



Disclosure

Julio C. Bai will present research findings from his own group as well as those of other researchers. Nothing to disclosure.



2022 ICDS. Clinical Presentation and Associated Conditions.

Sorrento , October 29, 2022



ICDS2022SORRENTO

19th INTERNATIONAL CELIAC DISEASE SYMPOSIUM

Celiac disease and bone health

Julio C. Bai, MD

Consultant

“Dr. C. Bonorino Udaondo” Gastroenterology Hospital

Professor Emeritus
Research Institute
Universidad del Salvador

Buenos Aires. Argentina



Goals

- Historical perspective.
 - Bone densitometry. DEXA.
 - Pathogenesis of osteoporosis.
 - Clinical consequences. Fracture risk.
 - Pathogenesis of fractures.
 - Therapeutics.
 - Take home messages.
-

Historical perspective of bone health in CeD

- Osteoporosis, osteomalasia, rickets

bone osteoporotic fractures, skeletal deformities, etc.



Holms W, JAMA 1929; Bennett et al., QJM 1932; Salvesen et al. AMSc 1953

- Bone density in CeD (DEXA). Seminal studies.

*Caraceni et al. AJG 1988 ; Molteni, et al. AJG 1990;
Bodé, et al. Gut 1991; Mora et al. AJCN 1993;*

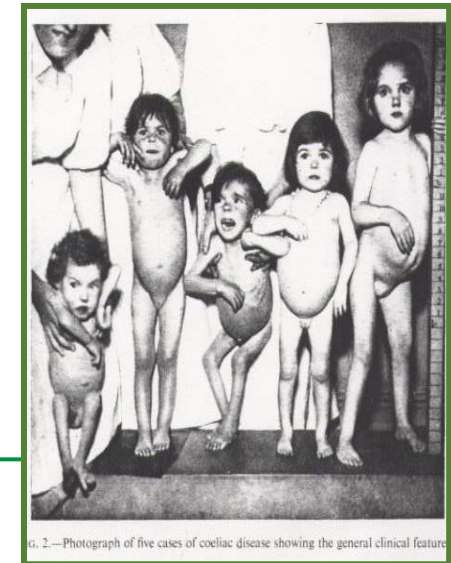
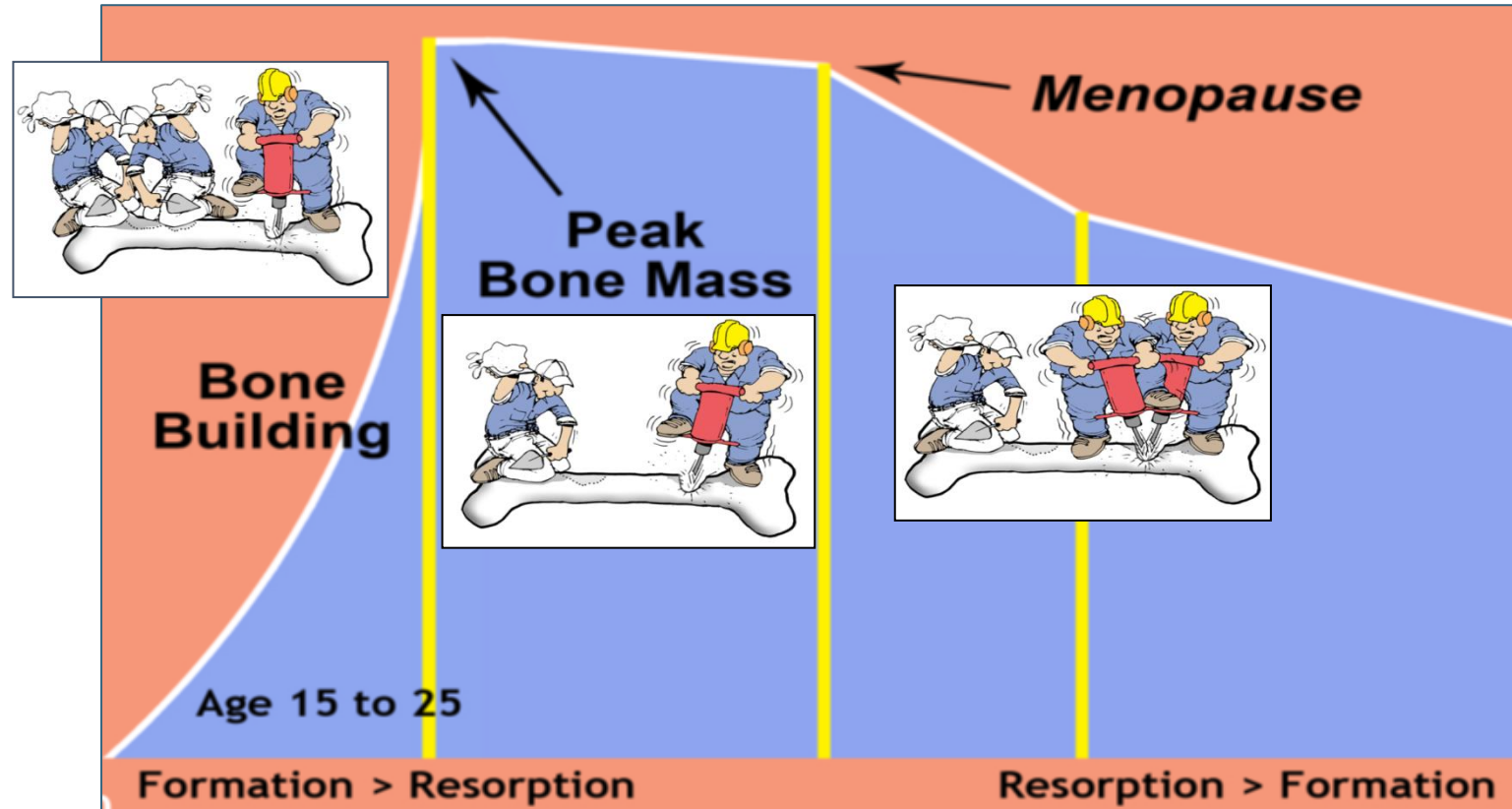


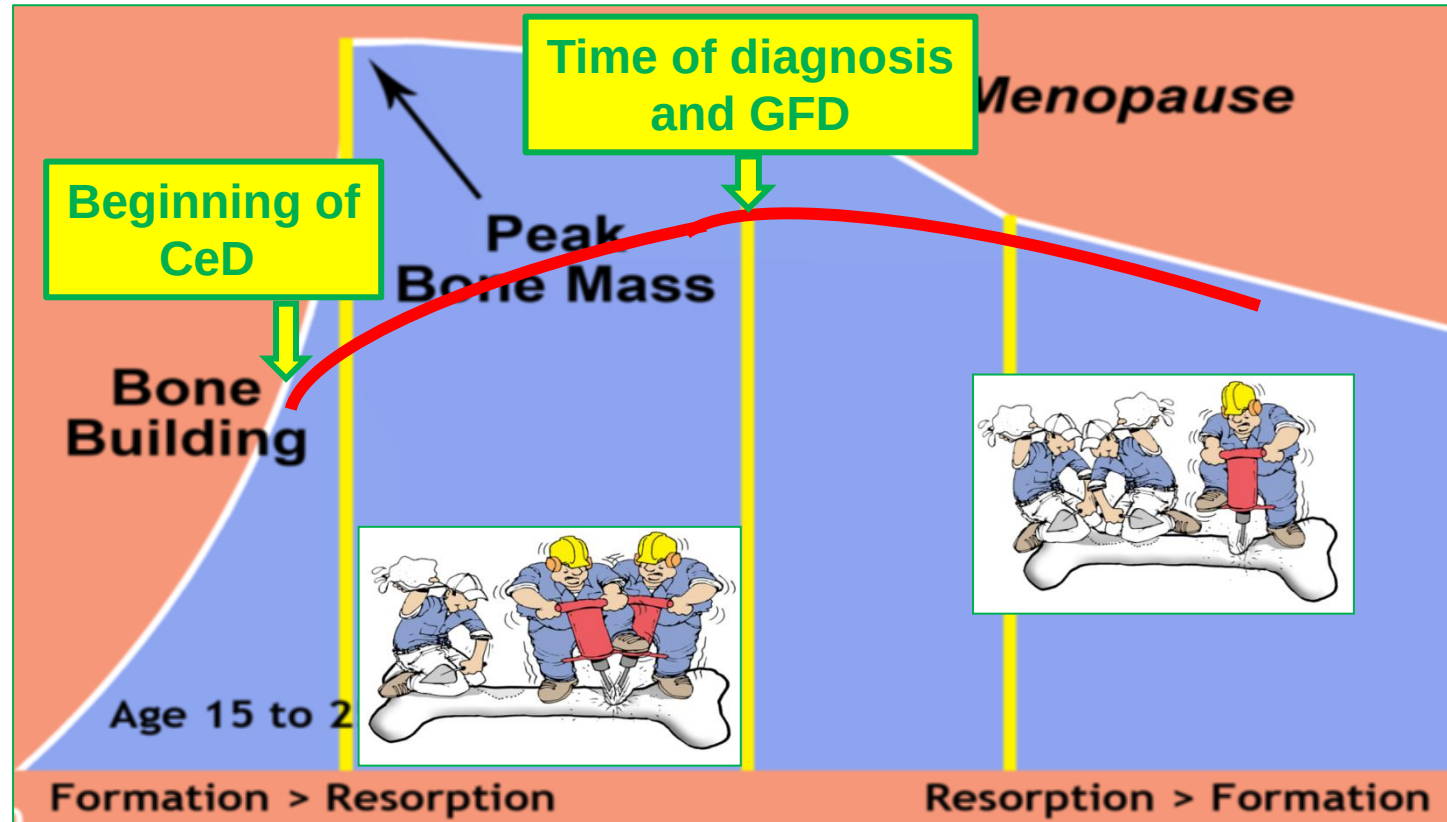
Fig. 2.—Photograph of five cases of coeliac disease showing the general clinical feature



Natural history of bone health. DEXA



Natural history of bone health. Effect of CeD.



For bone metabolism and the chance of achieving normal BMD, the interval between the CeD diagnosis and the start of a GFD is crucial (peak bone mass).



Goals

- Historical perspective.
 - **Bone densitometry. DEXA.**
 - **Pathogenesis of osteoporosis.**
 - Clinical consequences. Fracture risk.
 - Pathogenesis of fractures.
 - Therapeutics.
 - Take home messages.
-



Bone density by DEXA. Osteopenia y osteoporosis at time of diagnosis.

DEXA



BMD is measured by DEXA as:
Mineral concentration (g/cm²)
T-score; Z-score

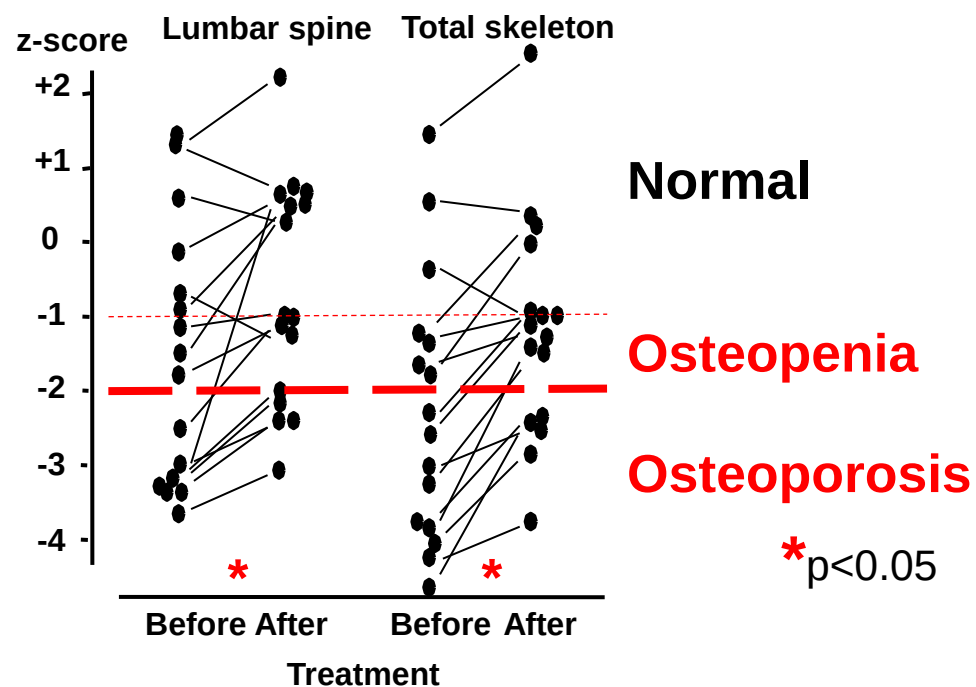
	Osteopenia	Osteoporosis
	%	%
Untreated CD	40 - 50	1.7 - 45
Treated CD	30 - 50	20 - 30
Asymptomatic CD	30	25

Caraceni, et al, AJG 1998; Molteni, et al. AJG 1990; Bodé, et al. Gut 1991; Mora et al. AJCN 1993; Mazure et al. AJG 1994; Gonzalez, et al. Bone 1995

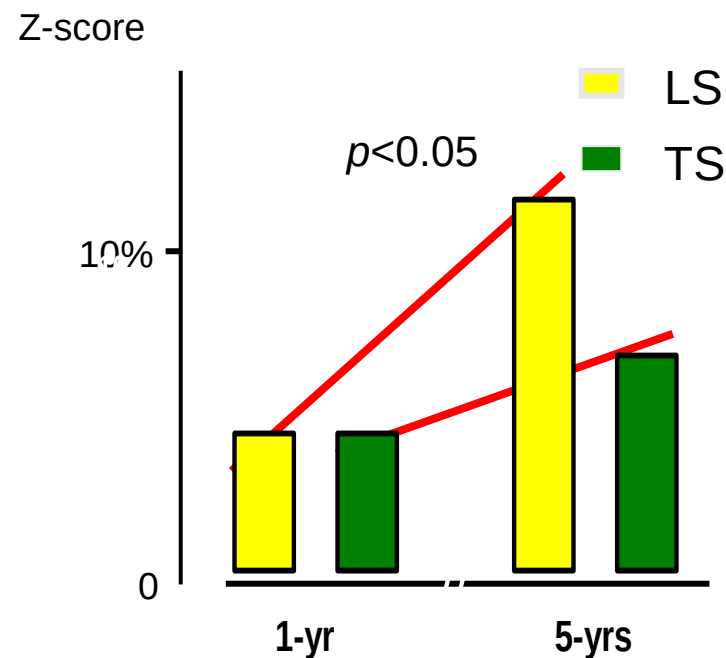


Baseline, and 1-yr and 5-yrs. DEXA in symptomatic CeD patients on a GFD.

