, is also expressed in adipocytes and the pancreas. It regulates glucose and lipid metabolism through pleiotropic actions in these tissues and the brain. In mice, fasting leads to increased PPAR-α mediated expression of FGF21 in the liver where it stimulates gluconeogenesis, fatty acid oxidation, and ketogenesis, as an adaptive response to fasting and starvation. In the fed state, FGF21 acts as an autocrine factor in adipocytes, regulating the activity of PPAR-γ through a feed-forward loop mechanism. Administration of recombinant FGF21

J Clin Invest. 2014;124(2):515–527. Research article

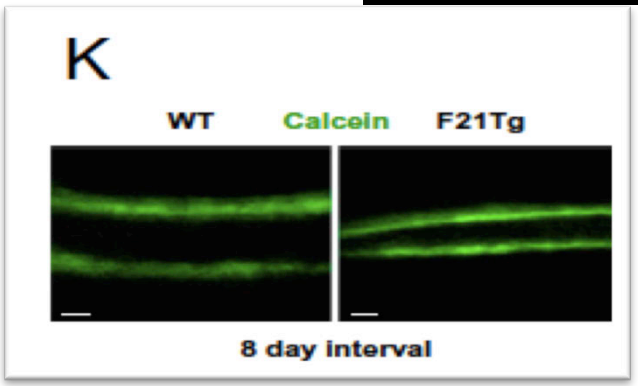
Interplay between FGF21 and insulin action in the liver regulates metabolism

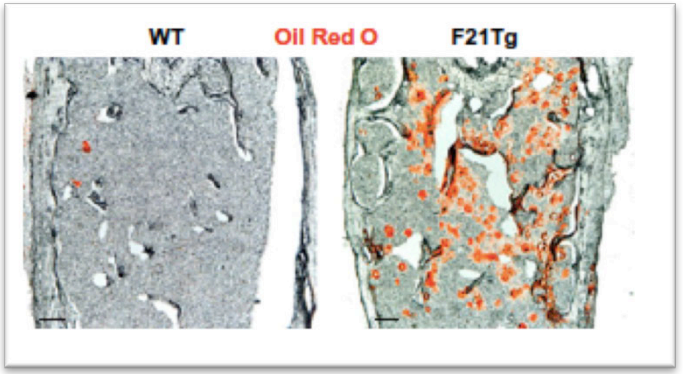


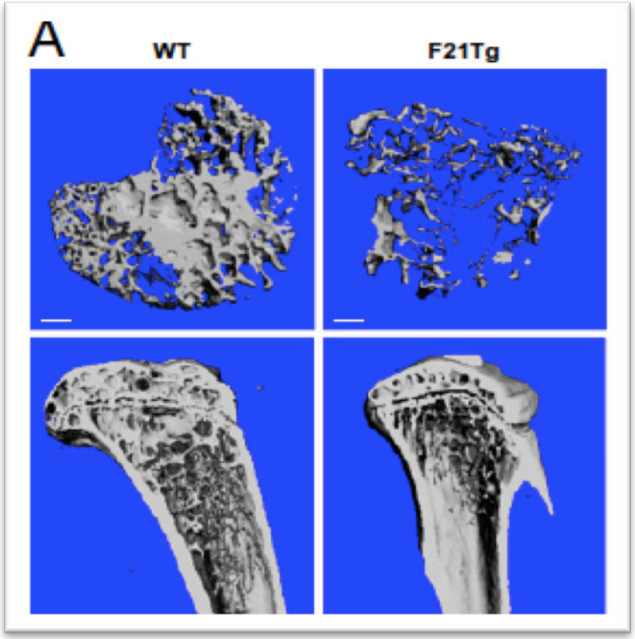
Fibroblast growth factor 21 promotes bone loss by potentiating the effects of peroxisome proliferator-activated receptor γ

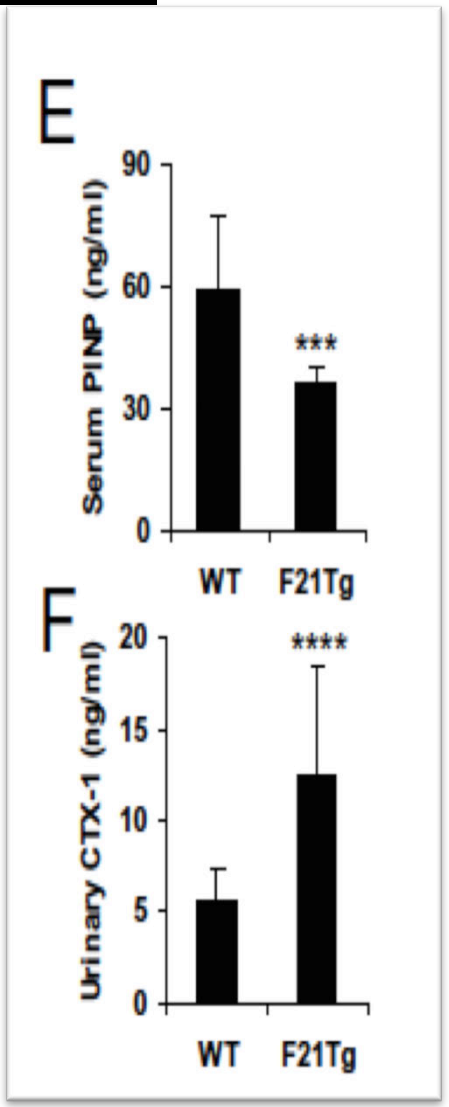
FGF 21 Tg

Wei Wei[a], Paul A. Dutchak[a,b], Xunde Wang[a], Xunshan Ding[a,b], Xueqian Wang[a], Angie L. Bookout[a,c,d], Regina Goetz[e], Moosa Mohammadi[e], Robert D. Gerard[b,d], Paul C. Dechow[f], David J. Mangelsdorf[a,g,1], Steven A. Kliewer[a,b], and Yihong Wan[a,1]



