Turk J Gastroenterol 2010; 21 (1): 100-106

TURKISH INFLAMMATORY BOWEL DISEASE SOCIETY RECOMMENDATIONS ON SELECTED TOPICS OF CROHN'S DISEASE

TÜRK İNFLAMATUVAR BARSAK HASTALIKLARI DERNEĞİNİN CROHN HASTALIĞI İLE İLGİLİ SEÇİLMİŞ KONULARDA ÖNERİLERİ

When and how frequently DEXA should be performed for the diagnosis and follow-up of osteoporosis in Crohn's disease?

Crohn hastalığında görülen osteoporozun tanı ve takibinde DEXA ne zaman ve ne sıklıkla kullanılmalıdır?

Key words: Crohn's disease, osteoporosis, DEXA, diagnosis, follow up

Anahtar kelimeler: Crohn hastalığı, osteoporoz, DEXA, tanı, takip

Gökhan KABAÇAM[1], Ahmet TEZEL[2]

Department of [1]Gastroenterology, Ankara University, School of Medicine, Ankara

Department of [2]Gastroenterology, Trakya University, School of Medicine, Edirne

INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory disease, which causes serious morbidities due to the systemic effects besides gastrointestinal effects. As in the other chronic inflammatory diseases, bone metabolism is highly affected in CD, as well. It was reported that the prevalence of osteoporosis and osteomalacia range between 3% and 57%, depending on the methodology, localization of the examined bone and the age (1). The etiology of osteoporosis in CD is multifactorial, and some causes like age, corticosteroid usage, malnutrition, inflammatory activation, Ca and vitamin D malabsorption and immobility, can be listed (2).

The clinicians consider osteoporosis as a pathology which has serious consequences. Osteoporosis particularly causes additional morbidities such as increase in the risk for fractures of femoral head and vertebra, deterioration of quality of life and increase in the health care costs. Therefore, it is a pathology that precautions should be taken, and that early diagnosis, treatment and monitoring is necessary. Bone mineral density (BMD) measurement is the most important tool for the diagnosis of osteoporosis as well as the determination of in vitro skeletal strength and fracture risk. Dual Energy X-Ray Absorbtiometry (DEXA), quantitative computed tomography (QCT), radiographic absorbtiometry and ultrasonography can be used for the measurement of BMD (3). DEXA is the most commonly used and accurate method for this purpose (3). BMD of the patients is defined as the standard deviation from the average BMD values of either the young adults (T score) or the same age group (Z score) (4). Osteoporosis is the term used for the BMD measurements of T-score ≤2.5.

In the special circumstances section of CD diagnosis and treatment guideline of European Crohn's and Colitis Organization (ECCO) in 2006, metabolic bone diseases were discussed in the statements numbered 13C and 13D. Accordingly: Osteoporosis and osteopenia are defined in 13C, and DEXA is suggested for BMD measurements. The therapeutic agents have been explained in 13D. No certain comment was made about the time and the frequ-

Address for correspondence: Ahmet TEZEL
Department of Gastroenterology, Trakya University, Faculty of Medicine, Edirne, Turkey
Phone: + 90 284 236 11 66
E-mail: atezel@trakya.edu.tr

doi: 10.4318/tjg.2010.0065

ency to perform DEXA in CD monitoring (5). In the framework of ECCO, we discussed when and how frequently BMD should be measured for the diagnosis and monitoring of osteoporosis in CD.

METHODS

We used 3e systematic literature search in order to find the answer to the question which is not elucidated in ECCO 2006 guidelines; "When and how frequently DEXA should be performed for the diagnosis and follow-up of osteoporosis in Crohn's disease?"

Literature review was performed only in Pubmed database. Furthermore, additional studies were found with literature reference review. Key words were "Inflammatory Bowel Diseases"[Mesh] AND "osteoporosis" [Mesh]. Only the English literature performed in adult patients older than 18 years old were taken into consideration. These key words were used because significant number of CD studies were within the titles of "Inflammatory Bowel Disease (IBD)" together with "Ulcerative Colitis", and data about CD in these literatures were evaluated.

RESULTS

We have found 55 publishes to evaluate, which suit our scenario in the literature review (Table 1).