Baseline and 1-year GFD



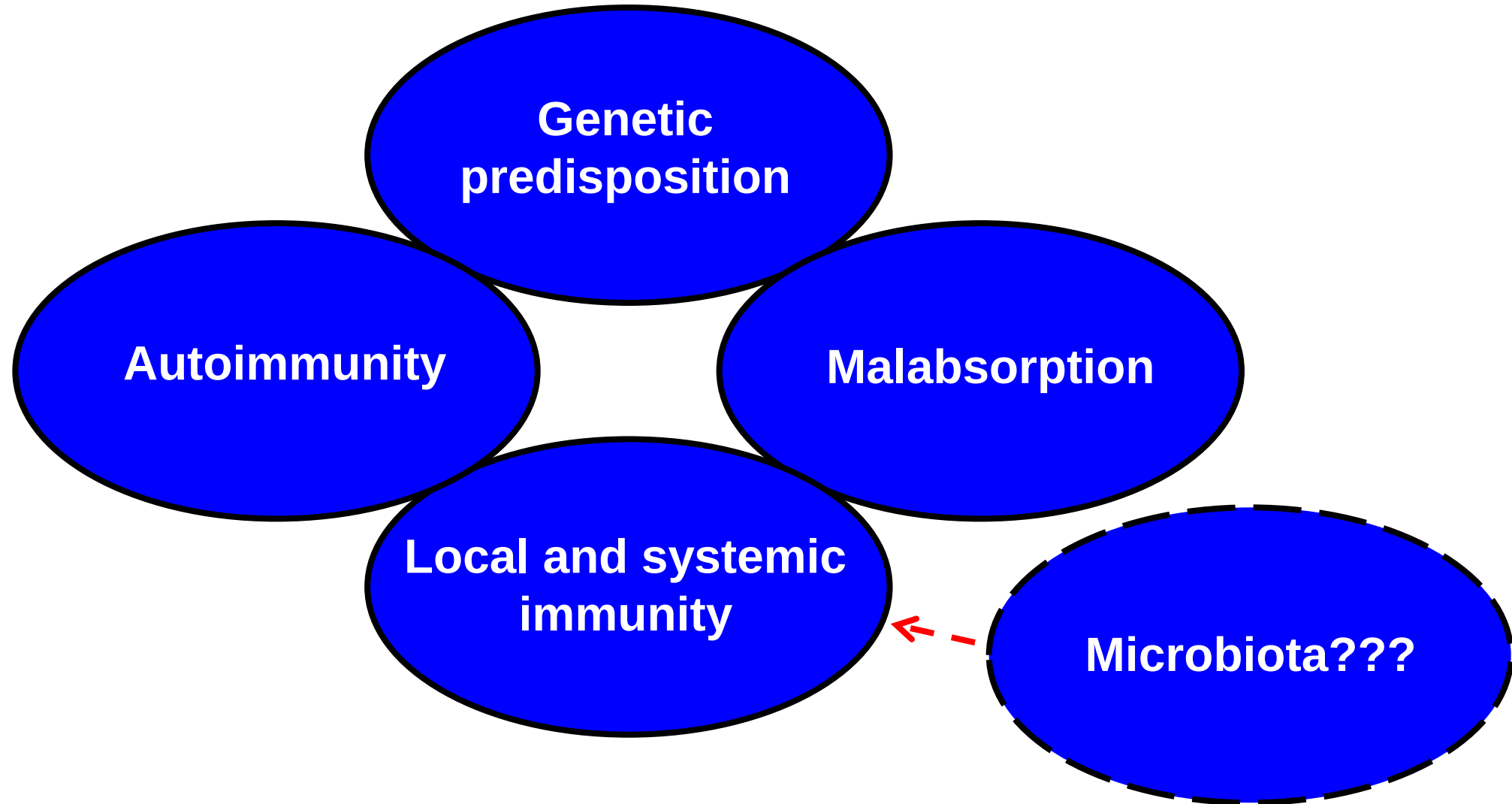
Long-term GFD



GFD for 1-year increases the BMD both at lumbar spine and total skeleton. The effect of treatment persists five years after diagnosis.

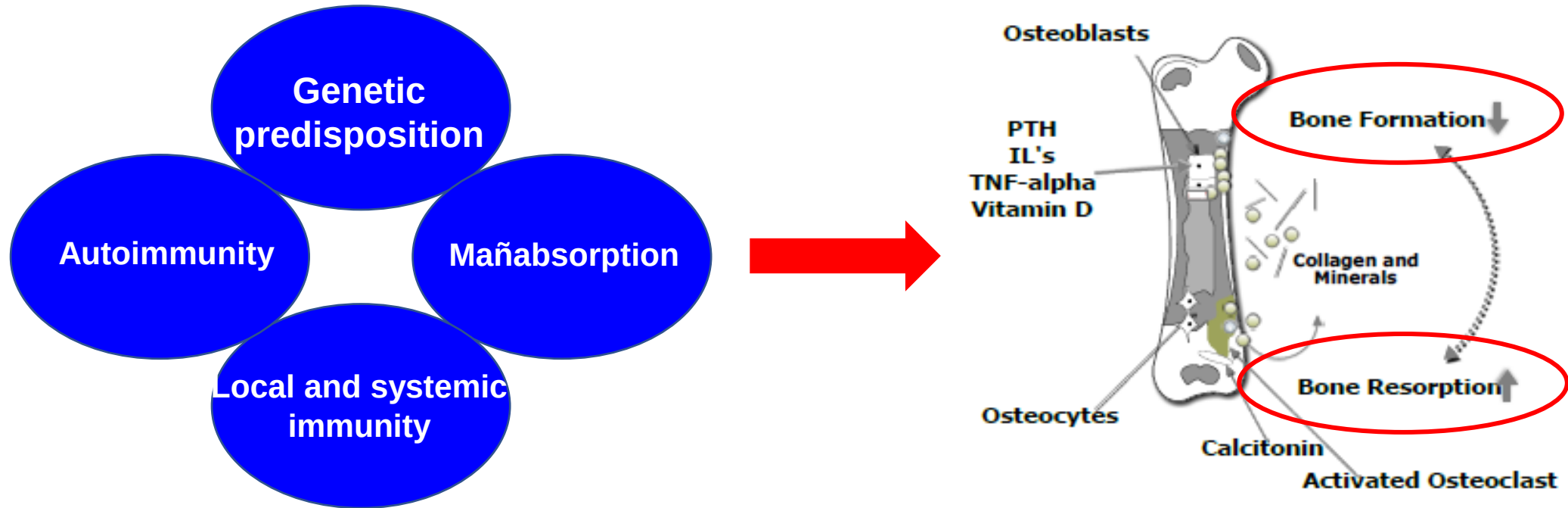


Pathogenesis of impaired bone strength. Multifactorial





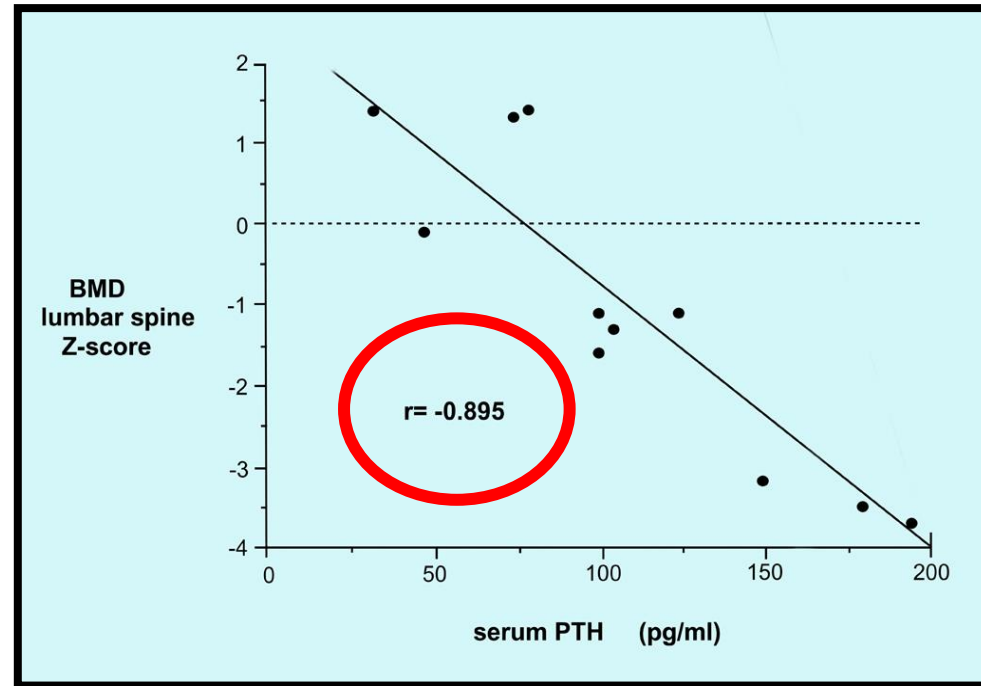
Interaction of factors increasing risk of fractures.



Imbalance between synthesis and resorption of bone material



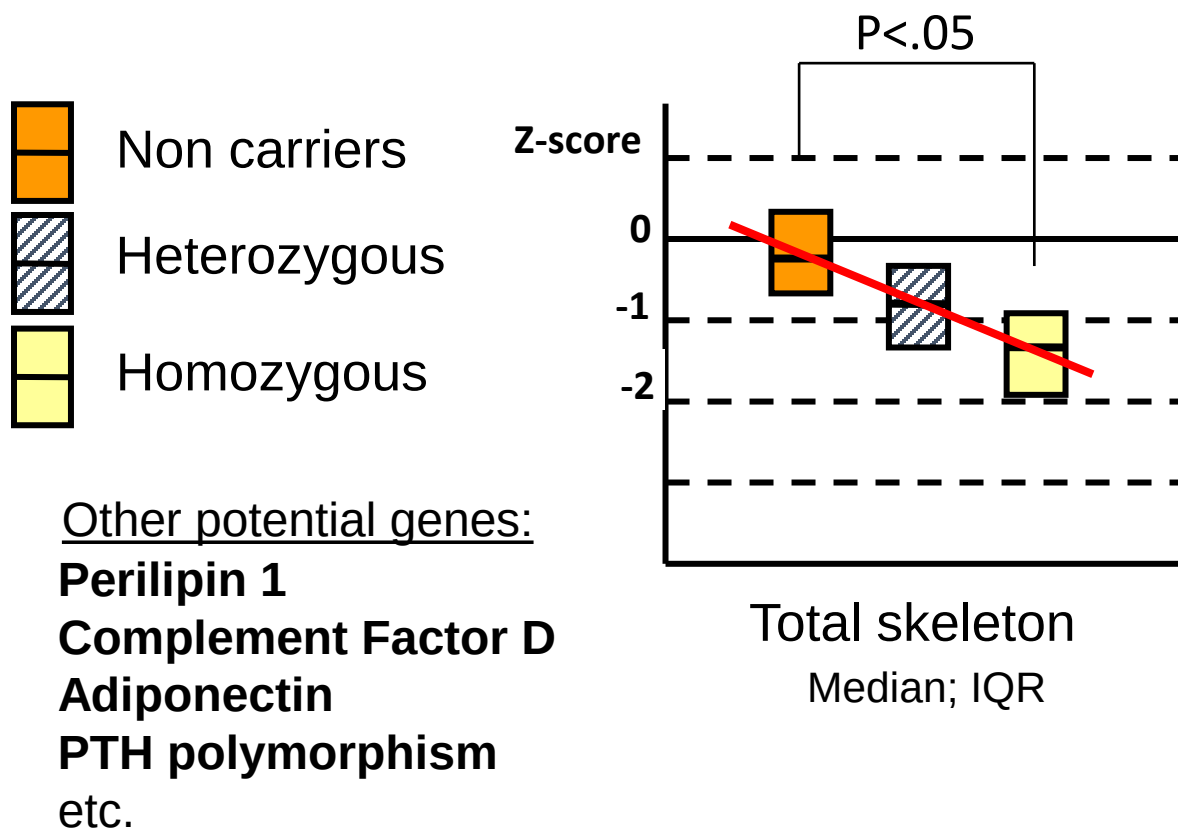
Malabsorption. Secondary hyperparathyroidism.