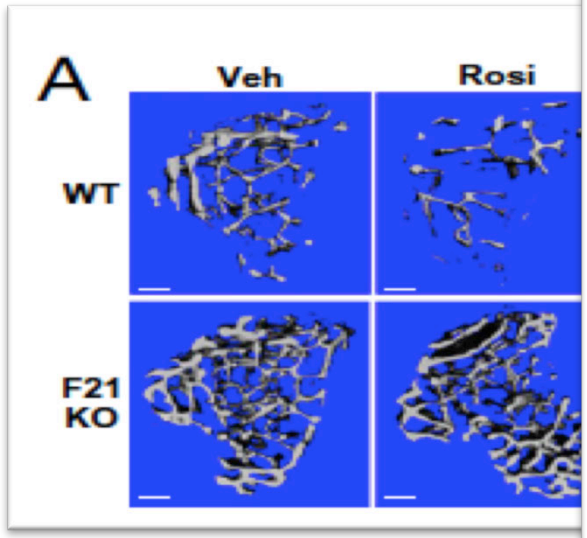


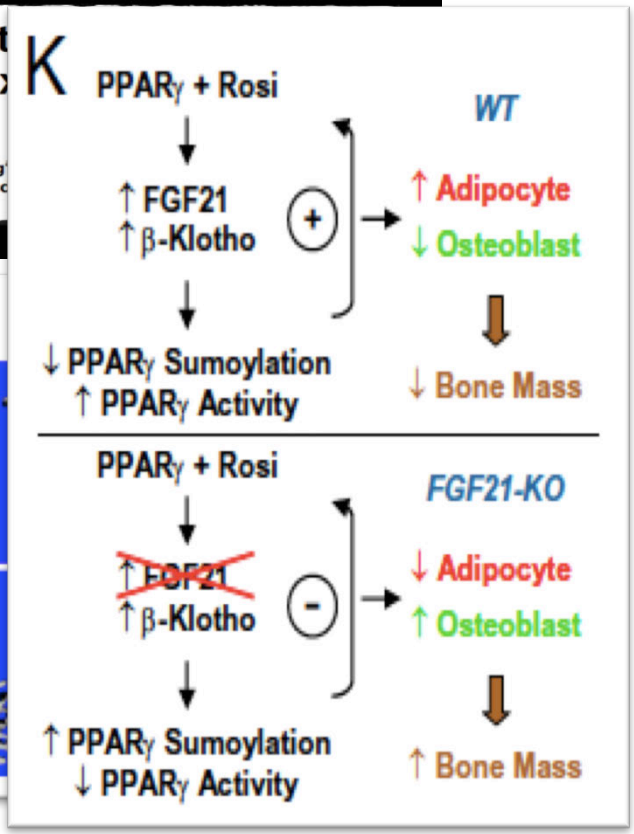


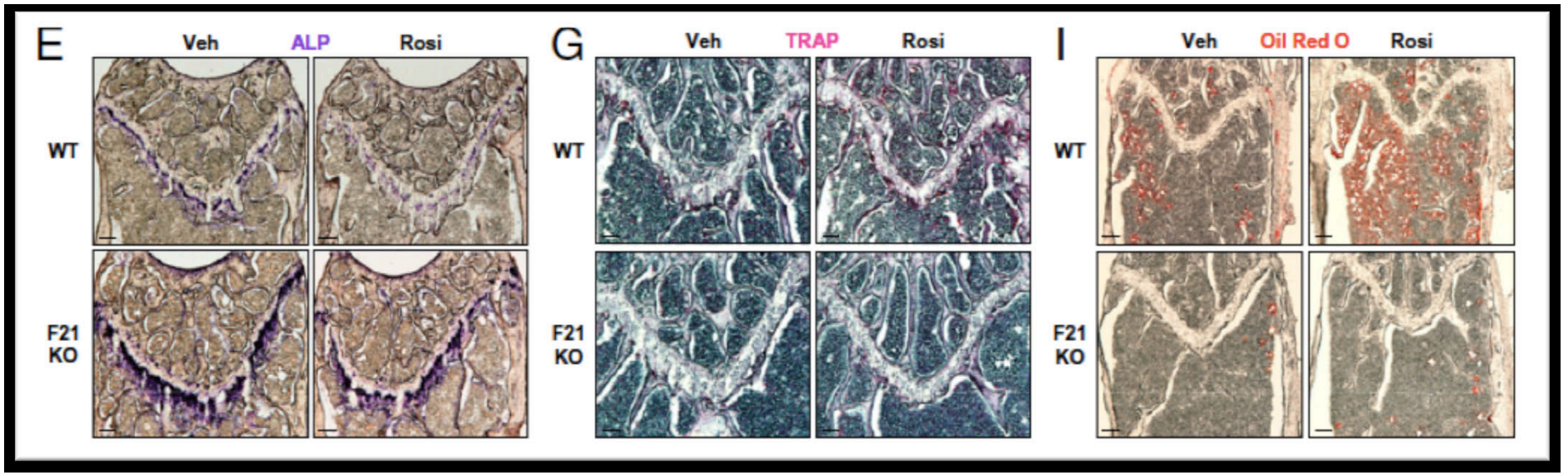


Fibroblast growth factor 21 promot
by potentiating the effects of perox
proliferator-activated receptor γ

Wei Wei[a], Paul A. Dutchak[a,b], Xunde Wang[a], Xunshan Ding[a,b], Xueqian Wang
Moosa Mohammadi[e], Robert D. Gerard[b,d], Paul C. Dechow[f], David J. Mangelsc
and Yihong Wan[a,1]