Prevalence of osteoporosis in Crohn's Disease

23 published studies were found related with this subject (Table 2) (6 -28). According to these results, prevalence of osteoporosis in CD was found in the range of 5.1% to 37% and the prevalence of osteopenia was found in the range of 18% to 65%. Given that the patients were under 50 years old, and the recommendations indicate the Z scores to be more significant in the diagnosis of OP in this age group, Z scores in most of the studies, but T scores in some of them were demonstrated. Accordingly;

- Mean Vertebral Z score: between -0.09 and -1.60
- Mean Vertebral T score: between -0.33 and -1.98

Table 1. Types of the trials evaluated

The type of the trials	Number
Prospective trials	28
Case-control trials	22
Retrospective trials	5

Table 2. Outcomes of the studies regarding the prevalence of osteoporosis and osteopenia in Crohn's disease

Author	Country	The Type of the Study*	N	Gender(M/F)	Age (Mean)	% Oporosis	% Openia
S. Ardızzone (6)	Italy	1	51	30 / 21	38,7	37	55
Sahli Héla (7)	Tunisia	1	56	22/34	32	35,7	23,2
KV Haderslev (8)	Denmark	1	35		47,6	33,30	52,00
J Klaus (9)	Germany	1	111	0/111	35	28,8	49,6
X. Roblın (10)	France	1	92	49/43	36,6	28	65
RA van Hogezand (11)	Holland	2	146	85/61	43,5	26	45
Claudia Schulte (12)	Germany	1	61	29/32	37,6	20	
Pascal Frei (13)	Switzerland	2	55	25/30	39	18	45
Naomi Lee (14)	Australia	2	304	64/37	42,9	18	45
R. J. Robınson (15)	UK	1	48	0/48	45,4	17	29
Naomi Lee (16)	Australia	2	60	38/22	43,7	17,00	32
C. L. Noble (17)	UK	3	286	179/107	31,9	16	18
K. L. E. Dear (18)	UK	3	95	95/0		15	45
Claudia Schulte (19)	Germany	2	104		38	15	36
E. J. Schoon (20)	Holland	1	26	13/13	38	15,00	31,00
Sarah A Bartram (21)	UK	2	258	166/92	44,5	13,6	29,8
Schoon EJ (22)	Holland	2	119	82/37	42	13	45
J. Jahnsen (23)	Norway	1	60	36/24	36	13	23
JS. Siffledeen (24)	Canada	1	242	134/108	38,7	12,9	50
Aida Habtezion (25)	Canada	2	168	95/73	33	11	45
R. J. Robınson (26)	UK	1	117	69/47	40,6	11	29
G. Haugeberg (27)	Norway	2	55	27/28	38,5	9,1	35,50
M. Zali (28)	Iran	2	39	21/18	35,1	5,1	38,5

* 1: Prospective; 2: Case – control; 3: Retrospective trials

- Mean femoral Z score: between -1.40 to + 0.03
- Mean femoral T score: between -1.80 to + 1.03

The prevalence of osteoporotic fractures in Crohn's Disease

Seven studies were detected, evaluating the prevalence of fracture which is considered as the major clinical end point of osteoporosis (Table 3) (11, 21, 23, 25, 26, 29, 30). With reference to this, osteoporotic fracture prevalence rate was reported in the range of 0% to 27%. Although multiple fractures were present in some patients, it was reported that these patients could remain asymptomatic, and screening of the patients through radiological procedures were recommended in terms of fracture development.

In a population based screening research, in which CD prevalence is found to be 156/100,000 in England, it was detected that the femoral fracture risk was increased 1.86 folds (95% confidence interval: 1.08 to 3.21) and this association existed after the adjustments for steroid usage (31). The fracture risk is higher in CD than in Ulcerative Colitis. It has been reported that only 13% of the patients with fracture risk were receiving fracture prevention treatment. It was noted in another important study that the prevalence of fracture in women was increasing gradually after the age of 50, and this prevalence showed more increase in men. It was determined that the fracture frequency was independent from BMD and T scores, and 55% of the patients with fractures had normal T scores. In the same study with multivariate analysis, no factors related with vertebral fractures were defined (29).

In a study, Klaus et al (30) evaluated the fracture frequency according to the age groups and they found the age-dependent increase of the frequency with rates; <21y: 20%; 21 – 30y: 22.5%; 31 - 40y, 18%; 41 - 50y: 18.7%; 51 - 60y : 26.3%; 61 - 70y: 50%. The frequency is 28.9% in cases with osteoporosis and it decreases to 18.9% in osteopenic cases. It is remarkable that, only 4 among 34 fracture cases are symptomatic while others are asymptomatic.