Calcium malabsorption.
Insufficient Vit. D.
Parathyroid dysfunction (?)

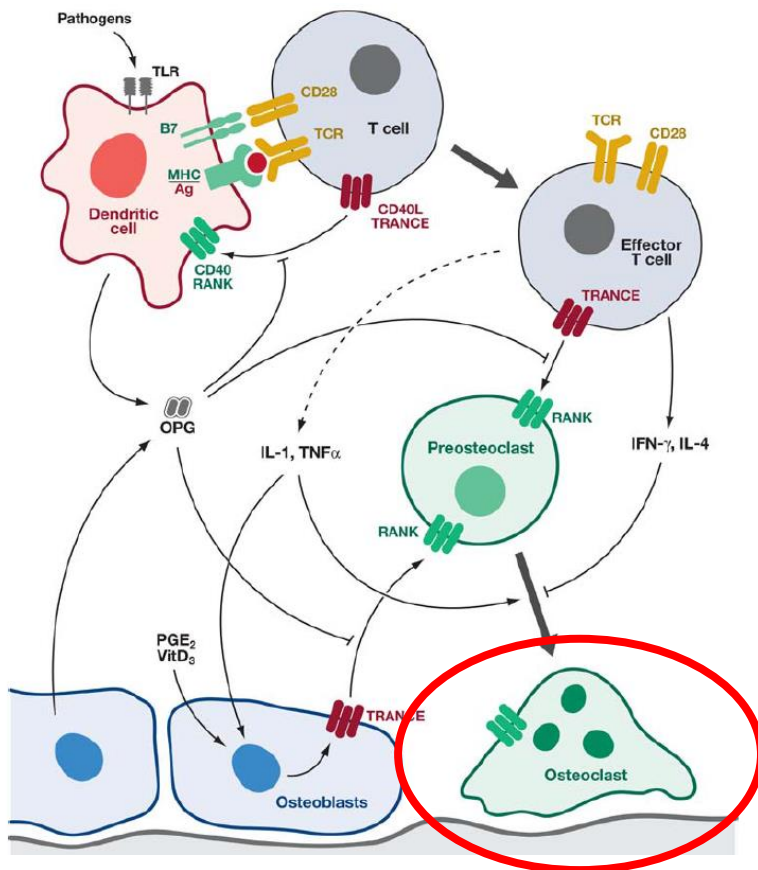


BMD z-score and genetics. The allele *IL1B*-511*2 variant.



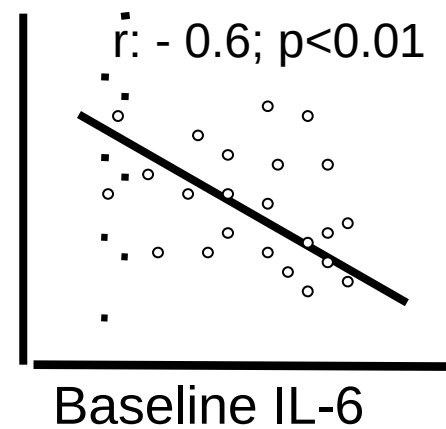


Local and systemic immunity.



IL-6

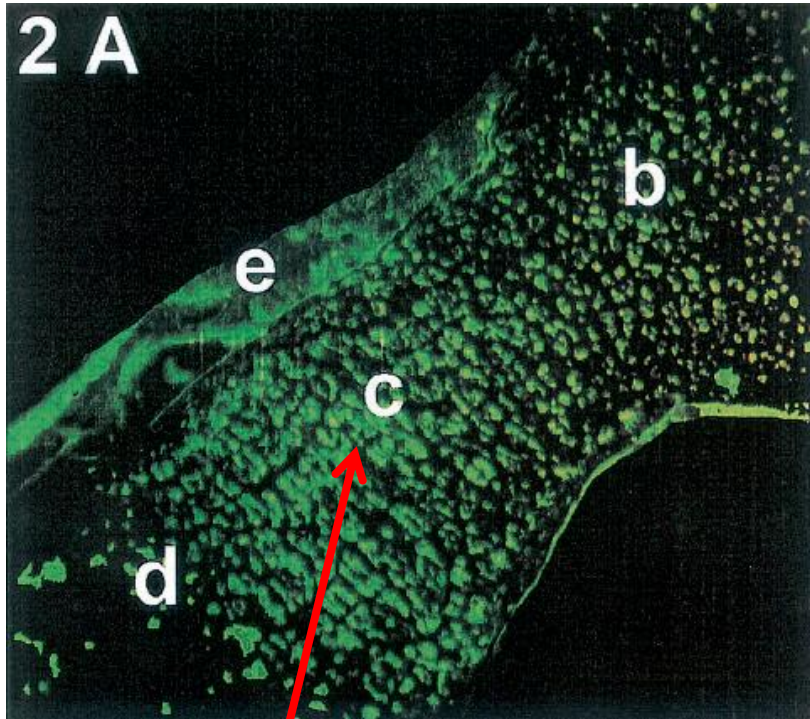
Baseline BMD



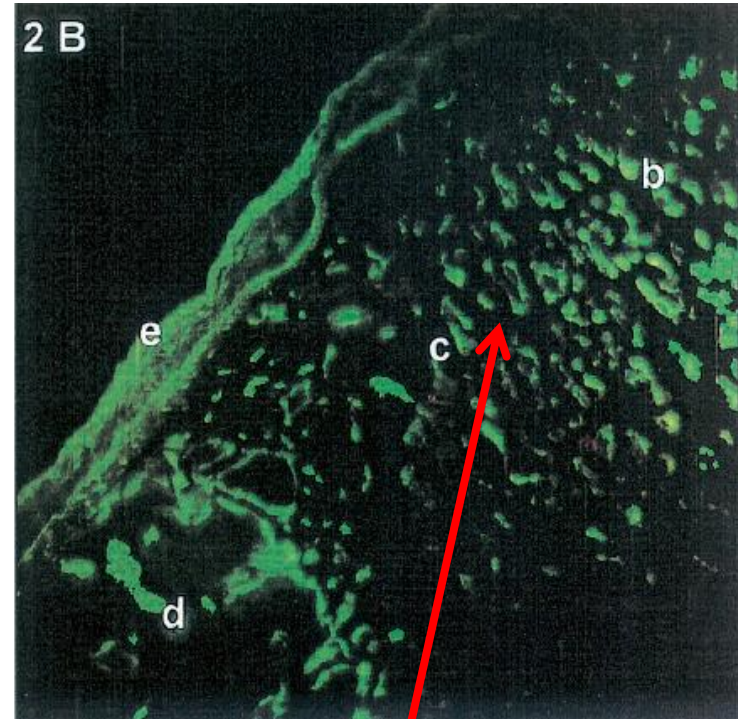
- Local and systemic immunity:
Imbalance between bone synthesis and catabolism.

Autoimmunity (anti-tTG) and BMD

Fetal rat tibia (IF & WB)



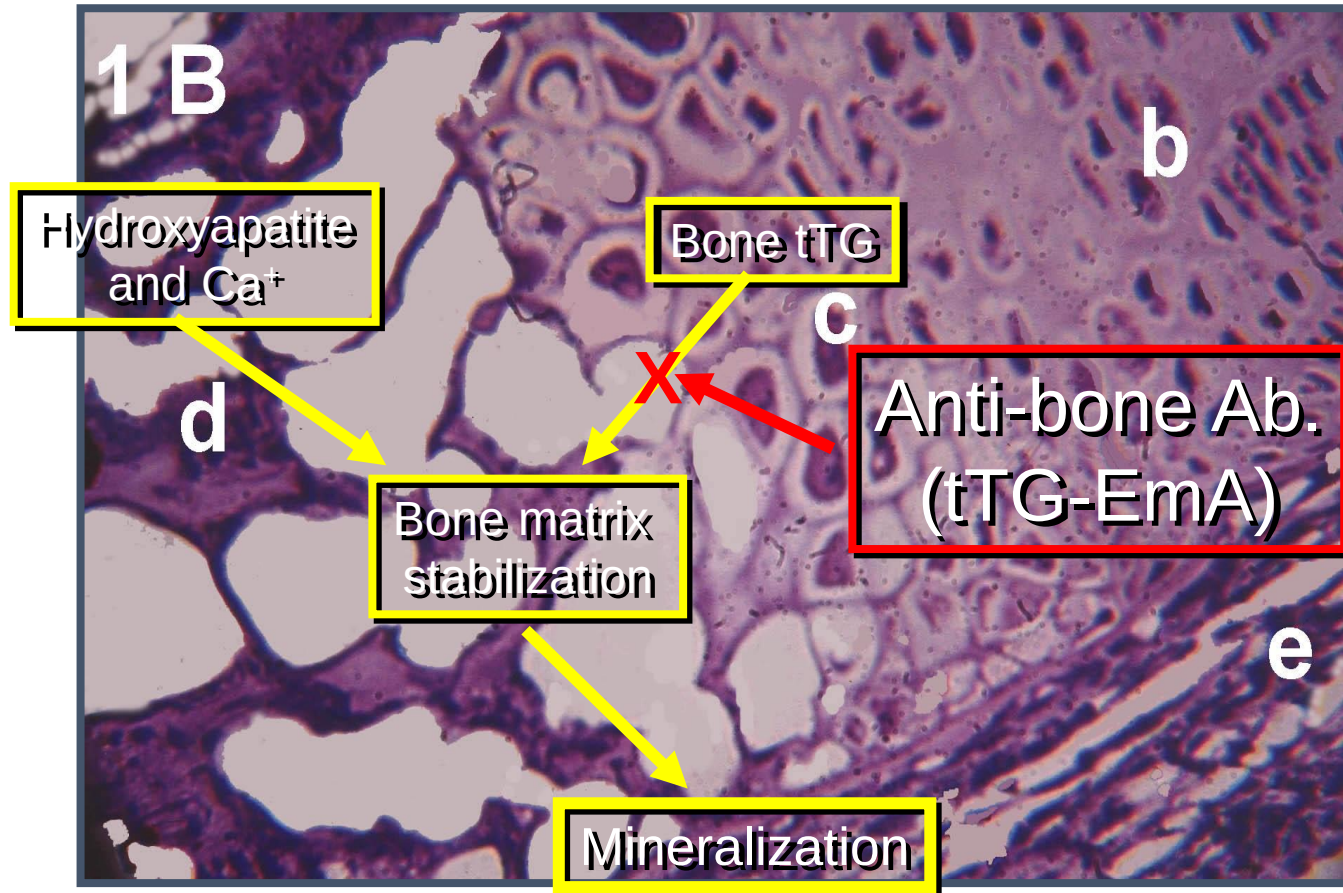
TG2 activity



TG2 + IgA anti-TG2
deposits



Role of CD-specific autoantibodies in impaired bone metabolism.

