ENFERMEDAD CELIACA
Y
OSTEOPOROSIS

José Luis Perez Castrillón
Servicio Medicina Interna
Hospital Rio Hortega
Valladolid

Facultad de Medicina
Universidad de Valladolid
www.med.uva.es

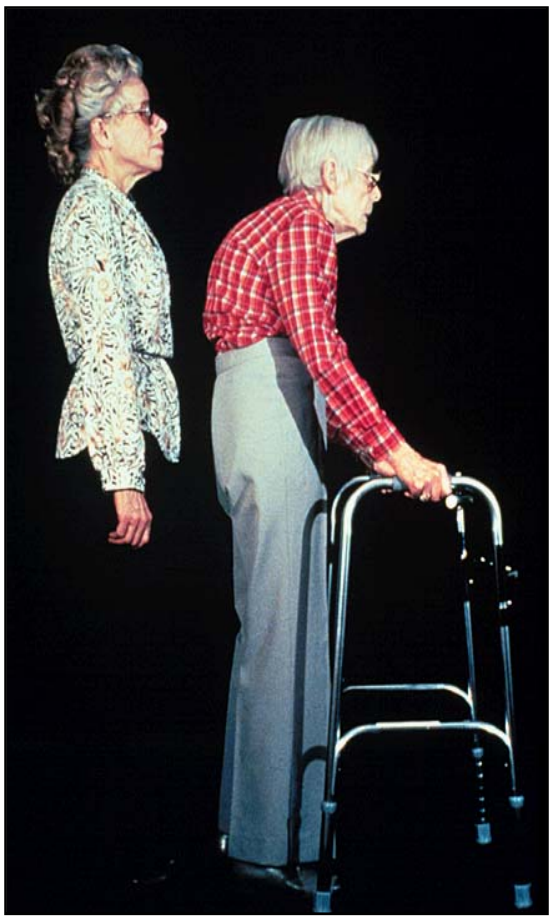
OSTEOPOROSIS Y ENFERMEDAD CELIACA

- **Hay una mayor incidencia de osteoporosis en los pacientes con enfermedad celiaca ?**
- **Existen mecanismos etiopatogénicos en la enfermedad celiaca que favorezcan la aparición de osteoporosis?**
- **Es necesario realizar una densitometría a todos los pacientes con enfermedad celiaca ?**
- **Cuál sería las medidas terapéuticas más adecuadas en estos pacientes ?**

Hay una mayor incidencia de osteoporosis en los pacientes con enfermedad celiaca ?

DIAGNÓSTICO DE OSTEOPOROSIS

OSTEOPOROSIS

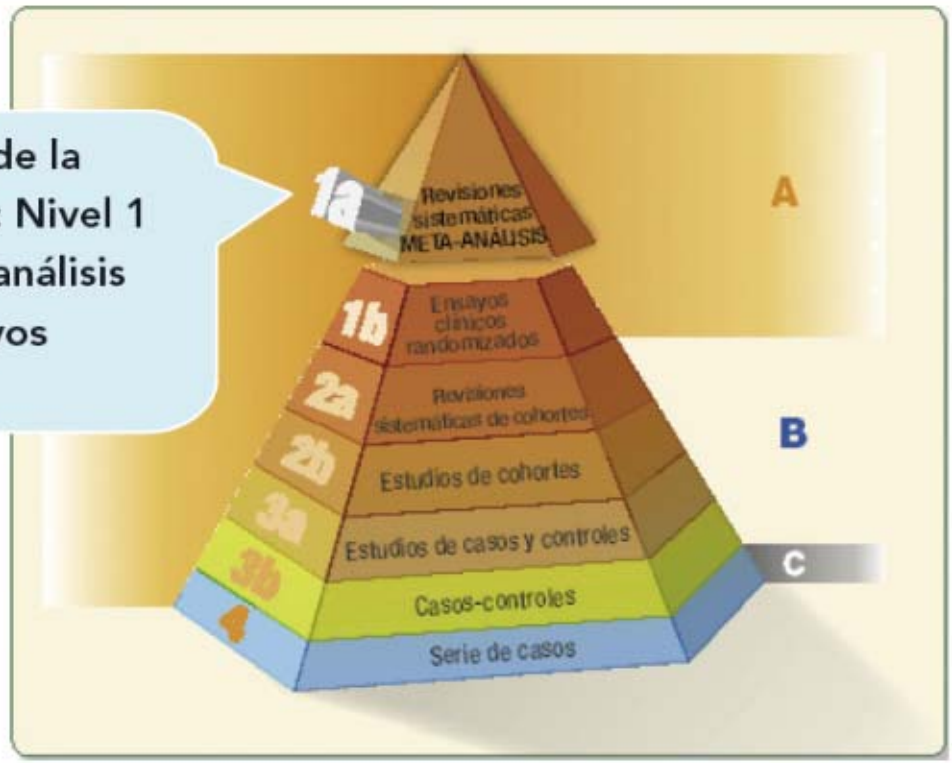


La osteoporosis puede ser diagnosticada por la presencia de una fractura de bajo impacto; sin embargo, la fractura no es requerida para el diagnóstico.

El diagnóstico de osteoporosis puede también basarse en la densidad mineral ósea (DMO).

Jerarquía de la evidencia científica (MBE)

Cúspide de la pirámide: Nivel 1
1a: Metaanálisis
1b: Ensayos clínicos



89) Philips B et al. Disponible en http://www.cebm.net/levels_of_evidence.asp. Consultado el 21 agosto 2007. 90) Ebell MH et al. *Am Fam Physician* 2004;69(3):548-56.

ENFERMEDAD CELIACA Y DENSITOMETRIA

- **18 Estudios publicados**
- **Deficiente calidad metodológica**
- **Datos ajustado por Z-score**

	Cadera	Columna
Osteopenia	43 %	41 %
Osteoporosis	11 %	56 %

Celiac Disease and Osteoporosis: A Review

José-Luis Pérez-Castrillón[*,1,4], Maria Andres-Calvo[1], Elena Izquierdo-Delgado[1], Marcelino Mendo[3], Daniel de Luis[2,4] and Antonio Dueñas-Laita[1]

[1]*Department of Medicine, University Hospital Rio Hortega, University of Valladolid, Spain*

[2]*Research Unit, University Hospital Rio Hortega, University of Valladolid, Spain*

[3]*Department of Radiology, University Hospital Rio Hortega, University of Valladolid, Spain*