Risk factors for osteoporosis in Crohn's Disease

Appropriate raw data for clustered analyze from seven studies were collected and "Odd's Ratio" of (7, 11, 14, 21, 24- 26) categorical risk factors were calculated (Table 4). The results showed that male gender (OR = 1.55), current corticosteroid usage (OR = 1.39) and previous corticosteroid usage (OR = 2.15) are factors for the increased risk.

Table 3. The prevalence of osteoporotic fractures in Crohn's disease

Author	Type of the trials*	N	Age (Mean)	The prevalence of Fx†
R. A. van Hogezand (11)	2	146	43,5	vertebral fx: 6%, non-vertebral fx: 12 %
R. J. ROBINSON (26)	1	117	40,6	11 Fx in 8 (6,8%) patients
R. W. STOCKBRÜGGER (29)	1	271		56 Fx in 38 (14,2%) patients
Sarah A Bartram (21)	2	258	44,5	10,80 %
J Klaus (30)	2	156		One or more fx 21,8%
J. Jahnsen (23)	1	60	36	27%
Aida Habtezion (25)	2	168	33	0

* 1: Prospective; 2: Case – control; 3: Retrospective trials † Fx: Fracture

Table 4. Cumulative analyzed trials and the related parameters

Author	The type of the trials *	Number of patients	Gender (M/F)	Age (Mean)	% OP	SI resec	% Smoking	% Currently-CS	% Received-CS
SA Bartram (21)	2	258	166/92	44,5	13,6	52,3	32,2	29,8	58,9
JS Siffledeen (24)	1	242	134/108	38,7	12,9		36,9		
A Habtezion (25)	2	168	95/73	33	11		55		76
RA van Hogezand (11)	2	146	85/61	43,5	26	66		43	86
R J Robinson (26)	1	117	69/47	40,6	11	65	40,2	22	86
Naomi Lee (14)	2	304	64/37	42,9	18	66			
Sahli Héla (7)	1	56	22/34	32	35,7	28,6			64,2

* 1: Prospective; 2: Case – control; 3: Retrospective trials SI resec: Small intestinal resection Currently-CS: Currently receiving corticosteroid Received-CS: Previously received corticosteroid

Table 5. The risk factors for the development of osteoporosis in Crohn's disease

Author	Risk Factors
S. Ardızzone (6)	Duration of the disease, age
Sarah A Bartram (21)	Low BMI, CS , duration of the disease
Pascal Frei (13)	Resection of SI, CS (duration and dosage), usage of AZA, low BMI, young age at diagnosis
Jesse S. Siffledeen (24)	Male: CS, Vit B12; Female: Low BMI, platelet, age, CS
Aida Habtezion (25)	Age, low BMI, cumulative dosage of CS (10gr vs 6,5gr)
K. L. E. Dear (32)	CS dosage>5gr
AP de Silva (33)	Age, menopause, CS
J -E Compston (34)	Low BMI, CS
Mohammadreza Zali (28)	Age, CS, Low BMI, smoking, Vit D and Phosphorus
R. A. van Hogezand (11)	Resection of SI
Tomoyuki Tsujikawa (35)	Risk is prominent when cumulative dosage of CS > 20gr
R. W. Stockbrügger (29)	CS
E. Tsironi (36)	Age ≥55, cumulative dosage of prednisolone ≥5gr
J. A. Silvennoinen (37)	Smoking in women
J A Silvennoinen (38)	Low BMI, cumulative CS (>5gr)
Claudia Schulte (19)	Duration of the disease, frequent relapses, CS
C. L. Noble (17)	BMI (<18,5), smoking
R. J. Robýnson (26, 39)	Body weight, gender, current usage of CS, the proportion of body fat, CS, involvement (jejunal, ileal)
X. Roblin (10)	Hyperhomocysteinemia, ileal CH, duration of the disease >5y
EJ Schoon (22)	Diagnosis at young age (<19y)
Naomi Lee (14, 40)	Haplotype of TNF, Low BMI, decrease in muscle mass
J Klaus (9)	Cumulative dosage of CS > 10gr, age, BMI<20
J. Jahnsen (23, 41 – 42)	CS, low BMI, CRP
Sahli Héla (7)	BMI(<18)
EJ Schoon (43)	Age, low BMI, duration of the disease
G. Haugeberg (27)	Female, CS, age, body weight
J. H. Tobias (44)	Involvement of SI, body weight, reduced Ca intake in diet