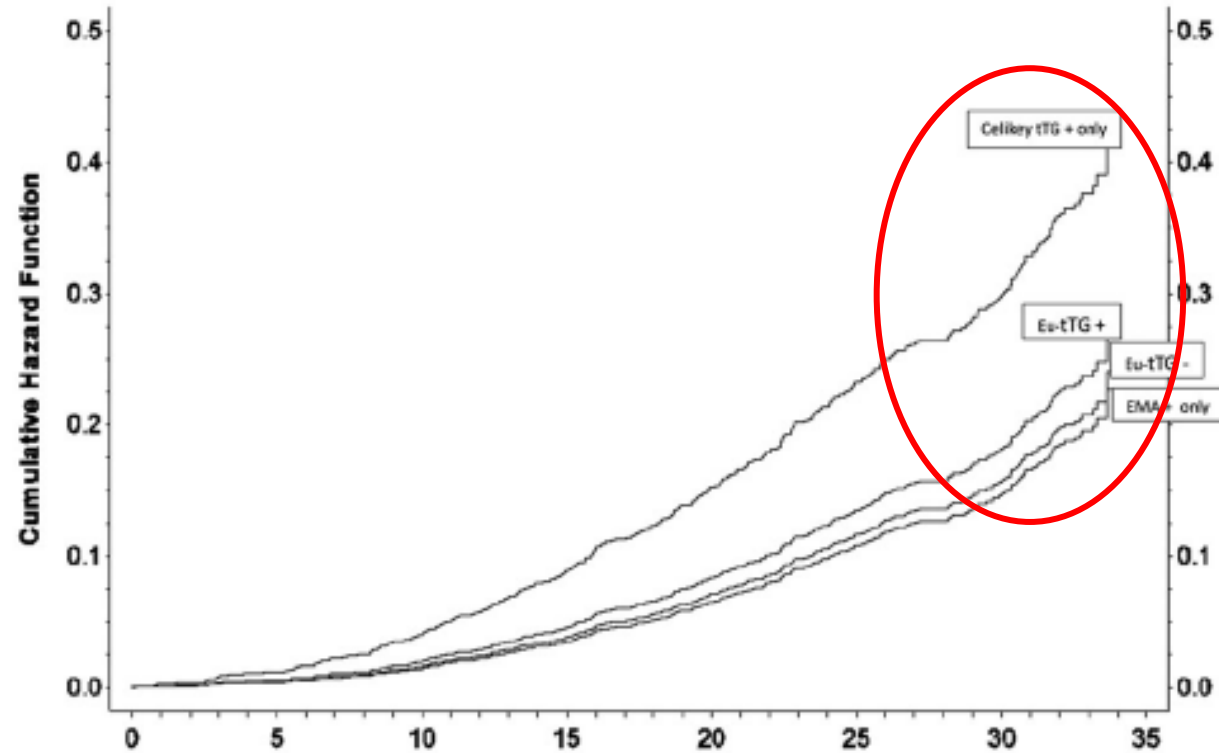


Bone TG2 causes stabilization of the bone matrix and allows for mineralization.

Circulating tTG antibodies may interfere with this pro-mineralization process, contributing to a low BMD.



Hip fracture and autoimmunity before diagnosis (tTG)

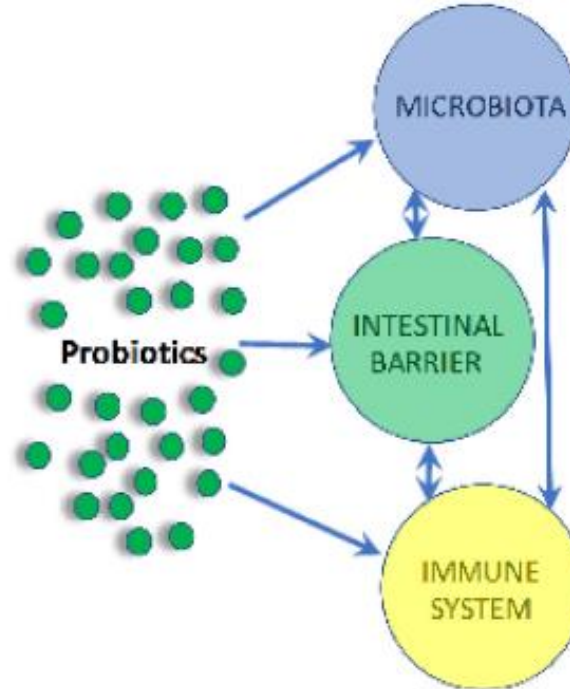


tTG +ve vs. tTG -ve: 1.6 – 2.2 folds higher risk

Higher serum tTG levels are associated with worse BMD impairment.



Does the microbiota have a role in osteoporosis pathogenesis?



Dysbiosis has been suggested to have a role in primary and secondary osteoporosis and in CeD. Clinical studies are necessary for supporting such a role and the potential use of probiotics.



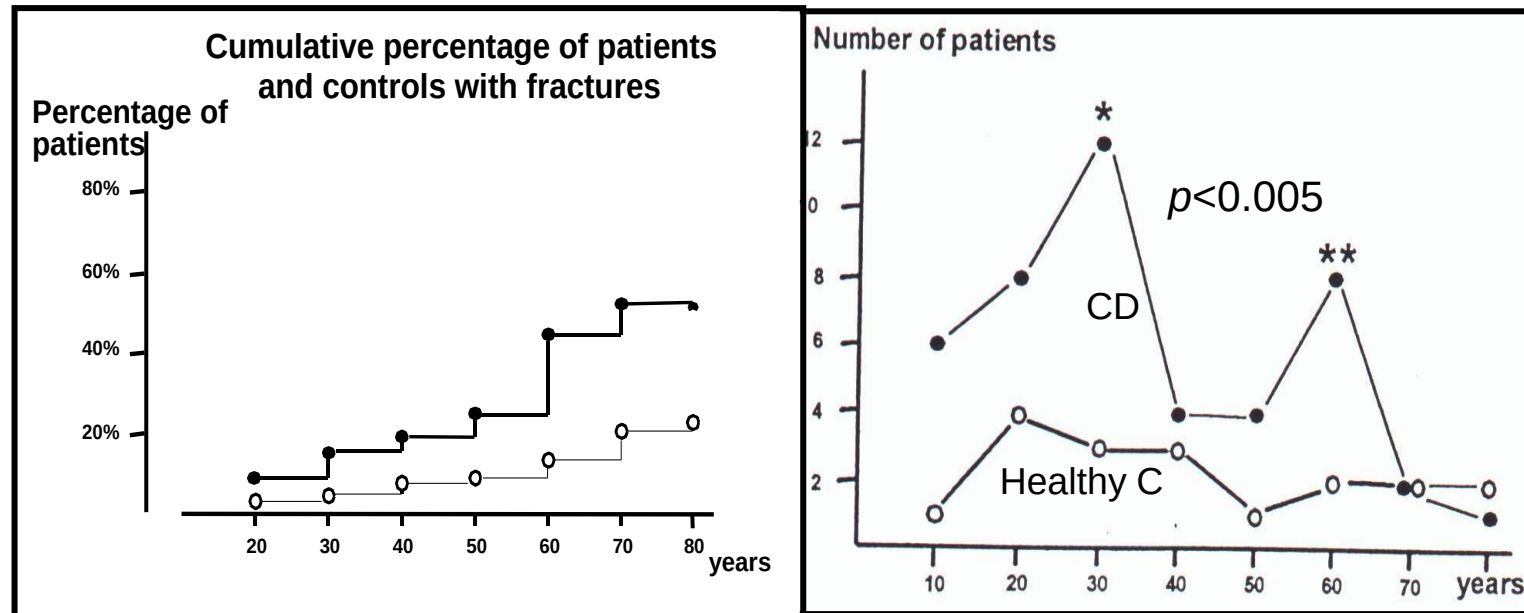
Goals

- Historical perspective.
 - Bone densitometry. DEXA.
 - Pathogenesis of osteoporosis.
 - **Clinical consequences. Fracture risk.**
 - **Pathogenesis of fractures.**
 - Therapeutics.
 - Take home messages.
-



Prevalence of fractures in classical CeD

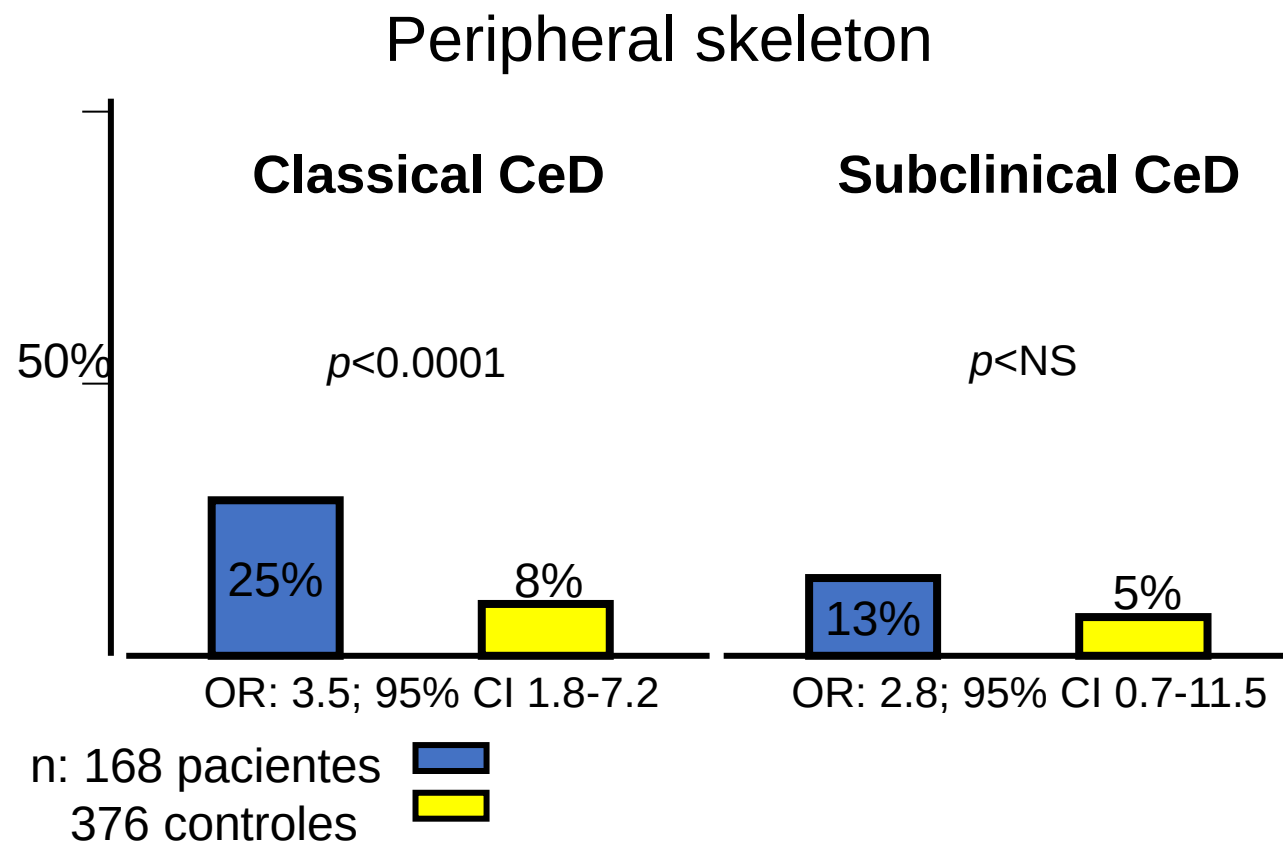
Longitudinal estimations



Compared with “healthy” controls, there is an excess of fractures in CeD patients.



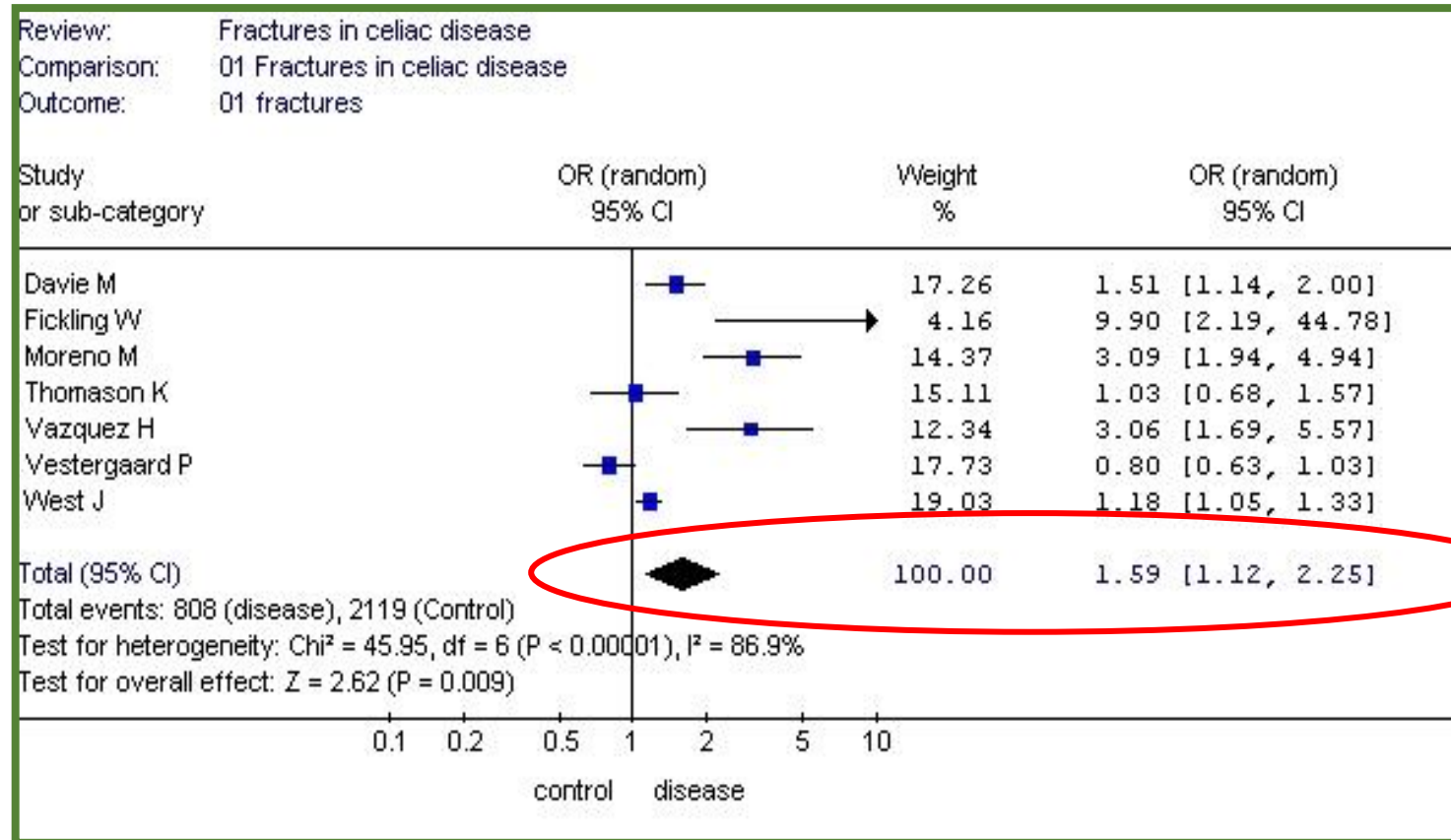
Prevalence of fractures in classical vs. subclinical CeD



The excess of fractures was significant in symptomatic CeD patients.