[4]*RETICEF (Thematic Network of Cooperative Research into Aging and Fragility)*

The Open Bone Journal, 2009, *1*, 23-27

Author	Study	Population	Objective	OR (95% CI)
Vazquez *et al.* [18]	Case-Control	330 165 celiac patients and 165 controls	Peripheral fractures Spine	3.5 (1.8-7.2) 2.8 (0.7-11.5)
Fickling *et al.* [19]	Case-Control	150 75 celiac patients and 75 controls	Previous fractures	7%
West *et al.* [24]	Retrospective cohorts	28352 1100 celiac patients and 23620 controls	Fractures Hip fractures Colles fractures	1.3 (1.16-1.46) 1.9 (1.2-3.02) 1.77 (1.35-2.34)
Thomson *et al.* [22]	Case-Control	410 244 celiac patients and 166 controls	Previous fracture Fractures Low intensity Colles fractures	1.29 (0.65-2.39) 1.21 (0.66-2.25) 1 (0.68-1.2) 1.16 (0.65-2.39)
Vertergard *et al.* [23]	Retrospective cohorts	31090 7774 celiac patients and 23316 controls	Fractures Vertebral Ribs and pelvis	0.94 (0.71-1.24) 2.14 (0.6-6.75) 1.07 (0.39-2.95)
Moreno *et al.* [20]	Case-Control	311 14 celiac patients and 296 controls	Fractures	3.6 (1.7-7.5)
Davie *et al.* [21]	Case-Control	812 (> 50 years) 383 celiac patients and 445 controls	Fractures	1.51 (1.13-2.02)
Ludvigsson *et al.* [25]	Retrospective cohort	78000 15000 celiac patients and 65000 controls	Fractures Hip	1.4 (1.3-3.5) 2.1 (1.8-2.4)
Jafri *et al.* [26]	Retrospective-prospective cohorts	249 83 celiac patients and 166 controls	Retrospective fractures Prospective fractures	2.0 (1-3.9) 2.5 (1.5-5.6)
Olmos *et al.* [27]	Meta analysis	117732 23955 celiac patients and 96777 controls	Fractures	1.45 (1.15-1.78)

Riesgo de Fracturas y Enfermedad Celiaca

Table 5. Any Fracture, Hip Fracture, and Ulna/Radius Fracture Analyses Restricted to Those Cases With 1 Celiac Code Plus at Least 1 Gluten-Free Prescription

	Subjects with 1 celiac code plus at least 1 gluten-free prescription[a]		
Variable	n[b]	Hazard ratio	95% CI
Any fracture			
Control cohort[c]	21,361	1	
Celiac disease cohort	4280	1.31	1.16–1.48
Hip fracture			
Control cohort[c]	21,365	1	
Celiac disease cohort	4280	1.99	1.25–3.18
Ulna/radius fracture			
Control cohort[c]	21,364	1	
Celiac disease cohort	4280	1.84	1.39–2.44

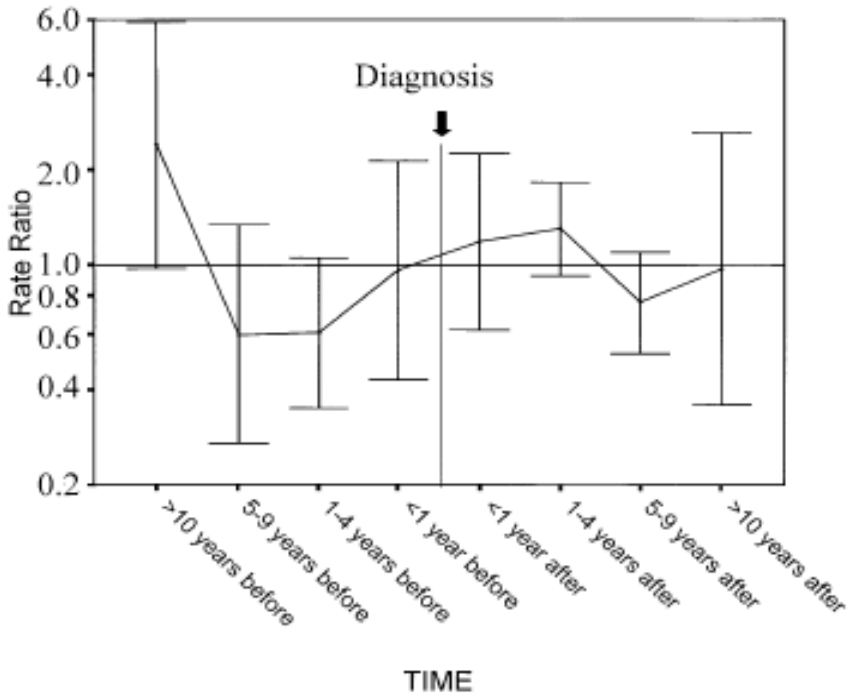
[a]For these analyses, only the matched controls of those subjects with celiac disease were used.
[b]Total numbers vary because those individuals who had a fracture on the same date as the start of their GPRD record were excluded.
[c]Baseline category.

GASTROENTEROLOGY 2003;125:429–436

Fracture Risk in People With Celiac Disease: A Population-Based Cohort Study

JOE WEST,* RICHARD F. A. LOGAN,* TIM R. CARD,* CHRIS SMITH,† and RICHARD HUBBARD*
*University of Nottingham, Division of Epidemiology and Public Health, Medical School, Queen's Medical Centre; and †University of Nottingham, School of Medical and Surgical Sciences, Nottingham City Hospital, Nottingham, United Kingdom

Riesgo de Fracturas y Enfermedad Celiaca



Vertergaard P et al. American Journal of Epidemiology 2002; 156: 1-10

Riesgo de Fracturas y Enfermedad Celiaca

	Original data			Corrected for height and weight		
	n #	*p*	OR (95% CI)	*n* *	*p*	OR (95% CI)
Any fracture	817	<0.01	1.51 (1.13:2.02)	674	<0.02	1.55 (1.11:2.18)
Any fracture after age 50 years	801	<0.001	2.20 (1.49:3.25)	659	<0.001	2.38 (1.52:3.75)
Any wrist fracture	817	<0.05	1.65 (1.12:2.44)	674	n.s.	1.45 (0.92:2.29)
Wrist fracture after age 50 years	808	<0.01	2.17 (1.22:3.87)	666	n.s.	1.80 (0.93:3.49)
Any non-wrist fracture	817	<0.005	1.66 (1.21:2.27)	674	<0.001	1.86 (1.29:2.68)
Non-wrist fracture after age 50 years	807	<0.001	2.34 (1.51:3.63)	665	<0.001	2.73 (1.64:4.54)
More than 1 fracture	817	<0.001	2.96 (1.81:4.83)	674	<0.001	3.36 (1.94:5.83)

#Calculations were made on 817 subjects. In some cases data for age at fracture and site were unavailable (see results)
*Height and weight were not measured in all subjects (see results)

Davie MW et al. Osteoporos Int 2005; 16:1150-5

Riesgo de Fracturas y Enfermedad Celiaca

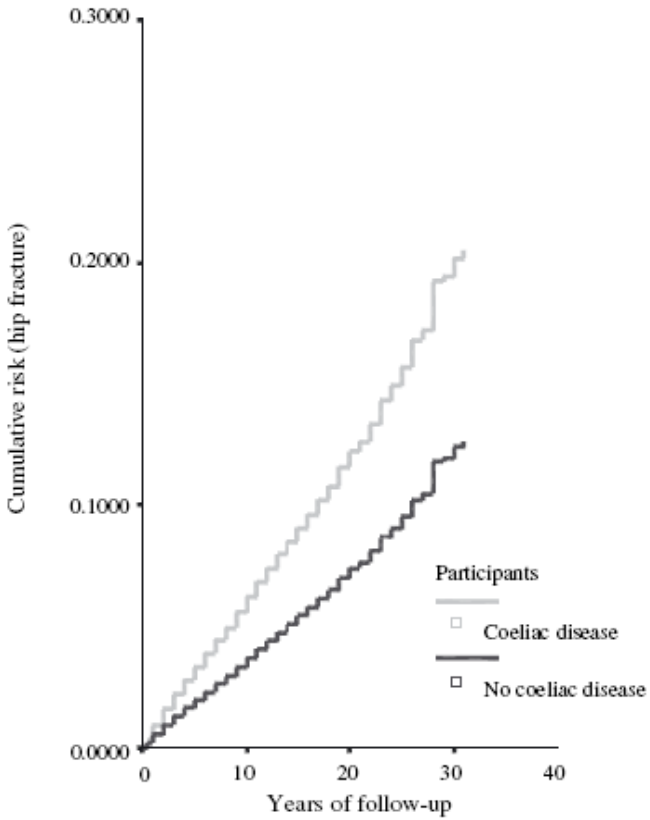


Figure 2. Hip fractures in adults.