BMI: Body Mass Index CS: Corticosteroid AZA: Azathiopurine SI: Small Intestine TNF: Tumor Necrosis Factor CRP: C – Reactive Protein

Table 6. The annual change rate of bone mass density in Crohn's disease and the outcomes related with the effecting factors

Author	The type of the trial *	Number of patients	% Loss rate of bone
D Clements (45)	1	22	With Hormone Replacement Therapy and Calcium, all IBD: BMD: % + 2,6/y
A Habtezion (25)	2	168	Femoral: % -0,64 ± 0,28 / y, p=0,03 vertebral: +0,01 / y, p=0,1
R J Motley (50)	2	75	%3 / year, this decrease is inversely proportional with BMI, and increasing with CS and malnutrition
D. Clements (51)	1	32	Overall IBD: Female: % - 0,74 / y, post-menopause: % -1,16/y, Male: % - 0,07/y
M. Staun (52)	3	108	Intact vertebral column: -0,85 / y, femoral:-2,2 / y; Resected vertebral column: -0,13 / y, femoral: -1,21 / y Femoral Z: -2,2 % (resected), -1,21 % (unresected)
C Schulte (12)	1	61	Ver: +0,8 ± 2,9 / y; Fem: +0,12 ± 5,3 / y
J. Jahnsen (23)	1	60	0-1 year: 0,8% (Range: -0,8-2,4); 0-2 year: 1,9% (Range: -0,5-4,3)
KV Haderslev (8)	1	35	Vertebral: 0,2% / y, Femoral: 0,65% / y
Roux C (53)	1	14	- 3,1% ± 4,9% / year; Those who received CS: - 6,2% ± 7,0% Those who did not receive CS: % 0,9 ± % 3,9
Dinca M (54)	1	54	- 0,31 ± 0,49% / 21 months
Bernstein M (55)	1	46	vertebral: 2,4 ± 0,7% / y increased, femoral: 2,8 ± 1,2% / y increased
D.J. De Jong (56)	3	29	vertebral: 0,12 ± 2,9% / y; femoral: 0,21 ± 2,8% /y

* 1: Prospective; 2: Case – control; 3: Retrospective trials

According to the studies whose raw data could not be obtained, the risk factors of osteoporosis were demonstrated in Table 5 (6, 7, 9 - 11, 13, 14, 17, 19, 21 - 25, 28, 29, 32 - 45).

In brief, major risk factors are

- Corticosteroid usage (significant risk with more than 5gr cumulative dose)
- Low body mass index (<20kg/m2); it is important as being an indicator of malnutrition.
- Age; increased risk is reported in the elderly and the post menopausal women

However, protective factors are the hormone replacement therapy, the usage of budesonide instead of prednisolone, remission period over 3 years, Azatiopurin (CS-sparing effect) as it provides corticosteroid reduction, body fat gain, increase of dry weight and muscle mass and infliximab treatment (16, 39, 45 - 50).

Annual bone density change rates in Crohn's Disease

Although the studies are limited and heterogeneous, the largest detected annual change was 6.2% decrease in patients receiving steroids. In the publications, there are statements, indicating no change, as well as decrease in the first 2 months followed by normalization in the 8th month (44). In the first year, usually a rapid decrease is observed. Bone density change rate is found to be higher in patients with low baseline levels (52). Determined mean annual changes in BMD are between 0% to 3% (8, 12, 23, 45, 50 - 56). The change rate of annual bone density in Crohn's disease is demonstrated in Table 6.

Some technical details of DEXA measurement

The most important issue related to DEXA is the variation of measurements even with the same device. Therefore, the follow-up of patients is always recommended to be performed with the same device. In order to avoid erroneous measurement, at least 3-5% change in the vertebral and 4-6% change in the femoral region is required (57).

CONCLUSION

Either in the studies related with the diagnosis and follow-up of osteoporosis or in the reviews of these studies, it is recommended that screening is necessary in all of the post-menopausal women, men over the age of 55, the patients with fragility fracture and those receiving steroids. Besides, there are recommendations for screening of the patients who have two of the three following risk factors (2-4, 58). These risk factors are;

- active disease
- weight loss, more than 10%
- mass index <20 kg/m2

Based on these results, national recommendations are seen in the box.