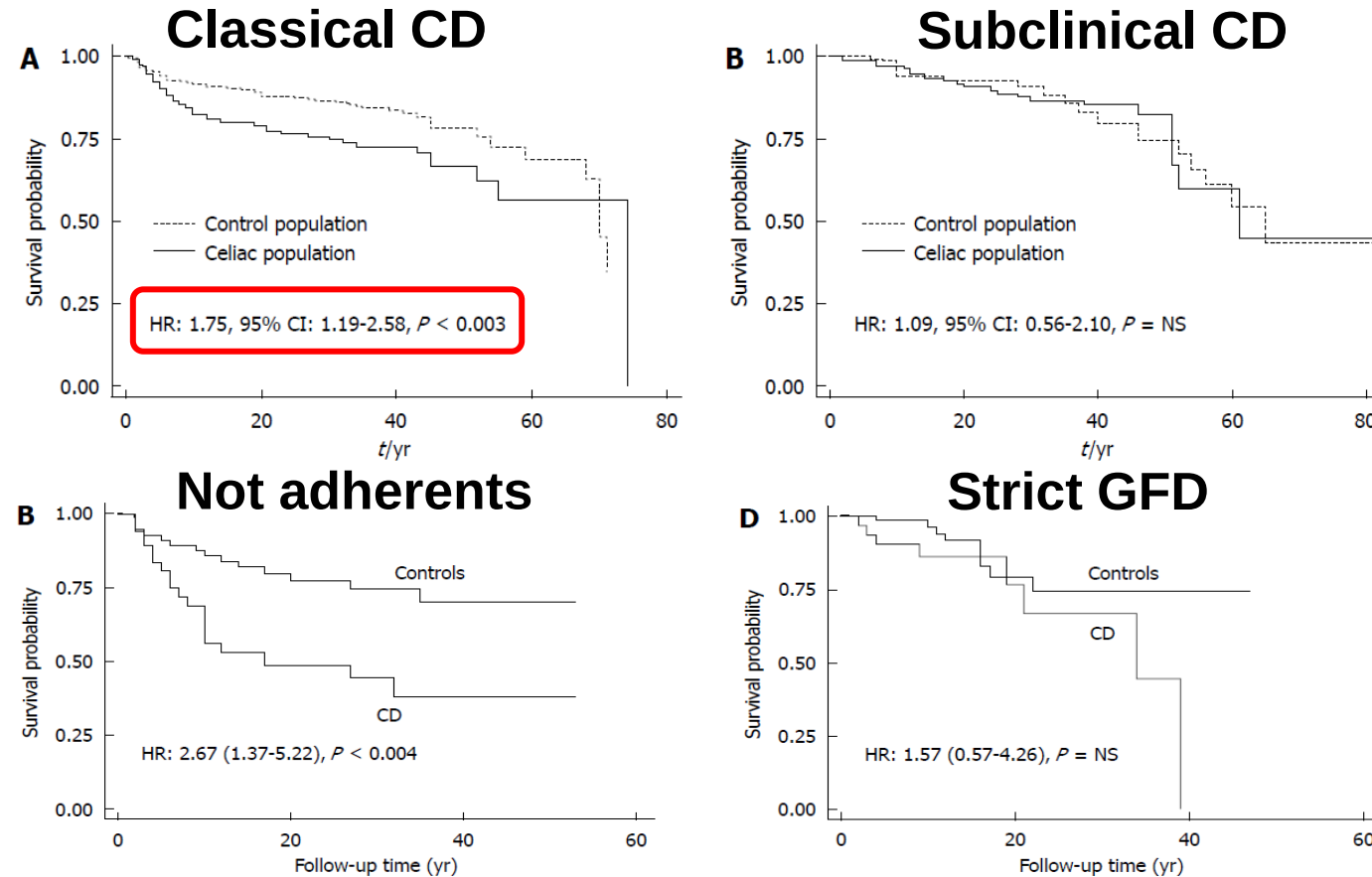
Meta-analysis of fractures in undiagnosed CeD 1. (2008)



- Despite some controversial studies, there was a 60% excess of fractures in CeD.



Risk of fractures. Multicenter, retrospective study.



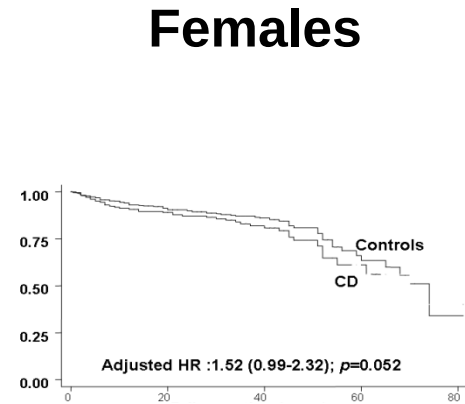
The study confirms a higher risk for symptomatic patients. Strict adherents to the GFD normalize risk of fractures.



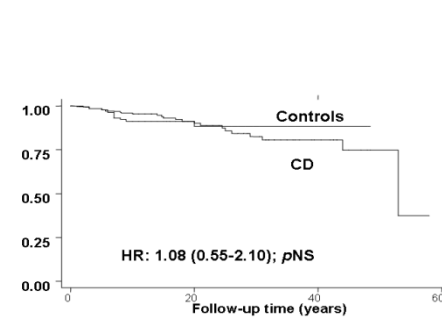
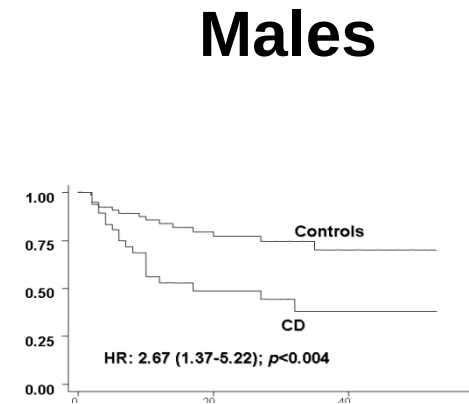


Risk of fractures. Multicenter, retrospective study.

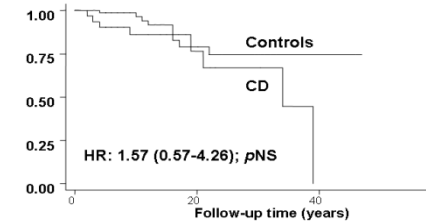
- Overall assessment:
9843 patient-years;
2815 patient-years
after diagnosis.



**Before
Diagnosis**



**After
Diagnosis**

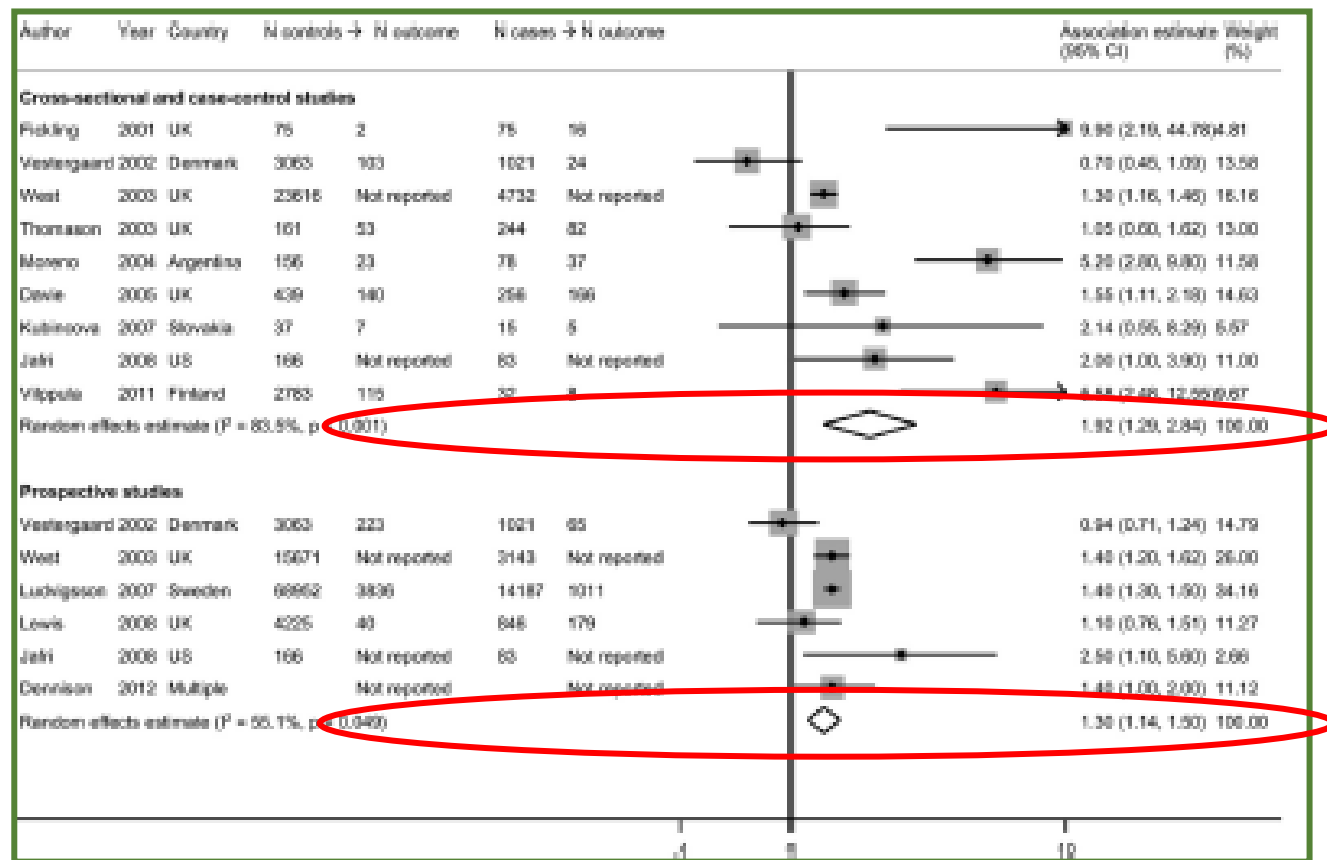


- **Excess of fractures is higher in males and normalizes in GFD strictly adherent patients.**