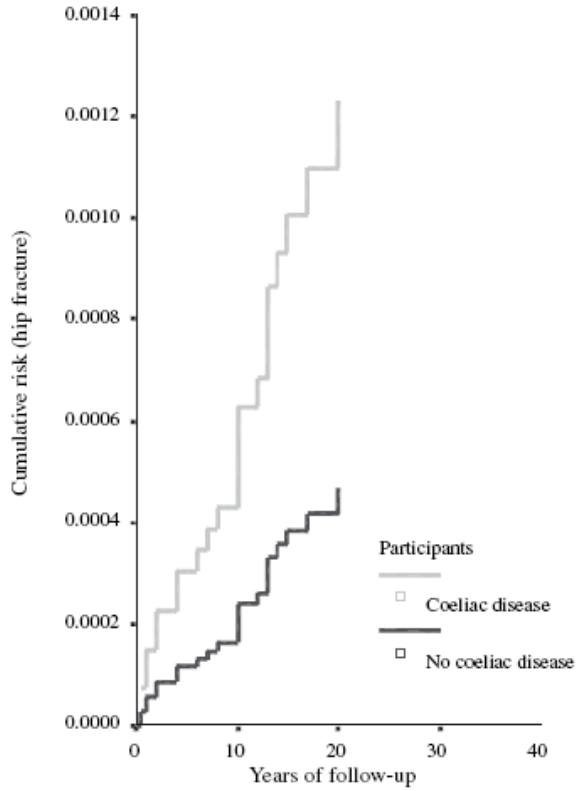


Figure 1. Hip fractures in children: no individual entering the study in childhood had a hip fracture more than 21 years after study entry.

Ludvigsson JF et al. Aliment Pharmacol Ther 2007; 25: 273-285

Riesgo de Fracturas y Enfermedad Celiaca

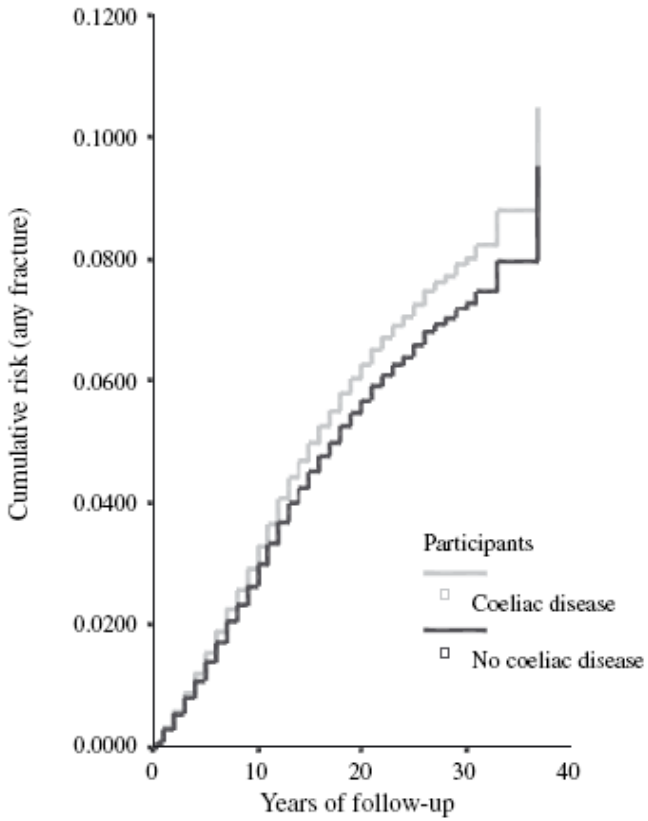


Figure 3. Any fractures in children.

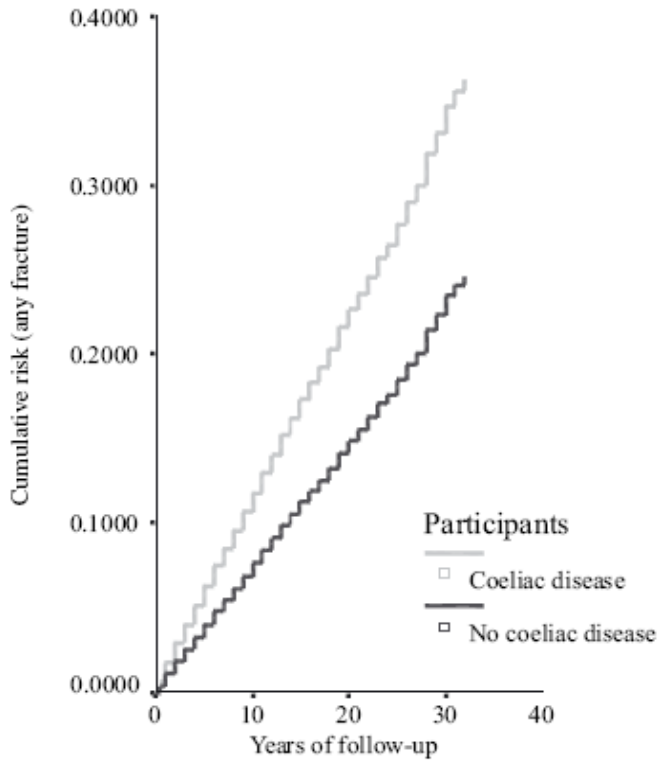


Figure 4. Any fractures in adults.