Recommendation:

BMD measurement via DEXA is necessary in the course of the diagnosis for all of the patients ***(EL 2a, RG B).***

Annual follow-up with DEXA in the patients currently receiving corticosteroid treatment (administered/suggested to administer more than 3 months) ***(EL 2a, RG B.)***

For other patients, 2 to 3 yearly follow-up is necessary according to their risk factors ***(EL 5, RG D).***

REFERENCES

1. Tauseef A, Lam D, Bronze MS, et al. Osteoporosis in Inflammatory Bowel Disease. Am J Med 2009; 122: 599-604.
2. Tilg H, Moschen AR, Kaser A, et al. Gut, Inflammation and Osteoporosis : Basic and Clinical Concepts. Gut 2008; 57: 684-9.
3. Lichtenstein G, Sands BE, Pazianas M. Prevention and Treatment of Osteoporosis in Inflammatory Bowel Disease. Inflamm Bowel Dis 2006; 12: 797-813.
4. Lewis NR, Scott BB. Guidelines for Osteoporosis in Inflammatory Bowel Disease and Coeliac Disease. http://www.bsg.org.uk, June 2007
5. Caprilli R, Gassull MA, Escher JC, et al. European Evidence Based Consensus on the Diagnosis and Management of Crohn's Disease : Special Situations. Gut 2006; 55 (Suppl I): i36-i58.
6. Ardizzone S, Bollani S, Bettica P, et al. Altered bone metabolism in inflammatory bowel disease: there is a difference between Crohn's's disease and ulcerative colitis. Journal of Internal Medicine 2000; 247: 63-70.
7. Héla S, Nihel M, Faten L, et al. Osteoporosis and Crohn's disease. Joint Bone Spine 2005; 72: 403-7.