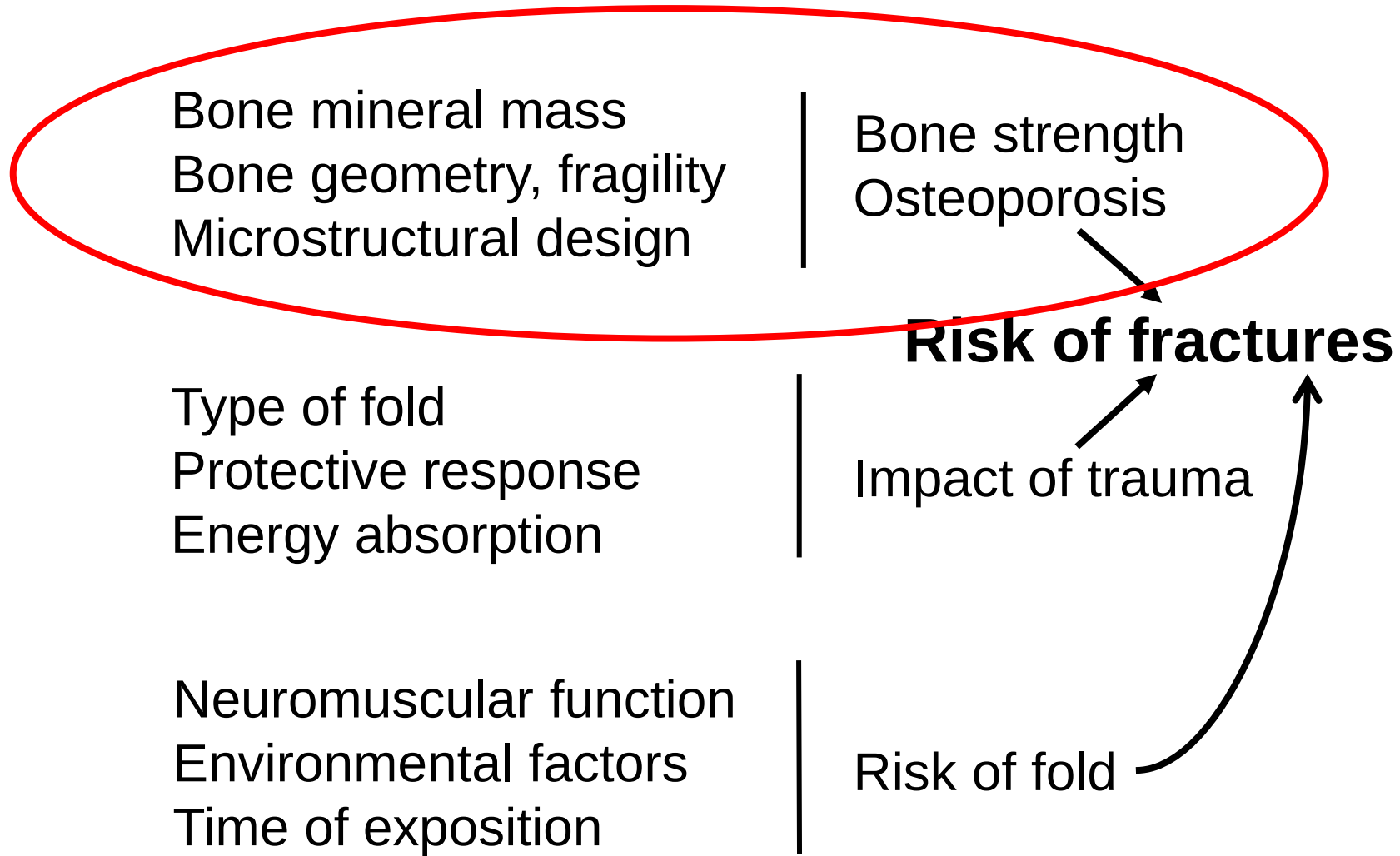
Meta-analysis of fractures in undiagnosed CeD



69% to 100% of excess of fractures in retrospective and prospective studies, respectively.

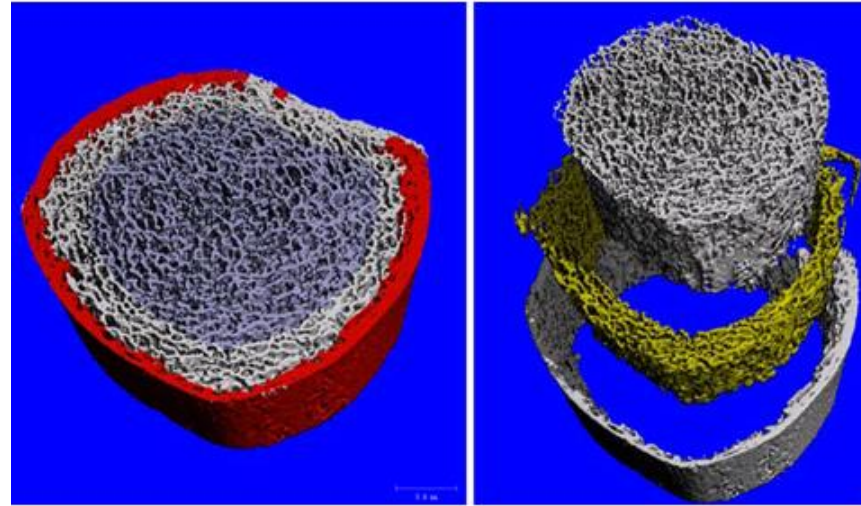


Factors associated with the risk of bone fractures.



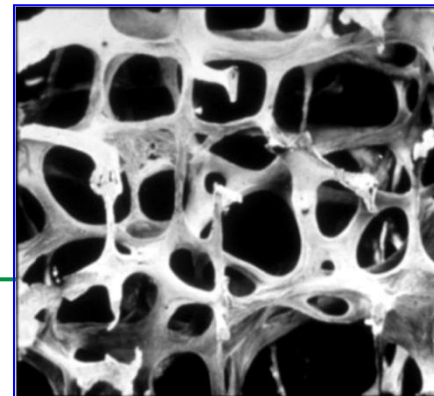
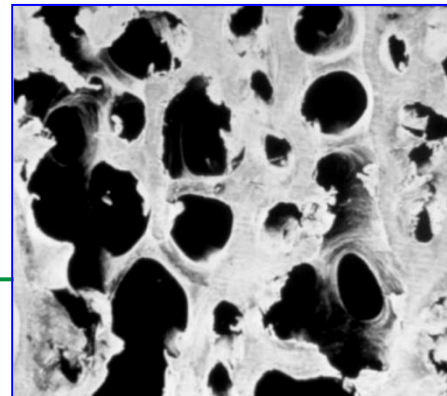
Microstructure of peripheral bones.

HR-pQCT “virtual biopsy”



3D analysis of structure:
Volumetric density (total, cortical, trabecular)

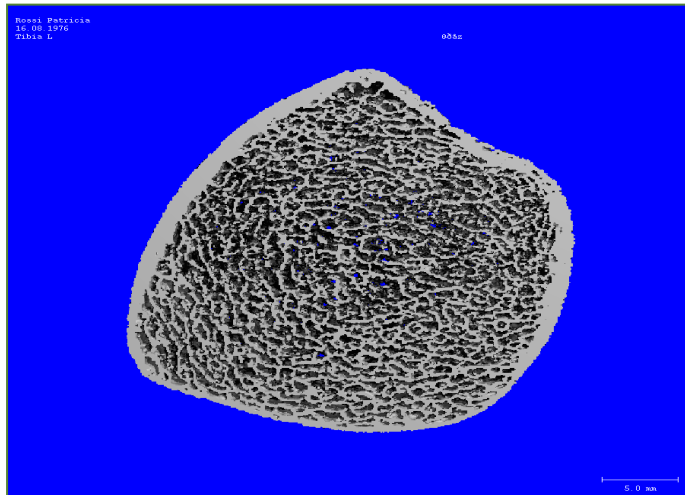
Normal trabecular
structure



Osteoporosis

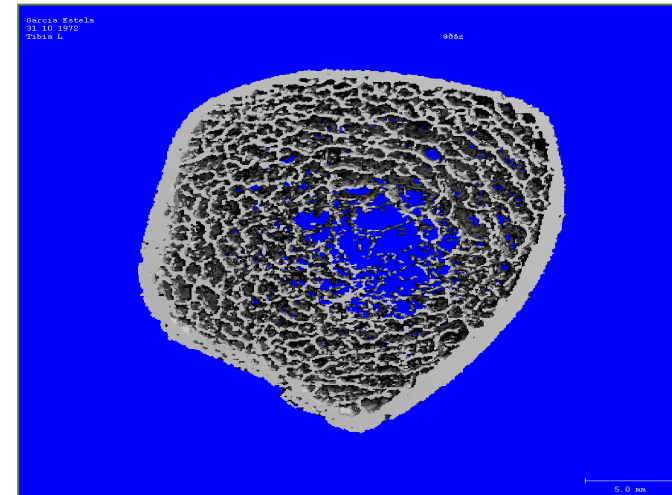
Microstructure of peripheral bones at diagnosis.

Cortical thickness, and trabecular number, thickness and spacing
Volumetric densities.



Healthy control

Distal
tibia

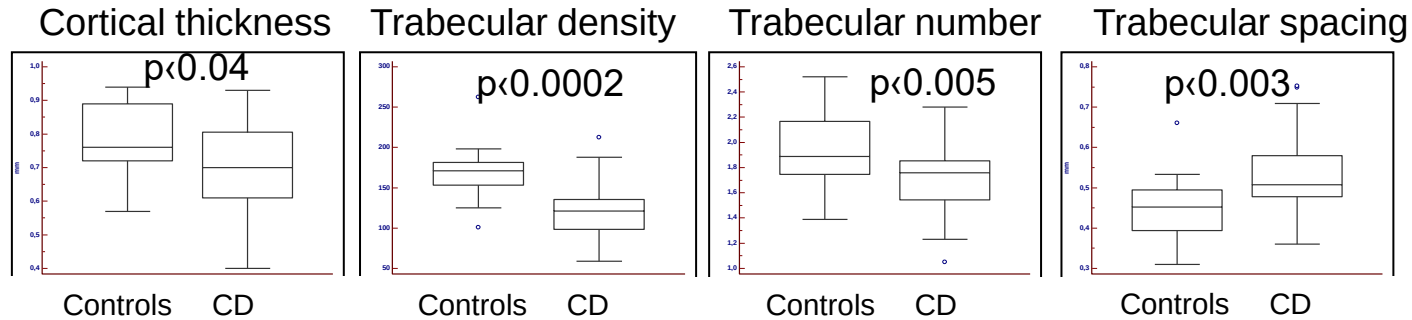


Untreated CeD



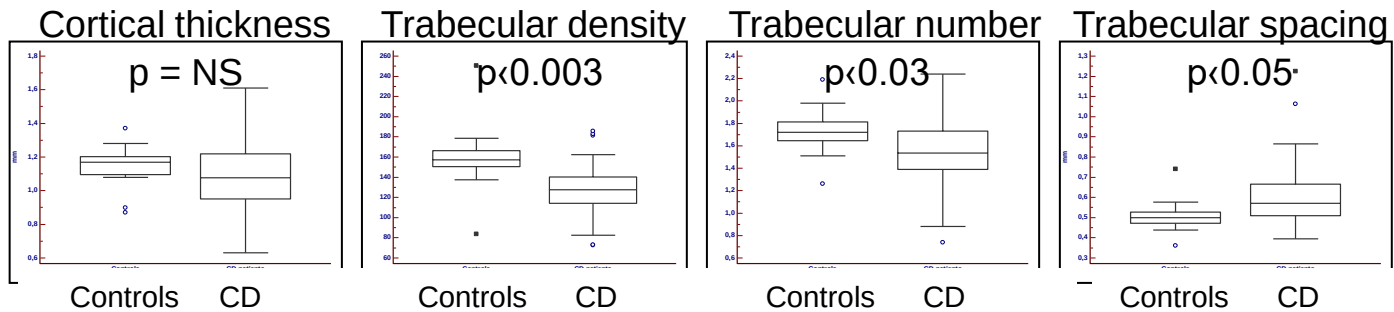
Microstructure of peripheral bones at diagnosis

Ultradistal radius



Cortical bone: stiffness and resistance to torsion are characteristics although less obvious.

Distal tibia



Trabecular bone: strength and resistance to pressure. Simple to prove and faster to recover.



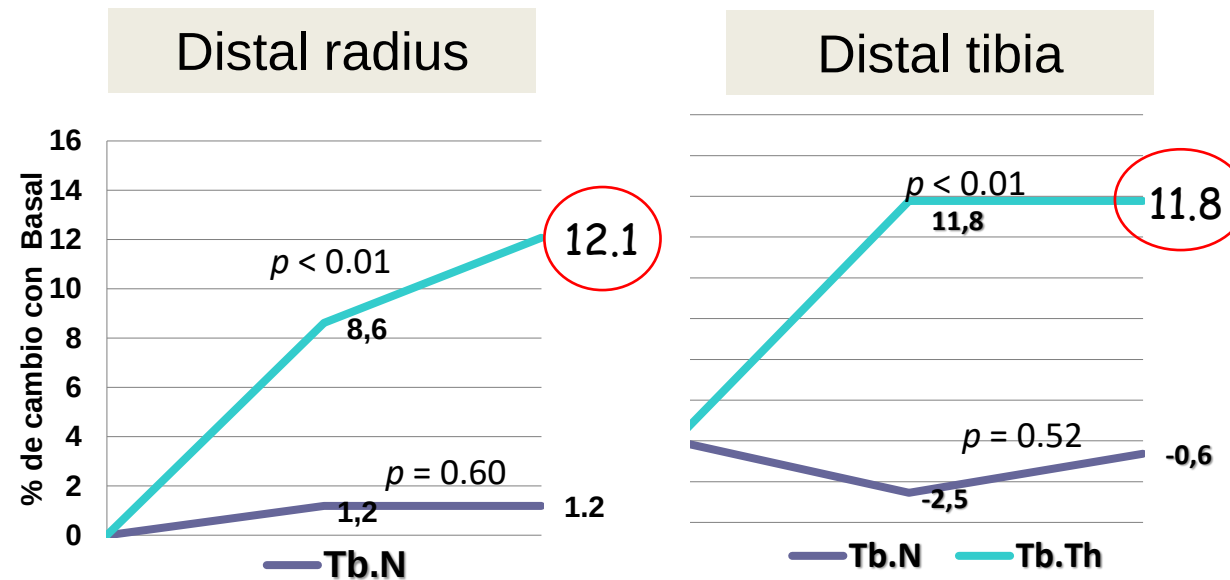
Goals

- Historical perspective.
 - Bone densitometry. DEXA.
 - Pathogenesis of osteoporosis.
 - Clinical consequences. Fracture risk.
 - Pathogenesis of fractures.
 - **Therapeutics.**
 - Take home messages.
-



Effect of the GFD at 1- and 3-yr. HR-pQCT

% of change; thickness and number of trabecules



- Bone microstructural parameters at HR-pQCT are evident at 1-yr on GFD even in young females with normal DMO, and continue after 3 years. (12%)



Therapeutic tips. Follow-up strategies.