Ludvigsson JF et al. Aliment Pharmacol Ther 2007; 25: 273-285

Riesgo de Fracturas y Enfermedad Celiaca

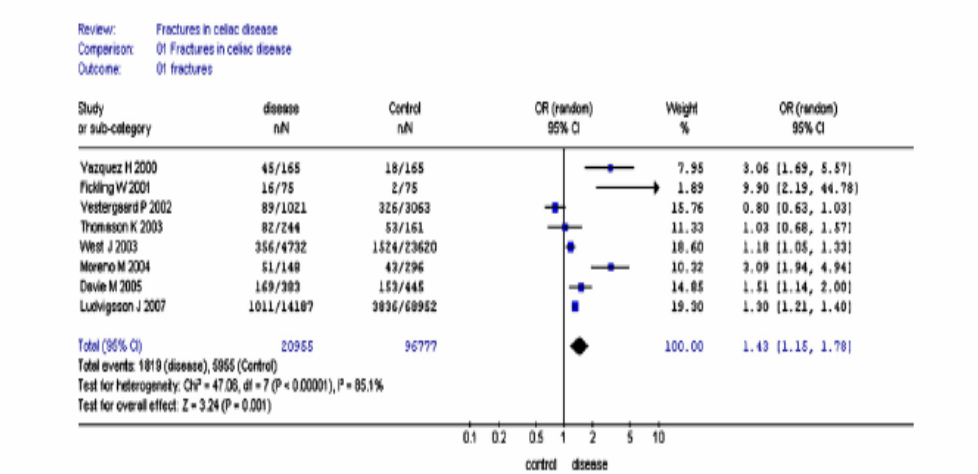


Fig. 2. Meta-analysis: overall, 1819 (8.7%) events (fractures) were detected in 20,955 CD patients, and 5955 (6.15%) in 96,777 controls (pooled OR = 1.43; 95% CI 1.15–1.78).

Olmos M et al. Digestive and Liver Disease 2008; 40: 46-53

Riesgo de Fracturas y Enfermedad Celiaca

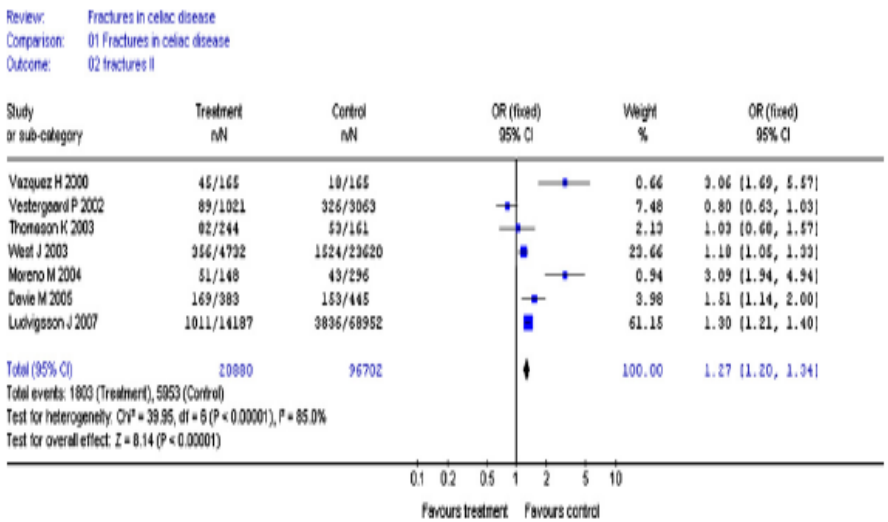


Fig. 3. Meta-analysis excluding the study with the least weight (pooled OR = 1.27, 95% CI 1.20–1.34).

Olmos M et al. Digestive and Liver Disease 2008; 40: 46-53

Riesgo de Fracturas y Enfermedad Celiaca

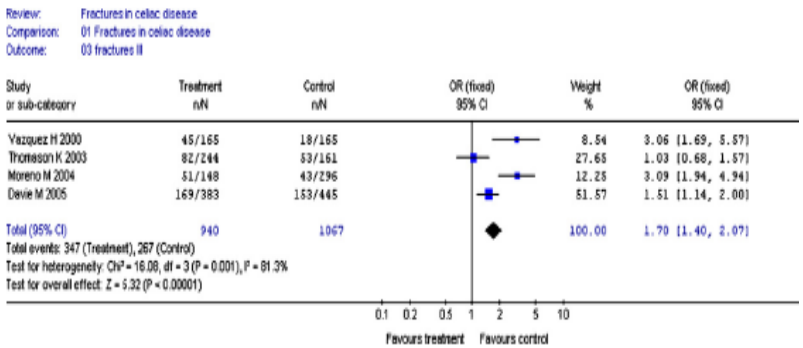


Fig. 4. Meta-analysis with studies enrolling hospital-based participants ($n = 4$) (pooled OR = 1.70; 95% CI 1.40–2.07).

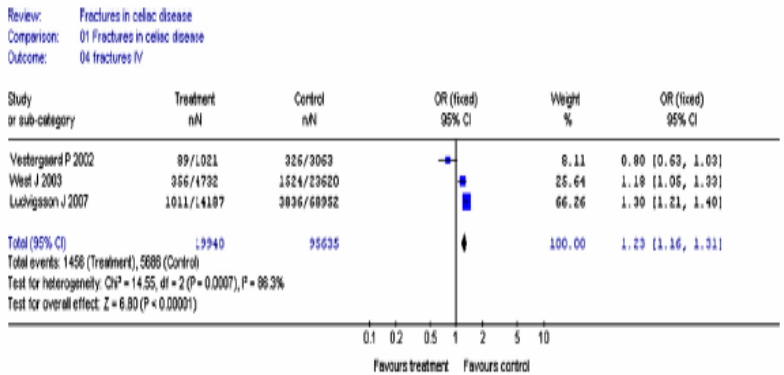


Fig. 5. Meta-analysis with only cohort studies reporting population-based data ($n = 3$) (pooled OR = 1.23, 95% CI 1.16–1.31).

Olmos M et al. Digestive and Liver Disease 2008; 40: 46-53

Celiac Disease and Osteoporosis: A Review

José-Luis Pérez-Castrillón[*,1,4], Maria Andres-Calvo[1], Elena Izquierdo-Delgado[1], Marcelino Mendo[3], Daniel de Luis[2,4] and Antonio Dueñas-Laita[1]

[1]*Department of Medicine, University Hospital Rio Hortega, University of Valladolid, Spain*

[2]*Research Unit, University Hospital Rio Hortega, University of Valladolid, Spain*

[3]*Department of Radiology, University Hospital Rio Hortega, University of Valladolid, Spain*

[4]*RETICEF (Thematic Network of Cooperative Research into Aging and Fragility)*

The Open Bone Journal, 2009, *1*, 23-27

Author	Study	Population	Objective	OR (95% CI)
Vazquez *et al.* [18]	Case-Control	330 165 celiac patients and 165 controls	Peripheral fractures Spine	3.5 (1.8-7.2) 2.8 (0.7-11.5)
Fickling *et al.* [19]	Case-Control	150 75 celiac patients and 75 controls	Previous fractures	7%
West *et al.* [24]	Retrospective cohorts	28352 1100 celiac patients and 23620 controls	Fractures Hip fractures Colles fractures	1.3 (1.16-1.46) 1.9 (1.2-3.02) 1.77 (1.35-2.34)
Thomson *et al.* [22]	Case-Control	410 244 celiac patients and 166 controls	Previous fracture Fractures Low intensity Colles fractures	1.29 (0.65-2.39) 1.21 (0.66-2.25) 1 (0.68-1.2) 1.16 (0.65-2.39)
Vertergard *et al.* [23]	Retrospective cohorts	31090 7774 celiac patients and 23316 controls	Fractures Vertebral Ribs and pelvis	0.94 (0.71-1.24) 2.14 (0.6-6.75) 1.07 (0.39-2.95)
Moreno *et al.* [20]	Case-Control	311 14 celiac patients and 296 controls	Fractures	3.6 (1.7-7.5)
Davie *et al.* [21]	Case-Control	812 (> 50 years) 383 celiac patients and 445 controls	Fractures	1.51 (1.13-2.02)
Ludvigsson *et al.* [25]	Retrospective cohort	78000 15000 celiac patients and 65000 controls	Fractures Hip	1.4 (1.3-3.5) 2.1 (1.8-2.4)
Jafri *et al.* [26]	Retrospective-prospective cohorts	249 83 celiac patients and 166 controls	Retrospective fractures Prospective fractures	2.0 (1-3.9) 2.5 (1.5-5.6)
Olmos *et al.* [27]	Meta analysis	117732 23955 celiac patients and 96777 controls	Fractures	1.45 (1.15-1.78)