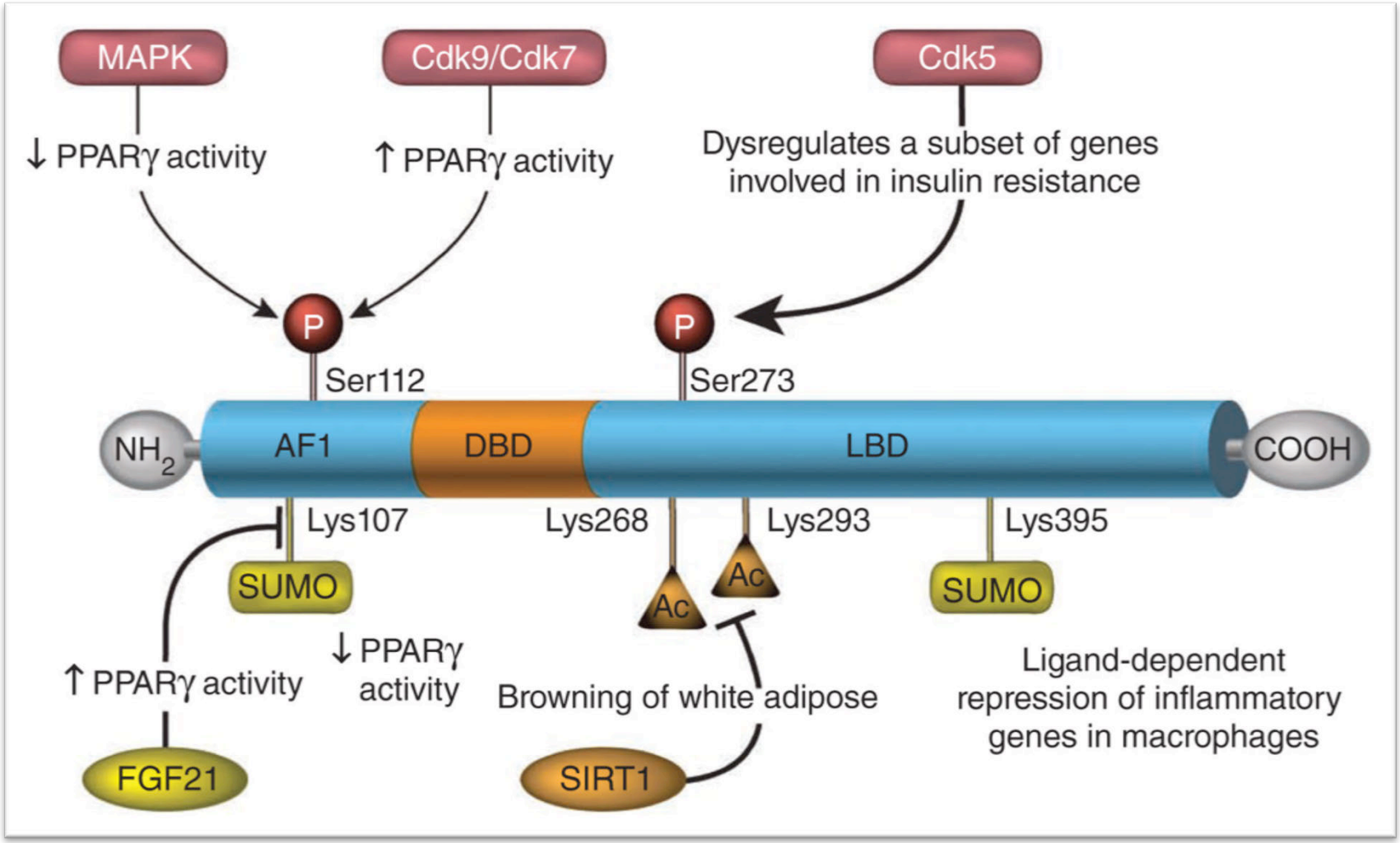






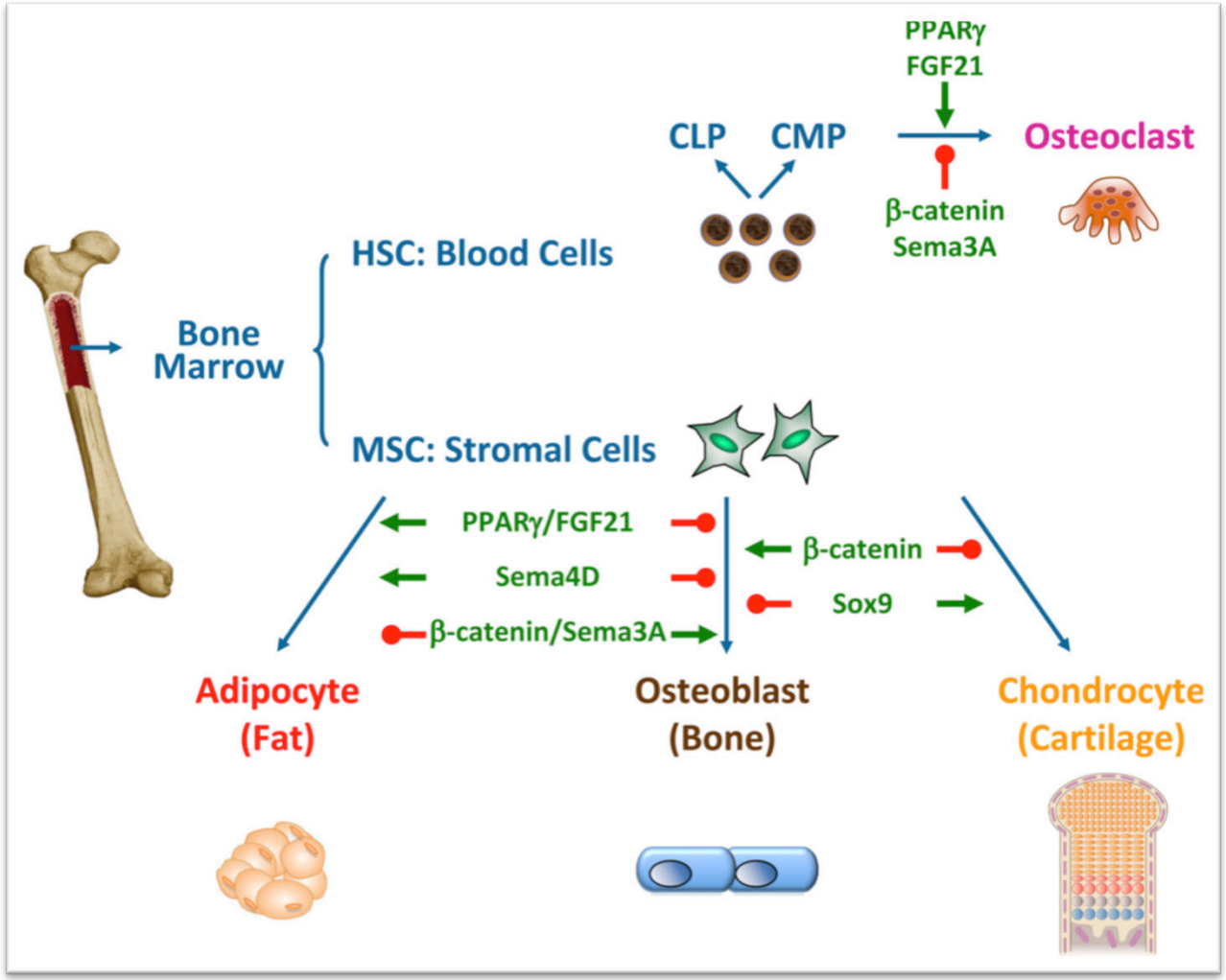
Published in final edited form as:
Nat Med. 2013 May ; 19(5): . doi:10.1038/nm.3159.

PPARγ signaling and metabolism: the good, the bad and the future



Published in final edited form as:
Int J Biochem Cell Biol. 2013 March ; 45(3): 546–549. doi:10.1016/j.biocel.2012.12.014.

Bone Marrow Mesenchymal Stem Cells: Fat On and Blast Off by FGF21



Archives of Biochemistry and Biophysics 561 (2014) 64–73

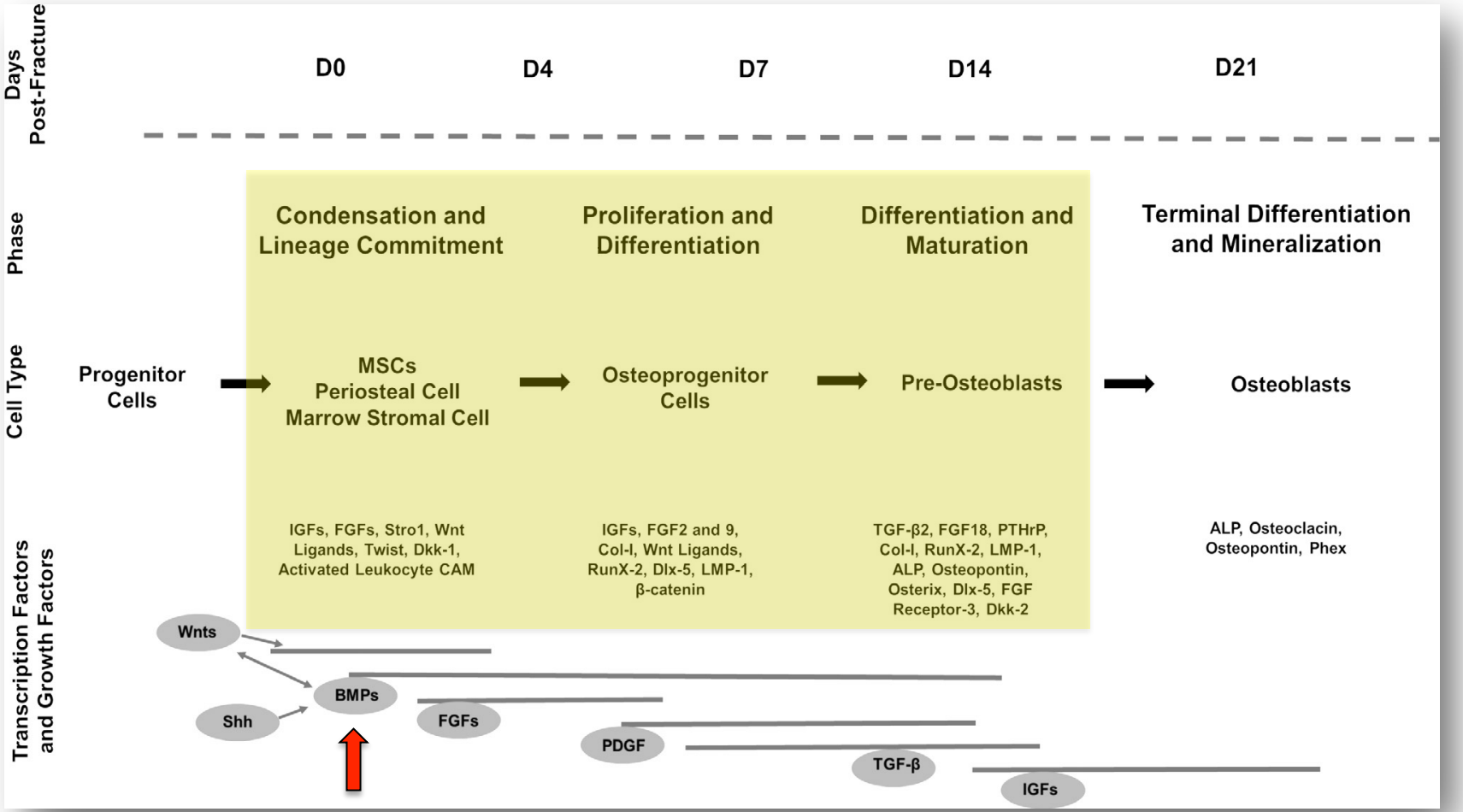
Contents lists available at ScienceDirect