- Until now, the GFD is the only effective treatment for op/OP in CeD.
 - In treated pts. with BMD deterioration, look for low GFD adherence.
 - Ca and vit. D supplementation if deficient or high PTH (first year?).
 - There is still no evidence to support the use of biphosphonates.
 - At baseline, all newly diagnosed adult patients should have their BMD measured (DEXA). Repeat on periodic bases depending of baseline BMD.
 - There is no evidence to support further study in the subclinical phenotype or when baseline BMD is normal (until menopause or andropause).
-



Take home messages

- A new era of knowledge started in 90's.
 - BMD was firstly shown as a relevant phenomenon
 - Early detection of CeD before BMD deterioration.
 - Classically symptomatic pts. mostly affected.
 - Subclinical CD also exhibit bone damage.
 - Fracture risk is increased (~60% increment)
 - Males have higher risk.
 - Subclinical CeD has normal fracture risk.
 - Fracture risk normalizes by the GFD (!!).
 - Multifactorial pathogenesis.
 - The trabecular bone seems mostly affected.
 - The GFD induces microstructural improvement.
-



“C. Bonorino Udaondo”
Gastroenterology Hospital

- R. Mazure
- S. Niveloni
- S. Pedreira
- E. Smecuiol
- E. Sugai
- M.L. Moreno
- P. Tanoue
- J.P. Stefanolo
- M.I. Pinto-Sánchez
- J.C. Bai



Columbia University . NYC

- M. Walker
- B. Lebwohl
- P. Green

McMaster University . Ca

- E. Verdú
- M.I. Pinto-Sánchez

Thank you!!!



UBA. Osteopathy Center

- D. Gonzalez
- C. Mautalen

IDIM. Argentina

- J. Ferretti
- A. Marino
- J. Zancheta
- MB. Zanchetta

UBA. Immunology Department

- R. Diez
- A. Cherñavsky
- G. Rabinovich

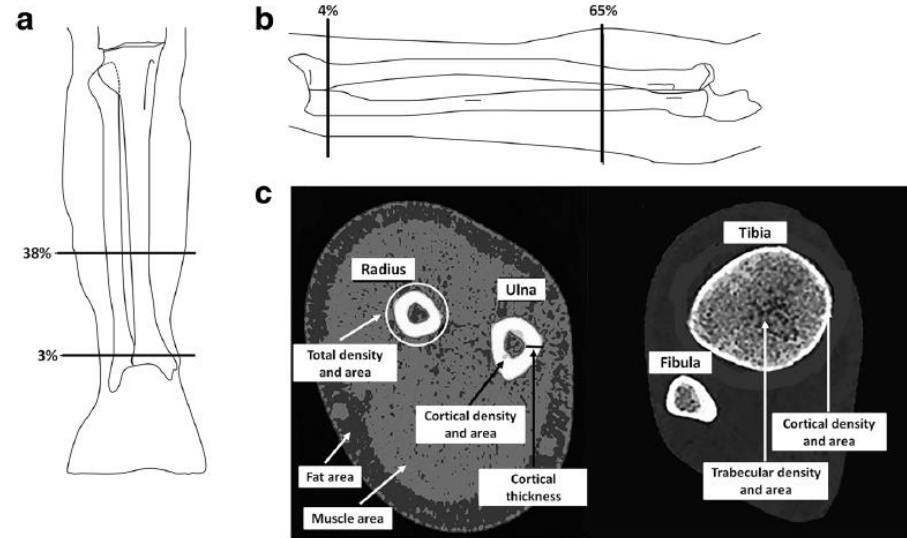
Vrije University. Amsterdam

- S. Peña



Scientific production on CD and bone disease

- 1- Bone mineral affectation in asymptomatic adult patients with celiac disease. AJG 1994
- 2- Body composition and bone mineral density in untreated and treated patients with celiac disease. Bone 1995
- 3- Early changes of body composition in asymptomatic celiac disease patients. AJG 1996
- 4- Longitudinal study on the effect of treatment on body composition and anthropometry of celiac disease patients. AJG 1997
- 5- Effect of treatment on bone mass, mineral metabolism, and body composition in untreated celiac disease patients. AJG 1997
- 6- Long-term effect of gluten restriction on bone mineral density of patients with coeliac disease. APT 1997
- 7- Bone mineral density in patients with pancreatic insufficiency and steatorrhea. AJG 1997
- 8- Enfermedad metabólica ósea asociada a la enfermedad celíaca. Gastroenterología y Hepatología 1997
- 9- Pre- and post-treatment serum levels of cytokines IL-1 β , IL-6, and IL-1 receptor antagonist in celiac disease. Are they related to the associated osteopenia? AJG 1998
- 10- Risk of fractures in celiac disease patients: a cross-sectional, case-control study. AJG 2000
- 11- Is it necessary to screen for celiac disease in postmenopausal osteoporotic women? Calcif Tissue Int 2002
- 12- Bone specific antibodies in sera from patients with celiac disease. Characterization and implications in osteoporosis. JCI 2002
- 13- Analysis of the structure and strength of bones in coeliac disease patients. AJG 2002
- 14- Bones in coeliac disease: diagnosis and treatment. Best Pract Res Clin Gastroenterol 2005
- 15- The IL-1 gene family and bone involvement in celiac disease. Immunogenetics 2005
- 16- Systematic review and meta-analysis of observational studies on the prevalence of fractures in celiac disease. Dig Liv Dis 2008
- 17- Risk of fracture in celiac disease. A matter of gender, compliance with the diet or both? WJG 2011
- 18- Significant bone microarchitecture impairment in premenopausal women with active celiac disease. Bone 2015
- 19- Bone and celiac disease. Curr Osteoporos Rep 2016
- 20- Impaired Bone Microarchitecture Improves After One Year On Gluten-Free Diet: A Prospective Longitudinal HRpQCT Study in Women With Celiac Disease. JBMR 2016.
- 21- Improvement of impaired bone microarchitecture in patients with celiac disease after three-years on a gluten-free diet. CGH 2018.
- 22- Measurement of Forearm Bone Density by Dual Energy X-Ray Absorptiometry Increases the Prevalence of Osteoporosis in Men With Celiac Disease. CGH 2020





Body Composition and Bone Mineral Density in Untreated and Treated Patients With Celiac Disease

D. GONZÁLEZ,¹ R. MAZURE,² C. MAUTALEN,¹ H. VAZQUEZ,² and J. BAI²

0002-9270/97/0204-0639\$03.00/0
THE AMERICAN JOURNAL OF GASTROENTEROLOGY
Copyright © 1997 by Am. Coll. of Gastroenterology

Bone Vol. 16, No. 2
February 1995:231-234

Vol. 92, No. 4, 1997
Printed in U.S.A.

Longitudinal Study on the Effect of Treatment on Body Composition and Anthropometry of Celiac Disease Patients

Edgardo Smecuol, M.D., Diana Gonzalez, M.D., Carlos Mautalen, M.D., Ana Siccardi, R.D., Monica Cataldi, R.D., Sonia Niveloni, M.D., Roberto Mazure, M.D., Horacio Vazquez, M.D., Silvia Pedreira, M.D., Graciela Soifer, M.D., Luis A. Boerr, M.D., Eduardo Mauriño, M.D., and Julio C. Bai, M.D.

Small Bowel Section, Clinical and Nutrition Services, Clinical Department, Gastroenterology Hospital, Salvador University, and Sección de Osteopatías Médicas, Hospital de Clínicas, Buenos Aires University, Buenos Aires, Argentina

Aliment Pharmacol Ther 1997; 11: 157-164.

Long-term effect of gluten restriction on bone mineral density of patients with coeliac disease

J. C. BAI, D. GONZALEZ*, C. MAUTALEN*, R. MAZURE, S. PEDREIRA, H. VAZQUEZ, E. SMECUOL, A. SICCARDI, M. CATALDI, S. NIVELONI, L. A. BOERR & E. MAURIÑO

Calcif Tissue Int (2002) 71:141-144
DOI: 10.1007/s00223-001-1027-9



Is it Necessary to Screen for Celiac Disease in Postmenopausal Osteoporotic Women?

Clinical Gastroenterology and Hepatology 2020;18:99-106

Measurement of Forearm Bone Density by Dual Energy X-Ray Absorptiometry Increases the Prevalence of Osteoporosis in Men With Celiac Disease

Marcella D. Walker,* John Williams,* Suzanne K. Lewis,* Julio C. Bai,[§] Benjamin Lebwohl,* and Peter H. R. Green[†]



THE AMERICAN JOURNAL OF GASTROENTEROLOGY
© 2000 by Am. Coll. of Gastroenterology
Published by Elsevier Science Inc.

Vol. 95, No. 1, 2000
ISSN 0002-9270/00/\$20.00
PII S0002-9270(99)00741-8

Risk of Fractures in Celiac Disease Patients: A Cross-Sectional, Case-Control Study

CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2004;2:127-134

Stratification of Bone Fracture Risk in Patients With Celiac Disease

Risk of Fractures in Celiac Disease Patients: A Cross-Sectional, Case-Control Study

Horacio Vazquez, M.D., Roberto Mazure, M.D., Diana Gonzalez, M.D., Daniel Flores, M.D., Silvia Pedreira, M.D., Sonia Niveloni, M.D., Edgardo Smecuol, M.D., Eduardo Mauriño, M.D., and Julio C. Bai, M.D.

Systematic review and meta-analysis of observational studies on the prevalence of fractures in coeliac disease

M. Olmos, M. Antelo, H. Vazquez, E. Smecuol, E. Mauriño, J.C. Bai*

BRIEF ARTICLE

Risk of fracture in celiac disease: Gender, dietary compliance, or both?

Bone and Celiac Disease

María Belén Zanchetta^{1,2} • Vanesa Longobardi^{1,2} • Julio César Bai³



Best Practice & Research Clinical Gastroenterology
Vol. 19, No. 3, pp. 453-465, 2005
doi:10.1016/j.bpg.2005.01.002
available online at: <http://www.sciencedirect.com>



12

Bones in coeliac disease: diagnosis and treatment



THE AMERICAN JOURNAL OF GASTROENTEROLOGY
Copyright © 1998 by Am. Coll. of Gastroenterology
Published by Elsevier Science Inc.

Vol. 93, No. 3, 1998
ISSN 0002-9270/98/\$19.00
PII S0002-9270(97)00115-9

Pre- and Post-Treatment Serum Levels of Cytokines IL-1β, IL-6, and IL-1 Receptor Antagonist in Celiac Disease. Are They Related to the Associated Osteopenia?

Bone-Specific Antibodies in Sera from Patients with Celiac Disease: Characterization and Implications in Osteoporosis

EMILIA SUGAL,¹ ALEJANDRA CHERŇAVSKY,² SILVIA PEDREIRA,¹ EDGARDO SMECUOL,¹ HORACIO VAZQUEZ,¹ SONIA NIVELONI,¹ ROBERTO MAZURE,¹ EDUARDO MAURIÑO,¹ GABRIEL A. RABINOVICH,² and JULIO C. BAI^{1,3}

THE AMERICAN JOURNAL OF GASTROENTEROLOGY
© 2003 by Am. Coll. of Gastroenterology
Published by Elsevier Science Inc.