Riesgo de Fracturas y Enfermedad Celiaca

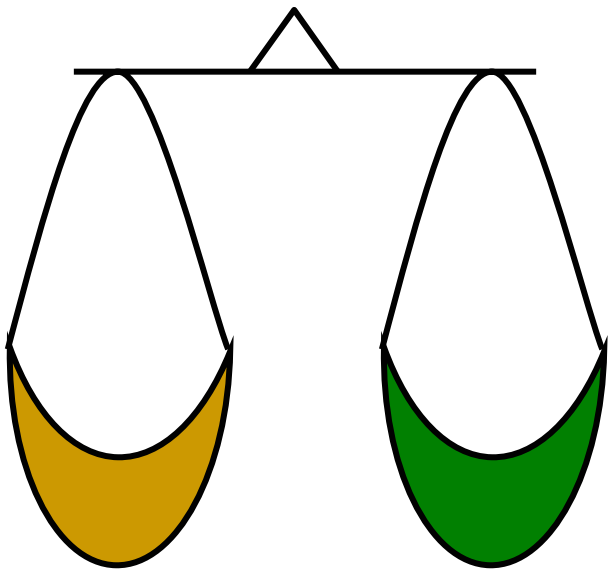
CONCLUSIONES:

1. No hay suficientes evidencias que muestren una mayor incidencia de osteoporosis, con criterios densitométricos, en pacientes con enfermedad celiaca
2. Los pacientes con enfermedad celiaca tienen un riesgo incrementado de fractura

Existen mecanismos etiopatogénicos en la enfermedad celiaca que favorezcan la aparición de osteoporosis?

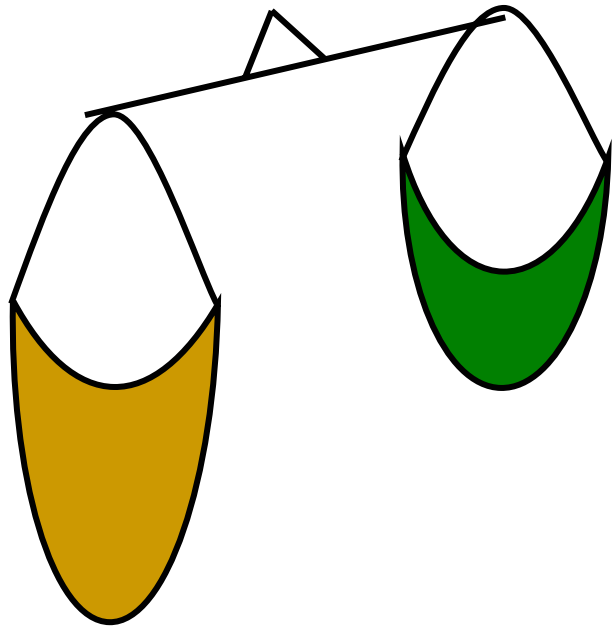
La osteoporosis es una enfermedad de desequilibrio metabólico entre la formación y la destrucción óseas, que provoca una pérdida de masa ósea y deterioro de su microarquitectura. Esto induce una pérdida de resistencia esquelética