8. Haderslev KV, Tjellesen L, Haderslev PH, Staun M. Assessment of the Longitudinal Changes in Bone Mineral Density in Patients Receiving Home Parenteral Nutrition. J Parenter Enteral Nutr 2004; 28: 289-94.
9. Klaus J, Reinshagen M, Adler G, et al. Bones and Crohn's's: Estradiol deficiency in men with Crohn's's disease is not associated with reduced bone mineral density. BMC Gastroenterology 2008; 8: 48-57.
10. Roblin X, Phelip JM, Genevois M, et al. Hyperhomocysteinaemia is associated with osteoporosis in patients with Crohn's disease Aliment Pharmacol Ther 2007; 25: 797-804.
11. Van Hogezand RA, Bänffer D, Zwinderman AH, et al. Ileum resection is the most predictive factor for osteoporosis in patients with Crohn's disease. Osteoporos Int 2006; 17: 535-42.
12. Schulte C, Dignass AU, Mann K, Goebell H. Bone Loss in Patients with Inflammatory Bowel Disease Is Less Than Expected: A Follow-up Study. Scand J Gastroenterol 1999; 34: 696-702.
13. Frei P, Fried M, Hungerbühler V, et al. Analysis of Risk Factors for Low Bone Mineral Density in Inflammatory Bowel Disease. Digestion 2006; 73: 40-6.
14. Lee N, Fowler E, Mason S, et al. Tumor necrosis factor-a haplotype is strongly associated with bone mineral density in patients with Crohn's disease. Journal of Gastroenterology and Hepatology 2007; 22: 913-9.
15. Robinson RJ, Iqbal SJ, Abrams K, et al. Increased bone resorption in patients with Crohn's's disease. Aliment Pharmacol Ther 1998; 12: 699-705.
16. Lee N, Radford-Smith GL, Forwood M, et al. Body composition and muscle strength as predictors of bone mineral density in Crohn's disease. J Bone Miner Metab 2009; 27: 456-63.
17. Noble C, Mccullough J, Ho W, et al. Low body mass not vitamin D receptor polymorphisms predict osteoporosis in patients with inflammatory bowel disease. Aliment Pharmacol Ther 2008; 27: 588-96.
18. Dear KLE, Compston JE, Hunter JO. Treatments for Crohn's's disease that minimise steroid doses are associated with a reduced risk of osteoporosis. Clinical Nutrition 2001; 20: 541-6.
19. Schulte C, Dignass AU, Mann K, Goebell H. Reduced Bone Mineral Density and Unbalanced Bone Metabolism in Patients with Inflammatory Bowel Disease. Inflamm Bowel Dis 1998; 4: 268-75.
20. Schoon EJ, Geerling BG, van Dooren IMA, et al. Abnormal bone turnover in long-standing Crohn's's disease in remission. Aliment Pharmacol Ther 2001; 15: 783-92.
21. Bartram SA, Peaston RT, Rawlings DJ, et al. Mutifactorial analysis of risk factors for reduced bone mineral density in patients with Crohn's disease. World J Gastroenterol 2006; 12: 5680-6.
22. Schoon EJ, van Nunen AB, Wouters RSME, et al. Osteopenia and Osteoporosis in Crohn's Disease: Prevalence in a Dutch Population – based Cohort. Scand J Gastroenterol 2000; Suppl. (232): 43-7.
23. Jahnsen J, Falch JA, Mowinckel P, Aadland E. Bone Mineral Density in Patients with Inflammatory Bowel Disease: A Population-Based Prospective Two-Year Follow-Up Study. Scand J Gastroenterol 2004; 39: 145-53.
24. Siffledeen JS, Fedorak RN, Siminoski K, et al. Bones and Crohn's Risk Factors Associated with Low Bone Mineral Density in Patients with Crohn's Disease. Inflamm Bowel Dis 2004; 10: 220-8.
25. Habtezion A, Silverberg MS, Parkes R, et al. Risk Factors for Low Bone Density in Crohn's Disease. Inflamm Bowel Dis, 2002; 8: 87-92.
26. Robinson RJ, Al Azzawi F, Iqbal SJ, et al. Osteoporosis and Determinants of Bone Density in Patients with Crohn's Disease. Digestive Diseases and Sciences 1998; 43: 2500-6.
27. Haugeberg G, Vetvik K, Stallemo A, et al. Bone Density Reduction in Patients with Crohn's Disease and Associations with Demographic and Disease Variables: Cross-sectional Data from a Population-based Study. Scand J Gastroenterol 2001; 36: 759-65.
28. Zali M, Bahari A, Firouzi F, et al. Bone mineral density in Iranian patients with inflammatory bowel disease. Int J Colorectal Dis 2006; 21: 758-66.
29. Stockbrügger RW, Schoon EJ, Bollani S, et al (On Behalf Of The Matrix Study Group). Discordance between the degree of osteopenia and the prevalence of spontaneous vertebral fractures in Crohn's disease. Aliment Pharmacol Ther 2002; 16: 1519-27.
30. Klaus J, Armbrecht G, Steinkamp M, et al. High prevalence of osteoporotic vertebral fractures in patients with Crohn's disease. Gut 2002; 51: 654-8.
31. van Staa TP, Cooper C, Brusse LS, et al. Inflammatory Bowel Disease and the Risk of Fracture. Gastroenterology 2003; 125: 1591-7.
32. Dear KLE, Compston JE, Hunter JO. Treatments for Crohn's's disease that minimise steroid doses are associated with a reduced risk of osteoporosis. Clinical Nutrition 2001; 20: 541-6.
33. de Silva AP, Karunanayake AL, Dissanayaka TGI, et al. Osteoporosis in adult Sri Lankan inflammatory bowel disease patients. World J Gastroenterol 2009; 15: 3528-31.
34. Compston JE, Judd D, Crawley EO, et al. Osteoporosis in patients with inflammatory bowel diseas. Gut 1987; 28: 410-5.
35. Tsujikawa T, Andoh A, Inatomi O, et al. Alendronate Improves Low Bone Mineral Density Induced by Steroid Therapy in Crohn's Disease.Inter Med 2009; 48: 933-7.
36. Tsironi E, Hadjidakis D, Mallas E, et al. Comparison of T- and Z-score in identifying risk factors of osteoporosis in inflammatory bowel disease patients. J Musculoskelet Neuronal Interact 2008; 8: 79-84.
37. Lehtola JA, Niemelä JK, Niemelä SE. Smoking Is a Risk Factor for Osteoporosis in Women with Inflammatory Bowel Disease. Scandinavian Journal of Gastroenterology 1996; 31: 367-71.
38. Silvennoinen JA, Karttunen TJ, Niemela SE, et al.A controlled study of bone mineral density in patients with inflammatory bowel disease. Gut 1995; 37: 71-6.
39. Robinson RJ, Iqbal SJ, Al-Azzawi F, et al. Sex hormone status and bone metabolism in men with Crohn's's disease. Aliment Pharmacol Ther 1998; 12: 21-5.
40. Lee N, Radford-Smith GL, Forwood M, et al. Body composition and muscle strength as predictors of bone mineral density in Crohn's disease. J Bone Miner Metab 2009; 27: 456-63.
41. Jahnsen J, Falch JA, Mowinckel P, Aadland E. Vitamin D Status, Parathyroid Hormone and Bone Mineral Density in Patients with Inflammatory Bowel Disease. Scand J Gastroenterol 2002; 37: 192-9.
42. Jahnsen J, Falch JA, Aadland E, Mowinckel P. Bone mineral density is reduced in patients with Crohn's's disease but not in patients with ulcerative colitis: a population based study. Gut 1997; 40: 313-9.
43. Schoon EJ, Blok BM, Geerling BJ, et al. Bone Mineral Density in Patients with Recently Diagnosed Inflammatory Bowel Disease. Gastroenterology 2000; 119: 1203-8.
44. Tobias JH, Sasi MR, Greenwood R, Probert CSJ. Rapid hip bone loss in active Crohn's disease patients receiving short-term corticosteroid therapy. Aliment Pharmacol Ther 2004; 20: 951-7.