Archives of Biochemistry and Biophysics

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

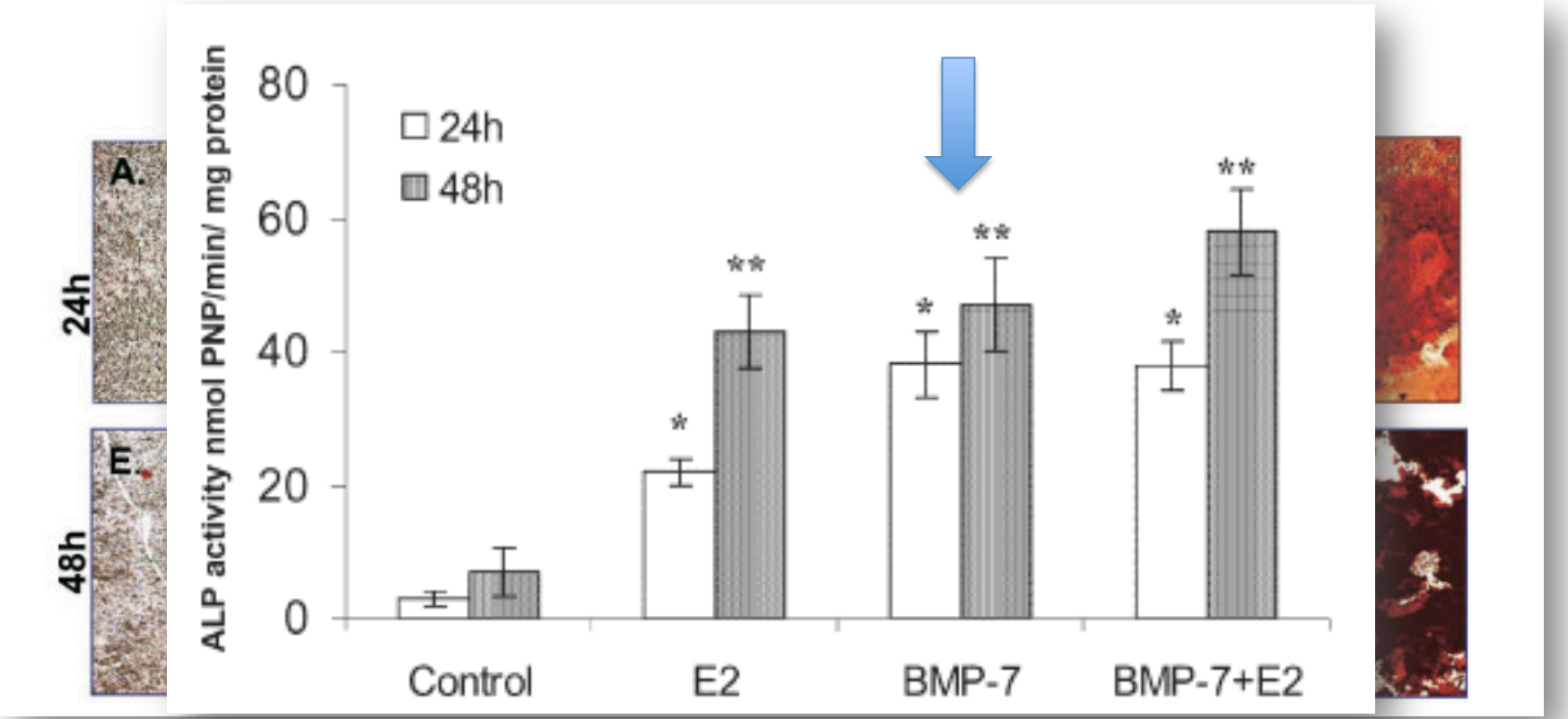
Review

Bone Morphogenetic Proteins: Structure, biological function and therapeutic applications