Normal



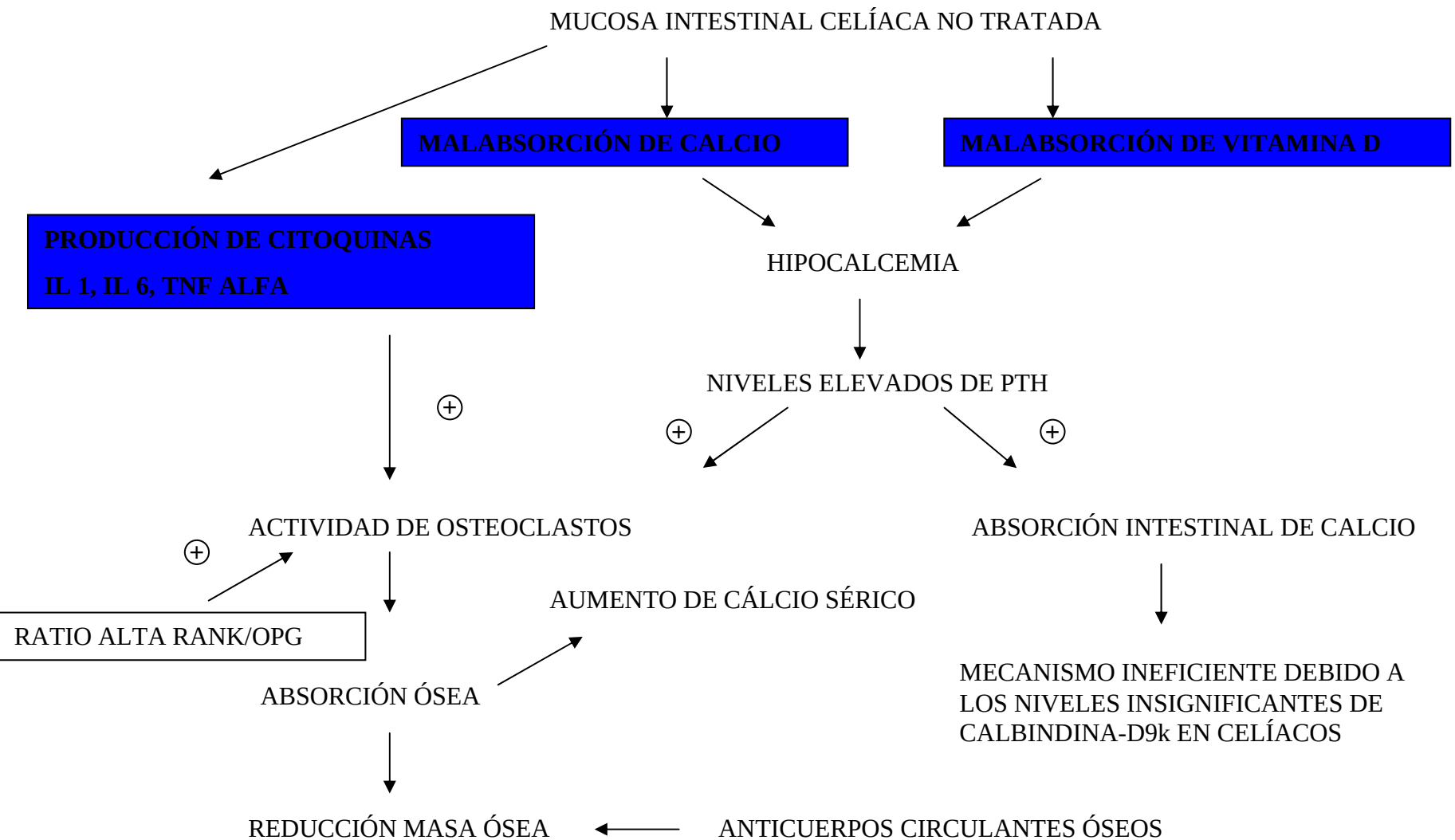
Osteoclastos Osteoblastos

Osteoporosis



Osteoclastos Osteoblastos

ENFERMEDAD CELÍACA Y OSTEOPOROSIS. MECANISMOS



Nutrition reviews 2009; 67:599

CITOCINAS Y MARCADORES EN PACIENTES CON CELIACA

	Serum calcium (mg/dl)	*Urinary calcium (mg/24 h)*	*Calcium/ creatinine (mg/mg)*	*Serum OC (ng/ml)*	*Urine NTx (nMBCE/ mMCr)*	*Serum PTH (pg/ml)*	*Serum 25(OH) vitamin D_3 (ng/ml)*	*Serum 1,25$(OH)_2$ vitamin D_3 (pg/ml)*
On GFD	9.6 ± 0.5	189 ± 15	0.19 ± 0.004	5.7 ± 2.5	49.4 ± 22	40.7 ± 19	18.8 ± 4.6	43.3 ± 16.9
Not on GFD	8.8 ± 0.5	273 ± 19*	0.31 ± 0.005*	9.9 ± 5.7†	66.4 ± 36†	67.2 ± 28†	13.5 ± 6	61.7 ± 20.3†
Normal ranges	8.1–10.4	100–300	0.14–0.4	2–10	25–49	13–64	10–48	18–62

Data are expressed as means ± SD.
* $p < 0.05$ and † $p < 0.005$ not on GFD vs. on GFD.

TABLE 4. SERUM CYTOKINES LEVELS

Cytokines	*Controls (pg/ml)*	*Patients on GFD (pg/ml)*	*Patients not on GFD (pg/ml)*
IL-6*	0.59 ± 0.6	0.38 ± 0.5	1.76 ± 1.2
IL-1β	0.55 ± 0.4	0.74 ± 0.9	0.83 ± 0.8
TNFα	1.10 ± 0.3	1.49 ± 1.1	2.09 ± 1.4
TNFβ	22 ± 20	12.4 ± 10	11.4 ± 8
IL-12†	2.95 ± 1.5	1.32 ± 1.7	0.98 ± 1.2
IL-18‡	256.1 ± 54	216.4 ± 64	318.2 ± 70
RANKL‡	0.38 ± 0.07	0.63 ± 0.7	1.97 ± 0.7
OPG*	1.38 ± 0.3	2.12 ± 0.9	3.05 ± 1.1

Data are expressed as means ± SD.
One-way ANOVA for the three groups: * $p < 0.002$; † $p < 0.03$; ‡ $p < 0.001$.

Taranta A et al. J Bone Miner Res 2004; 19: 1112-1121

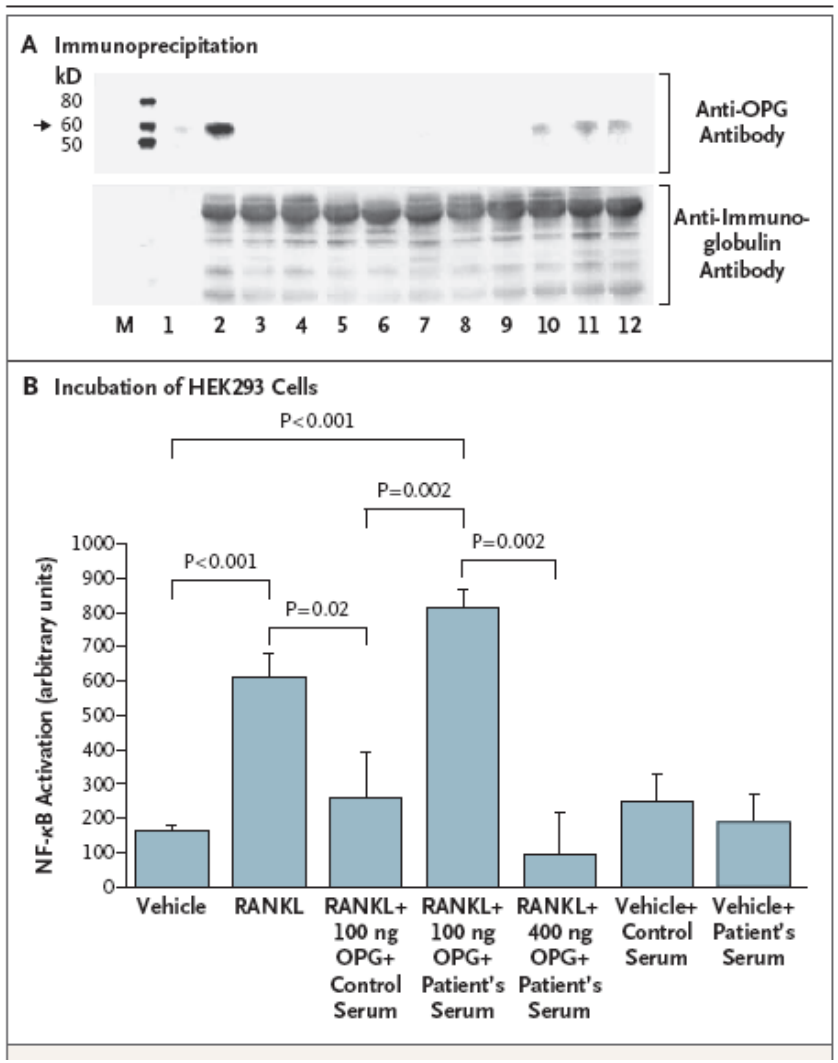
The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Osteoporosis Associated with Neutralizing Autoantibodies against Osteoprotegerin

Philip L. Riches, M.R.C.P., Euan McRorie, F.R.C.P., William D. Fraser, Ph.D., F.R.C.Path., Catherine Determann, B.Med.Sci., Rob van't Hof, Ph.D., and Stuart H. Ralston, M.D.

N ENGL J MED 361;15 NEJM.ORG OCTOBER 8, 2009



Es necesario realizar una densitometría a todos los pacientes con enfermedad celiaca ?