45. Clements D, Compston JE, Evans WD, Rhodes J. Hormone replacement therapy prevents bone loss in patients with inflammatory bowel disease. Gut 1993; 34: 1543-6.
46. Schoon EJ, Bollani S, Mills PR, et al (On Behalf Of The Matrix Study Group). Bone Mineral Density in Relation to Efficacy and Side Effects of Budesonide and Prednisolone in Crohn's Disease. Clinical Gastroenterology And Hepatology 2005; 3: 113-21.
47. Reffitt DM, Meenan J, Sanderson JD, et al. Bone density improves with disease remission in patients with inflammatory bowel disease. European Journal of Gastroenterology & Hepatology 2003; 15:1267-73.
48. Mauro M, Radovic V, Armstrong D. Improvement of lumbar bone mass after infliximab therapy in Crohn's disease patients. Can J Gastroenterol 2007; 21: 637-42.
49. Bernstein CN, Leslie WD, Taback SP. Bone Density in a Population-Based Cohort of Premenopausal Adult Women with Early Onset Inflammatory Bowel Disease. Am J Gastroenterol 2003; 98: 1094-100.
50. Motley RJ, Crawley EO, C Evans, et al. Increased rate of spinal trabecular bone loss in patients with inflammatory bowel disease. Gut 1988; 29: 1332-6.
51. Clements D, Motley RJ, Evans WD, et al. Longitudinal Study of Cortical Bone Loss in Patients with Inflammatory Bowel Disease. Scandinavian Journal of Gastroenterology 1992; 27: 1055-60.
52. Staun M, Tjellesen L, Thale M, et al. Bone Mineral Content in Patients with Crohn's's Disease: A Longitudinal Study in Patients with Bowel Resections. Scandinavian Journal of Gastroenterology 1997; 32: 226-32.
53. Roux C, Abitbol V, Chaussade S, et al. Bone loss in patients with inflammatory bowel disease: a prospective study. Osteoporos Int. 1995; 5: 156-60.
54. Dinca M, Fries W, Luisetto G, et al. Evolution of osteopenia in inflammatory bowel disease. Am J Gastroenterol. 1999; 94: 1292-7.
55. Bernstein M, Irwin S, Greenberg GR. Maintenance infliximab treatment is associated with improved bone mineral density in Crohn's's disease. Am J Gastroenterol 2005; 100: 2031-5.
56. De Jong DJ, Mannaerts L, Van Rossum LGM, et al . Longitudinal Study of Bone Mineral Density in Patients with Crohn's Disease. Digestive Diseases and Sciences 2003; 48: 1355-9.
57. Lewiecki EM, Baim S, Binkley N, et al. Report of the International Society for Clinical Densitometry 2007 Adult Position Development Conference and Official Positions. Southern Medical Journal 2008; 101: 735-9.
58. Bernstein CN, Leslie WD, Leboff MS. AGA Technical Review on Osteoporosis in Gastrointestinal diseases. Gastroenterology 2003; 124: 795-841.