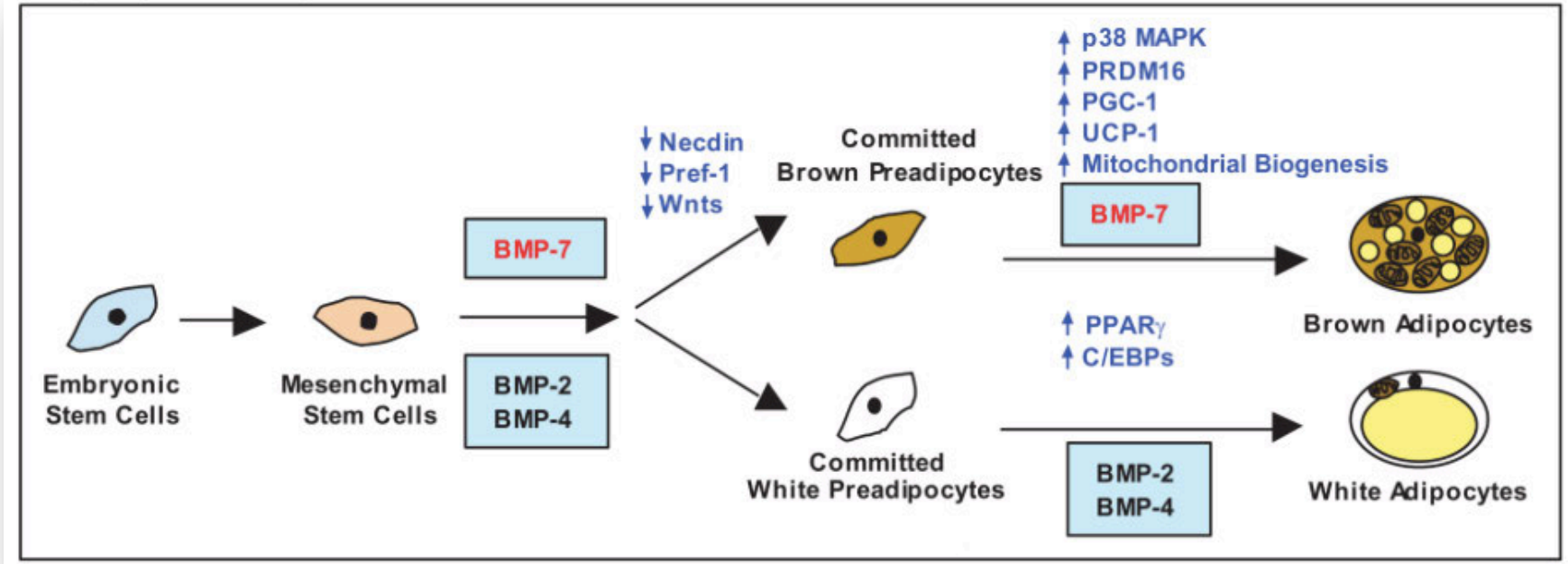
Tohoku J. Exp. Med., 2010, **221**, 61-68

BMP-7 in Combination with Estrogen Enhances Bone Formation in a Fracture Callus Explant Culture



Published in final edited form as:
Nature. 2008 August 21; 454(7207): 1000–1004. doi:10.1038/nature07221.

New role of bone morphogenetic protein 7 in brown adipogenesis



Cytokine & Growth Factor Reviews 22 (2011) 221–229

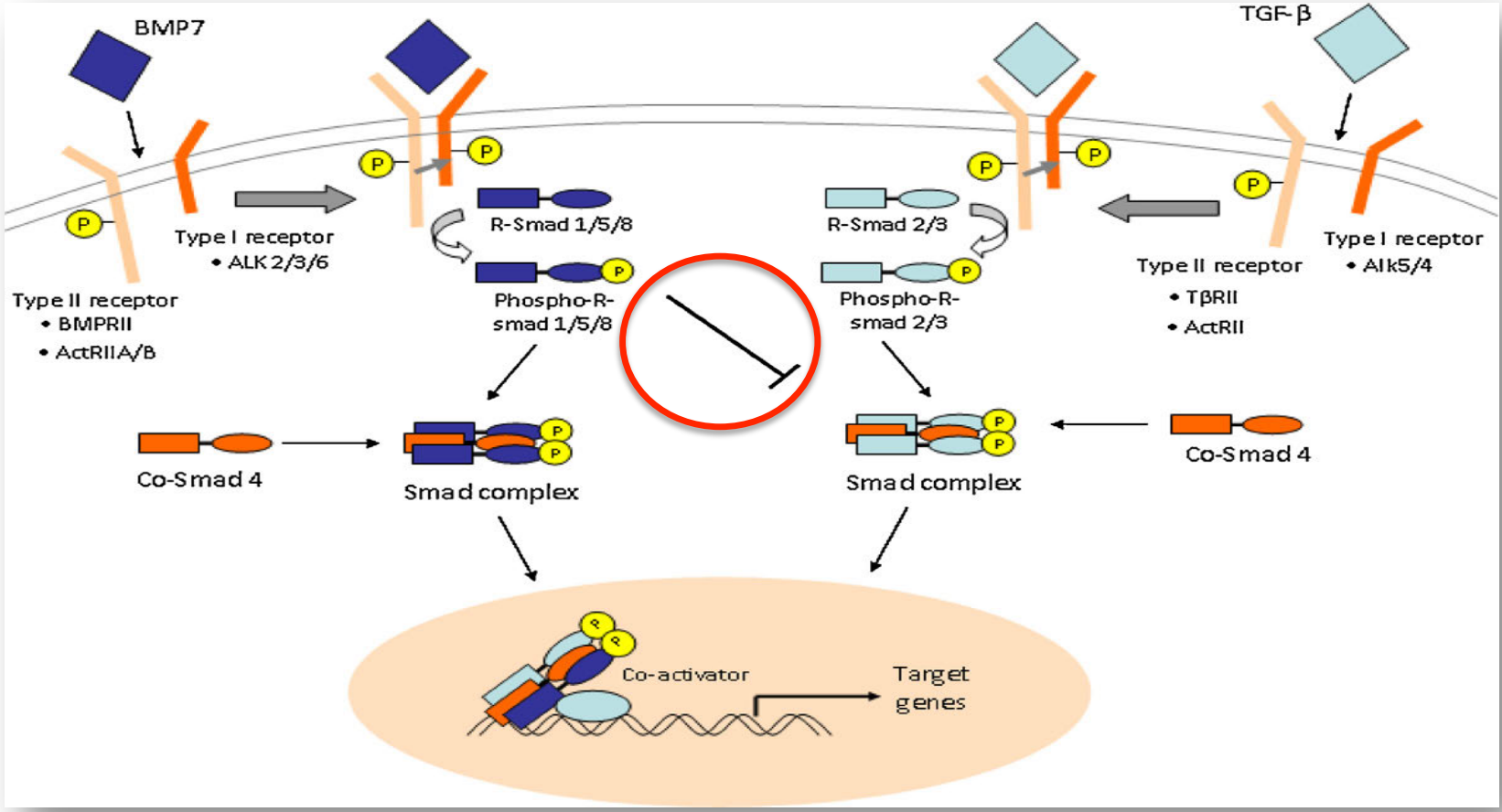
Contents lists available at SciVerse ScienceDirect