DENSITOMETRIA EN ENFERMEDAD CELIACA

Pacientes de alto riesgo :

- Pacientes no cumplidores
- Pacientes no respondedores
- Tratamiento con corticoides
- Presencia de hipogonadismo
- IMC inferior a 20
- Fractura previa por fragilidad

Compston J. Gut 2003; 52: 459-460

DENSITOMETRIA EN ENFERMEDAD CELIACA

Presencia de 2 o más de los siguientes factores:

- **Síntomas persistentes después de un año con dieta sin gluten o pobre adherencia**
- **Pérdida de peso superior al 10 %**
- **IMC < 20**
- **Edad > 70 años**

BSG Guidelines in Gastroenterology 2007

Increased Prevalence of Celiac Disease and Need for Routine Screening Among Patients With Osteoporosis

William F. Stenson, MD; Rodney Newberry, MD; Robin Lorenz, MD, PhD; Christine Baldus, RN, BSN; Roberto Civitelli, MD

Arch Intern Med. 2005;165:393-399

Table 2. Serologic Testing for Celiac Disease in the Osteoporotic and Nonosteoporotic Groups

Serologic Test*			Osteoporotic Group (n = 266)			Nonosteoporotic Group (n = 574)		
Antigliadin	TTG	EMA	No. (%)	No. With Biopsy Performed	No. With Positive Biopsy	No. (%)	No. With Biopsy Performed	No. With Positive Biopsy
–	–	–	201 (75.6)	0	0	444 (77.4)	0	0
+	–	–	53 (19.9)	0	0	124 (21.6)	0	0
+	+	–	1 (0.4)	1	0	2 (0.3)	2	0
–	+	–	1 (0.4)	1	0	2 (0.3)	0	0
–	–	+	1 (0.4)	1	0	0	0	0
+	–	+	0	0	0	1 (0.2)	1	0
+	+	+	9 (3.4)†	9	9	1 (0.2)	1	1

Abbreviations: EMA, antiendomysial antibody; TTG, antitissue transglutaminase.
*Minus sign indicates negative test result; plus sign, positive test result. Antigliadin is IgG or IgA.
†$P<.001$ compared with the nonosteoporotic group.

Risk Factors for Prediction of Inadequate Response to Antiresorptives.
Diaz A et al. ASBMR 2010.Toronto. USA
177 mujeres con osteoporosis.
Todas tenían Acs antitrasglutaminasa negativos

Cuál sería las medidas terapéuticas más adecuadas en estos pacientes ?

TRATAMIENTO

- **Dieta sin gluten**
- **Medidas saludables**:

1. **Ejercicio frente a resistencia**
2. **Nutrición adecuada**
3. **No fumar**
4. **Evitar exceso alcohol**
5. **Ingesta diaria de 1000-1200 mg/ dia de calcio**

TRATAMIENTO

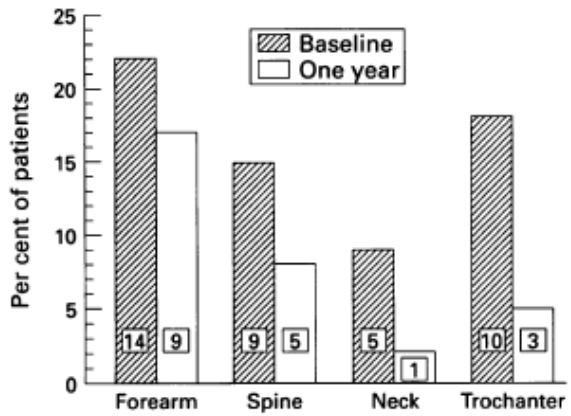


Figure 2: Per cent of patients with severe osteopenia (Z score <-2) before and after one year of a gluten free diet. Numbers of patients within bars.

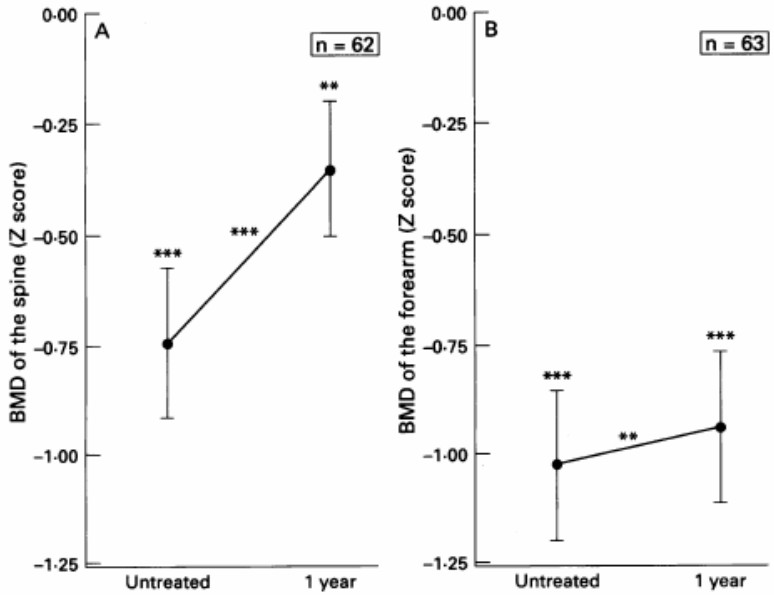


*Figure 4: Change in bone mineral density (Z score, mean and SEM) of the spine (A) and forearm (B) during one year of dietary treatment. **p<0·01; ***p<0·001.*

Valdimarsson T et al. Gut 1996; 38: 322-327

Increased Prevalence of Celiac Disease and Need for Routine Screening Among Patients With Osteoporosis

William F. Stenson, MD; Rodney Newberry, MD; Robin Lorenz, MD, PhD; Christine Baldus, RN, BSN; Roberto Civitelli, MD