Vol. 98, No. 2, 2003
ISSN 0002-9270/03/\$30.00
doi:10.1016/S0002-9270(02)05905-1

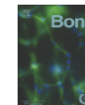
Analysis of the Structure and Strength of Bones in Celiac Disease Patients



Contents lists available at ScienceDirect

Bone

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



Original Full Length Article

Significant bone microarchitecture impairment in premenopausal women with active celiac disease



ORIGINAL ARTICLE

JBM[®]

Impaired Bone Microarchitecture Improves After One Year On Gluten-Free Diet: A Prospective Longitudinal HRpQCT Study in Women With Celiac Disease

Clinical Gastroenterology and Hepatology 2017;15:1-11

Improved Bone Microarchitecture in Patients With Celiac Disease After 3 Years on a Gluten-Free Diet

María B. Zanchetta,^{*,‡} Ana F. Costa,[§] Vanesa Longobardi,* Roberto Mazure,[§] Fernando Silveira,* María P. Temprano,[§] Horacio Vázquez,^{§,||} César Bogado,* Sonia I. Niveloni,^{§,||} Edgardo Smecuol,^{§,||} María L. Moreno,[§] Andrea González,[§] Eduardo Mauriño,[§] José R. Zanchetta,* and Julio C. Bai^{†,§}



**Peak
Bone Mass**



**Bone
Building**

Age 15 to 25

Formation > Resorption

Menopause



Resorption > Formation

Celiac disease and bone health

Julio C. Bai, MD

Consultant

“Dr. C. Bonorino Udaondo” Gastroenterology Hospital

Professor Emeritus
Research Institute
Universidad del Salvador

Buenos Aires. Argentina

Presentation by

22/11/2022



SORRENTOICDS2022



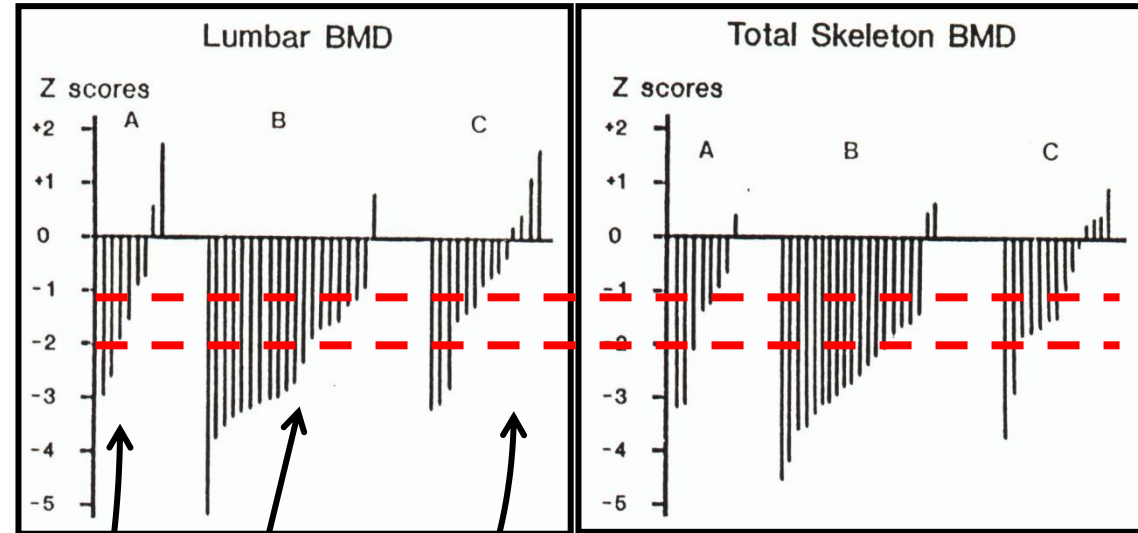
Incidence of fractures



- Multicenter study (n=5)
- Retrospective, case-control study
- Patients (n=265), controls (n=530)
- Overall assessment window:
9843 patient-years; 2815 patient-years after diagnosis.



Bone density (DXA). Osteopenia y osteoporosis at diagnosis



Normal

Osteopenia

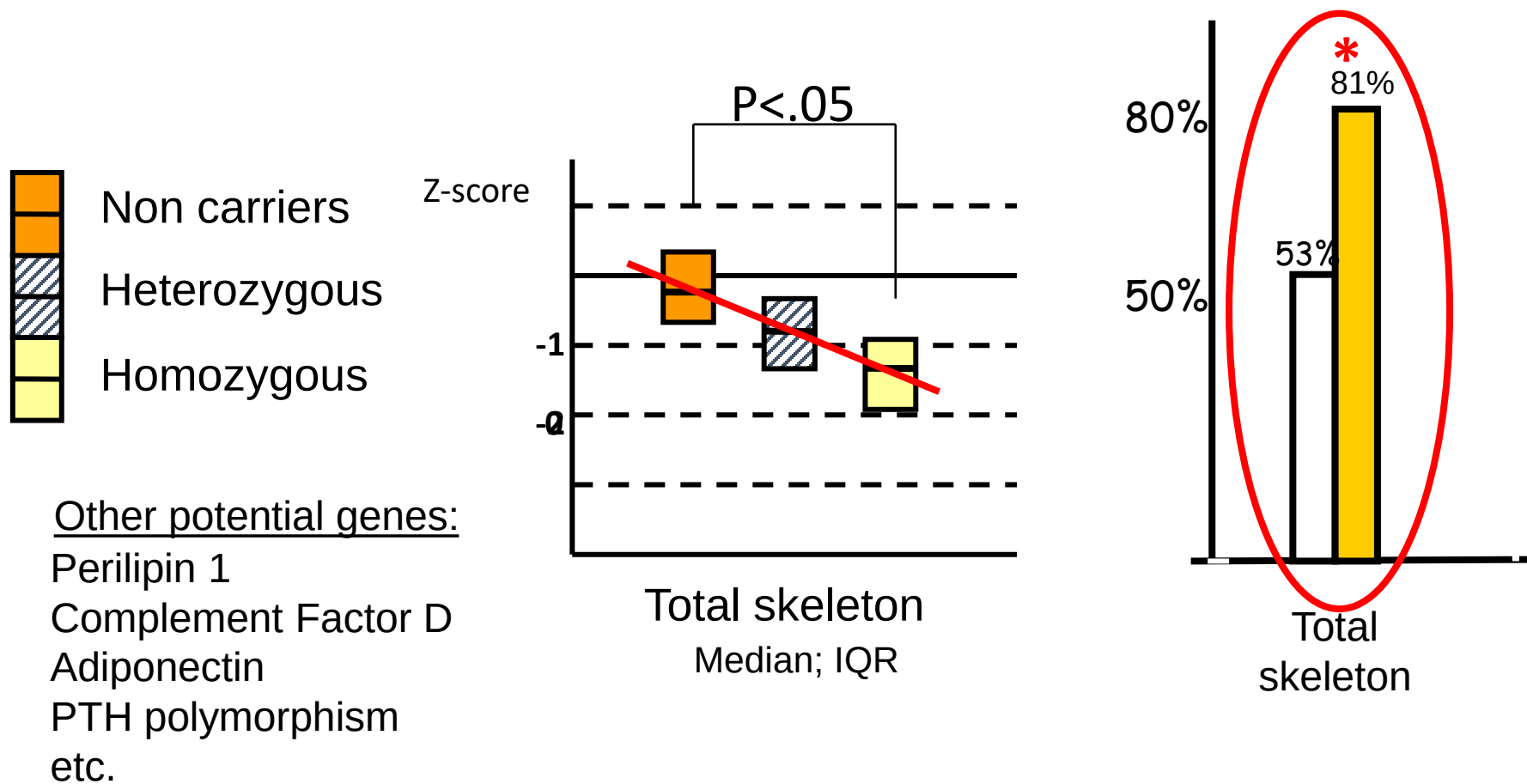
Osteoporosis

	Osteopenia	Osteoporosis
	%	%
Untreated CD	40 - 50	30 - 40
Treated CD	30 - 50	20 - 30
Asymptomatic CD	30	25

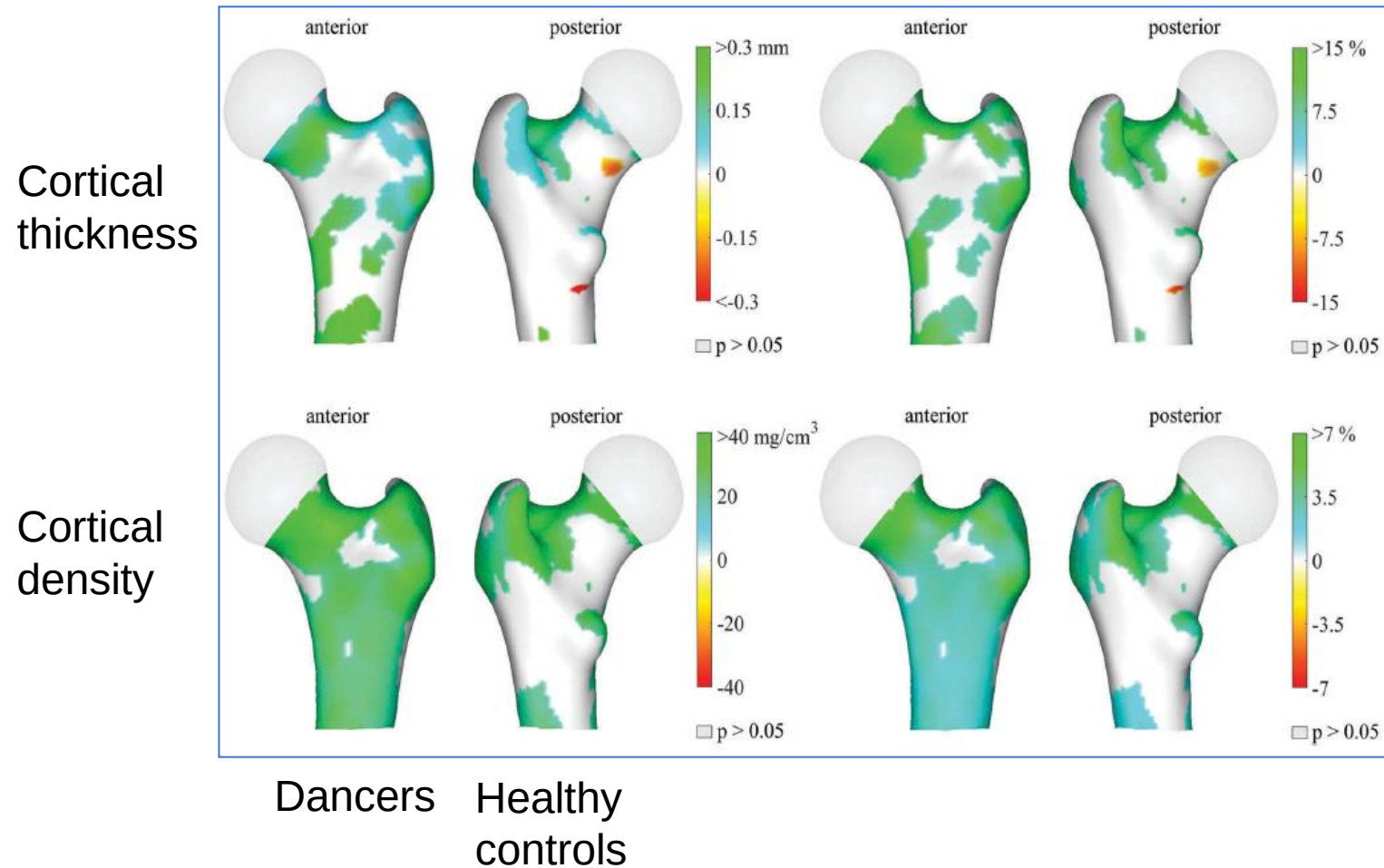
Caraceni, et al, AJG 1988; Molteni, et al. AJG 1990; Bodé, et al. Gut 1991; Mora et al. AJCN 1993; Mazure et al. AJG 1994; Gonzalez, et al. Bone 1995



BMD z-score and genetics. The allele *IL1B*-511*2 variant.

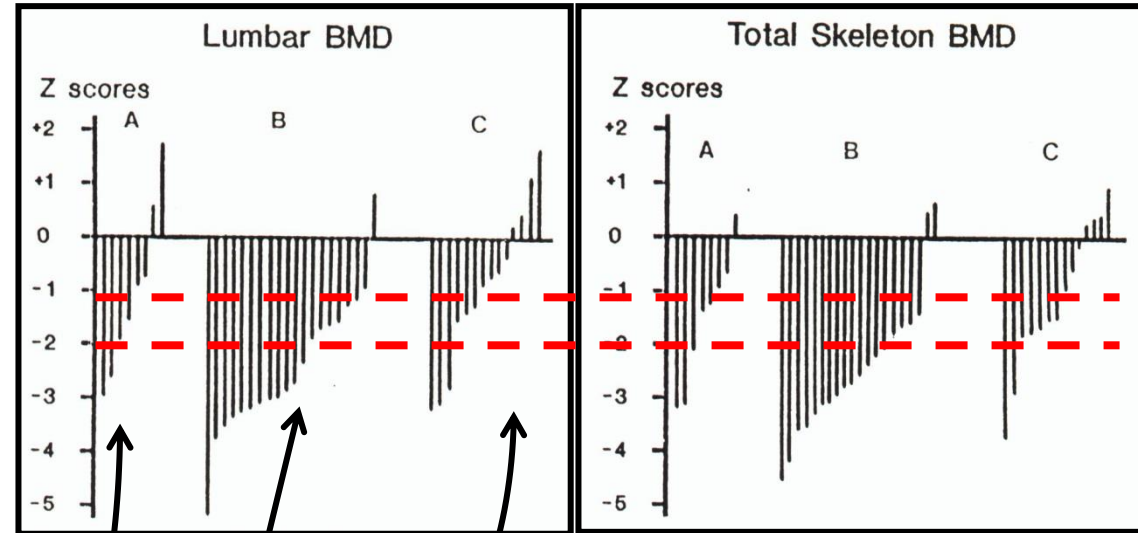


HR-pQCT can also determine bone spatial affectation.





Bone density (DXA). Osteopenia y osteoporosis at diagnosis



Normal

Osteopenia

Osteoporosis

	Osteopenia	Osteoporosis
	%	%
Untreated CD	40 - 50	30 - 40
Treated CD	30 - 50	20 - 30
Asymptomatic CD	30	25

Caraceni, et al, AJG 1988; Molteni, et al. AJG 1990; Bodé, et al. Gut 1991; Mora et al. AJCN 1993; Mazure et al. AJG 1994; Gonzalez, et al. Bone 1995