Cytokine & Growth Factor Reviews

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

Survey

Bone morphogenetic protein 7: A broad-spectrum growth factor with multiple target therapeutic potency

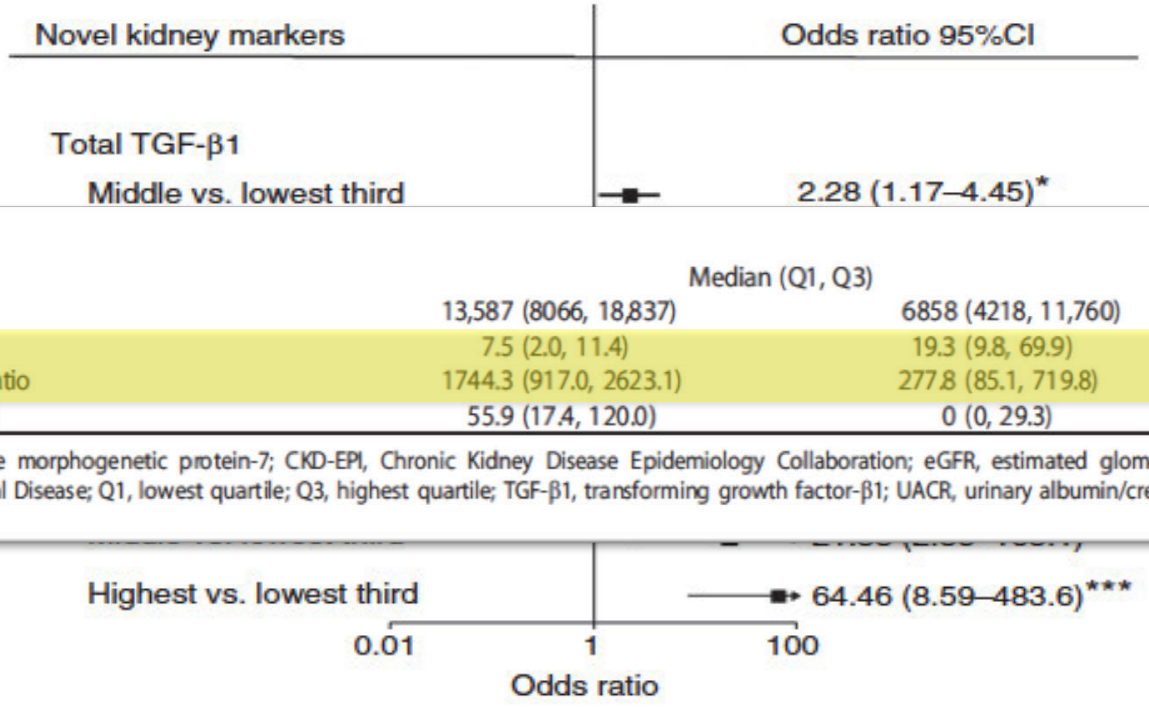


clinical investigation http://www.kidney-international.org

see commentary on page 189

Circulating bone morphogenetic protein-7 and transforming growth factor-β1 are better predictors of renal end points in patients with type 2 diabetes mellitus

Kidney International (2013) **83**, 278–284



C. *Novel kidney markers*

	Median (Q1, Q3)		
Total TGF-β1 (pg/ml)	13,587 (8066, 18,837)	6858 (4218, 11,760)	<0.0001
BMP-7 (pg/ml)	7.5 (2.0, 11.4)	19.3 (9.8, 69.9)	<0.0001
Total TGF-β1/BMP-7 ratio	1744.3 (917.0, 2623.1)	277.8 (85.1, 719.8)	<0.0001
Active TGF-β1 (pg/ml)	55.9 (17.4, 120.0)	0 (0, 29.3)	<0.0001

Abbreviations: BMP-7, bone morphogenetic protein-7; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; Q1, lowest quartile; Q3, highest quartile; TGF-β1, transforming growth factor-β1; UACR, urinary albumin/creatinine ratio.

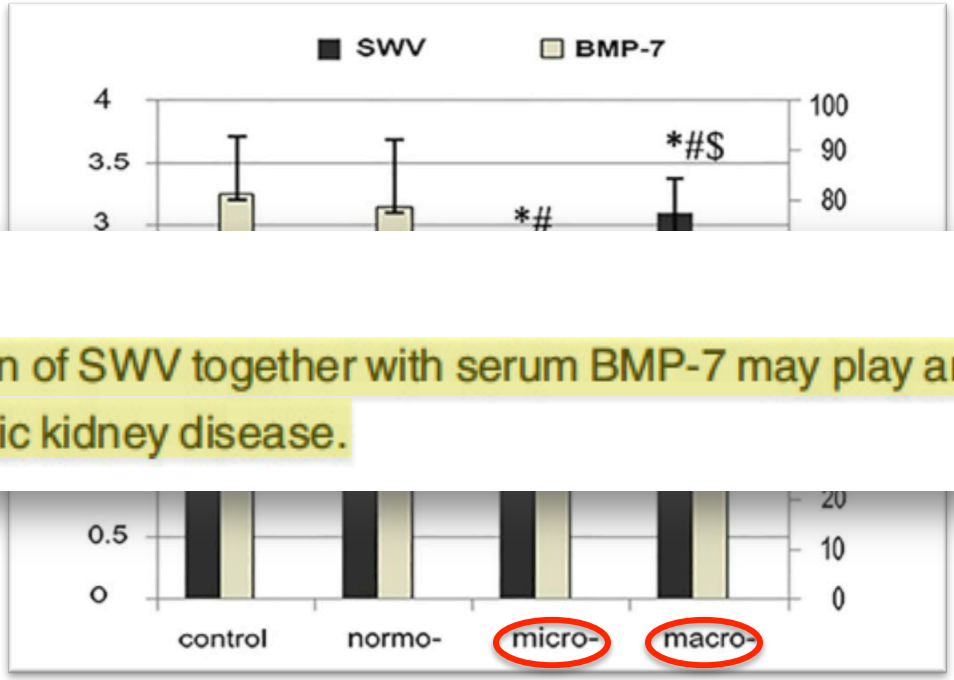
Figure 1 | Association of kidney markers with major renal end points in patients with type 2 diabetes mellitus. The lowest,