Arch Intern Med. 2005;165:393-399

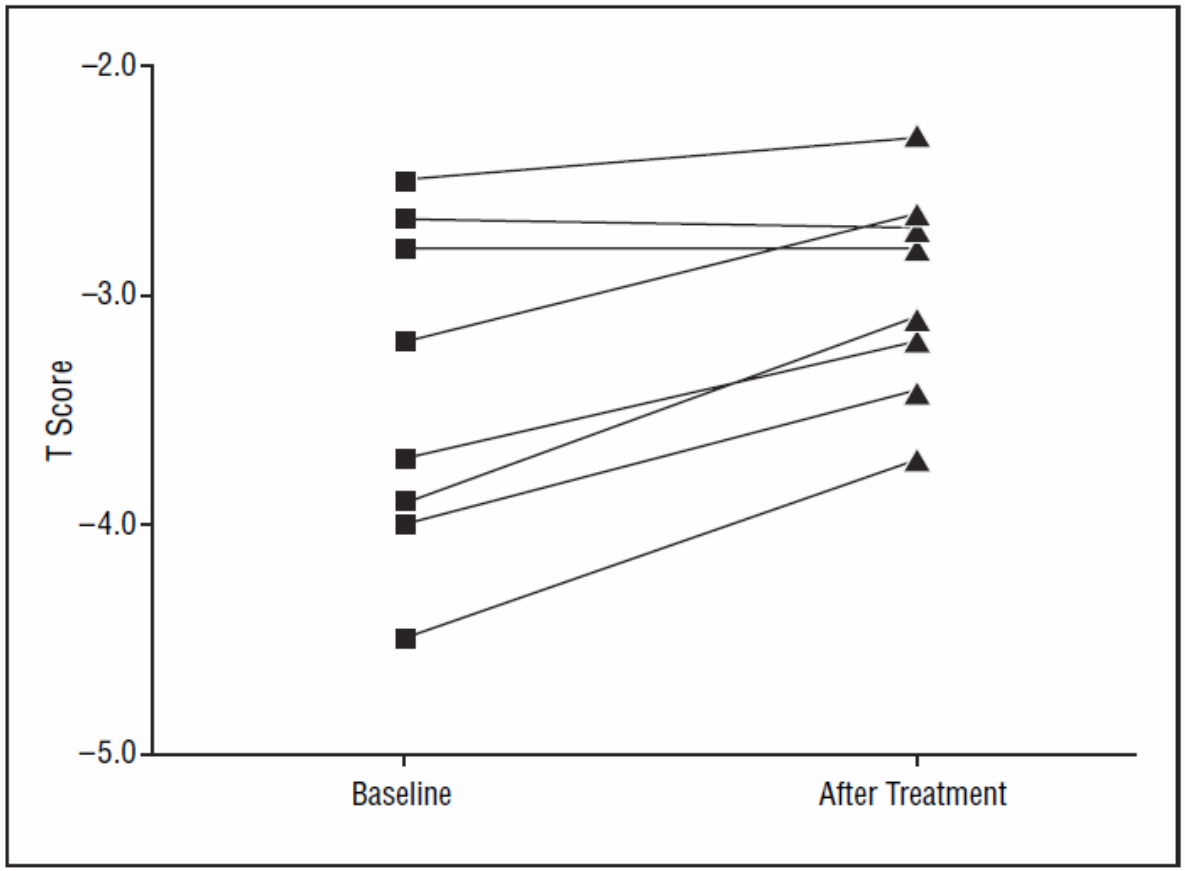


Figure 2. T scores at baseline and after 1 year of a gluten-free diet in the 8 patients with celiac disease and osteoporosis who completed a year of therapy. Posttreatment T scores are significantly higher than pretreatment T scores by paired samples *t* test (P=.02).

INDICACIONES TRATAMIENTO

- **Fractura por fragilidad**
- **Masa ósea baja con factores de riesgo de fractura riesgo de fractura**

Posmenopáusica
Inducida por glucocorticoides
Del varón

Osteoporosis posmenopáusica

≥ 2 fracturas

Mayoría de enfermas

< 65 años, sin fx,
OP sólo en columna

Raloxifeno
(o estándar)

Alendronato, risedronato
(estándar)
Zolendronato

Respuesta
inadecuada

Otra preferencia
Mala tolerancia

TRPT
(o estándar)

Estroncio
Ibandronato
Raloxifeno, Etidronato, Calcitonina

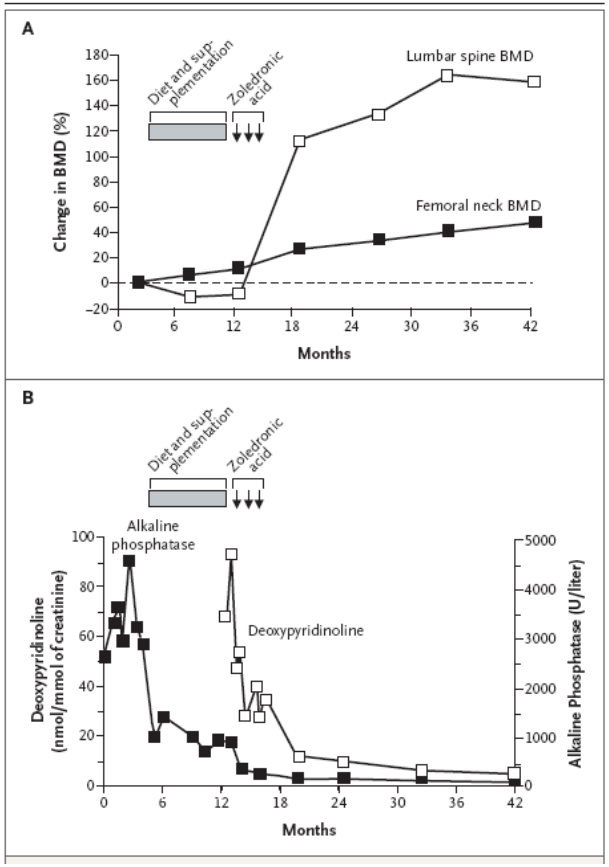
The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Osteoporosis Associated with Neutralizing Autoantibodies against Osteoprotegerin

Philip L. Riches, M.R.C.P., Euan McRorie, F.R.C.P.,
William D. Fraser, Ph.D., F.R.C.Path., Catherine Determann, B.Med.Sci.,
Rob van't Hof, Ph.D., and Stuart H. Ralston, M.D.

N ENGL J MED 361;15 NEJM.ORG OCTOBER 8, 2009



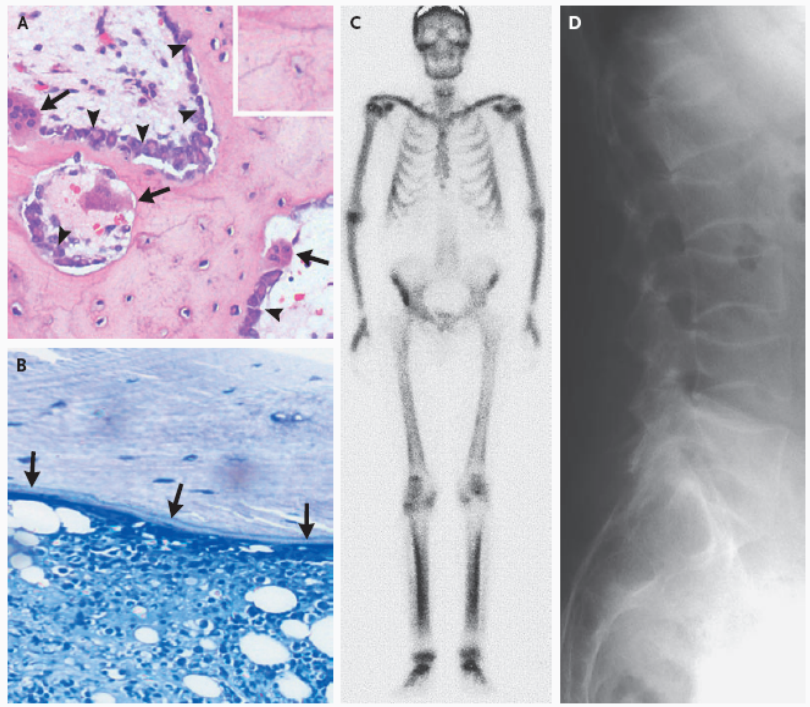


Figure 1. Results of Transiliac Bone Biopsy and Bone Radiography in the Patient.

A photomicrograph of the bone-biopsy specimen (Panel A, hematoxylin and eosin) shows an increase in the numbers of osteoclasts (arrows) and osteoblasts (arrowheads). Woven bone is present throughout the biopsy specimen, as evidenced by the irregular cement lines (higher-power view shown in inset). Staining of the biopsy specimen with toluidine blue (Panel B) shows extensive osteoid coverage, but the seams were of normal thickness (arrows). Radionuclide bone scanning (Panel C) showed a generalized increase in tracer uptake but no focal lesions. Radiography of the lumbar spine (Panel D) revealed osteopenia and multiple vertebral compression fractures.


MUCHAS GRACIAS