PLOS | ONE

PLOS ONE | DOI:10.1371/journal.pone.0119713 March 19, 2015

RESEARCH ARTICLE

Evaluation of Shear Wave Velocity and Human Bone Morphogenetic Protein-7 for the Diagnosis of Diabetic Kidney Disease



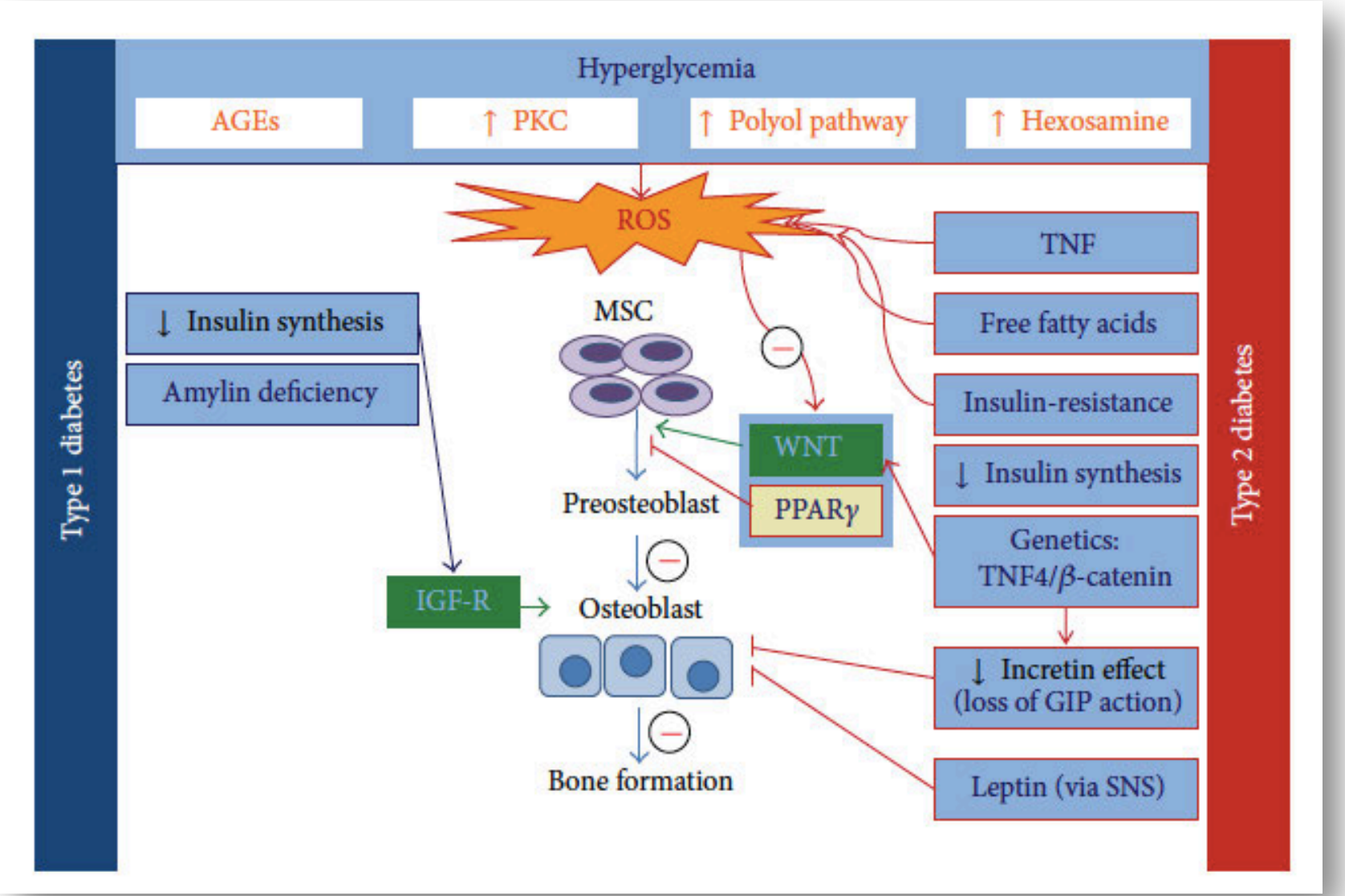
Conclusion

The determination of SWV together with serum BMP-7 may play an important role in the diagnosis of diabetic kidney disease.

Review Article

The Alliance of Mesenchymal Stem Cells, Bone, and Diabetes

International Journal of Endocrinology
Volume 2014, Article ID 690783, 26 pages



Il Vento del cambiamento

“Quando soffia il vento del cambiamento alcuni alzano pareti, altri costruiscono mulini a vento”

Anonimo

Grazie per l’attenzione