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Original Article

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Comparison of T- and Z-score in identifying risk factors of osteoporosis in inflammatory bowel disease patients

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Abstract

Objective: Most studies have shown contradictory results regarding predictive factors of osteoporosis in inflammatory bowel disease (IBD). Since in these studies either T- or Z-scores has been used, our aim was to compare T- and Z-score in identifying risk factors of osteoporosis in IBD patients. **Materials and methods:** Bone density was measured by dual X-ray absorptiometry (DXA) at L2-L4 of the spine and femoral neck in 122 patients. Twenty-two clinical parameters were recorded prior to DXA and evaluated by univariate and multivariate analysis. **Results:** On multivariate analysis, cumulative steroid dose was a predictive factor of femoral neck T-score ($p<0.001$) and Z-score ($p=0.001$). Age was a predictive factor of femoral neck T-score ($p<0.001$). BMI was a predictive factor of femoral neck Z-score ($p=0.03$). None of the other 19 variables tested had any predictive value for bone density. Age ≥55 years was a risk factor of low femoral neck T-score (OR 5.08, 95% CI 1.90-13.57, $p=0.001$), as was cumulative dose of prednisolone ≥5 g (OR 3.41, 95% CI 1.50-7.73, $p=0.004$). **Conclusions:** There is a discordance of results depending on whether T- or Z-scores are used in analysis. Among 22 parameters, cumulative steroid dose and age proved to be the most important factors.

Keywords: Bone Density, Osteoporosis, Inflammatory Bowel Disease, Crohn's disease, Ulcerative Colitis

Introduction

Low bone density is receiving increasing attention as a complication of ulcerative colitis (UC) and Crohn's disease (CD) over the past decade since an increased risk of fractures among inflammatory bowel disease (IBD) patients has been reported[1-4]. With the advent of dual-energy X-ray absorptiometry (DXA), it is easy to measure bone mineral density (BMD) non-invasively. BMD results are typically expressed as the number of standard deviations (SD) above or below the mean for a young adult population (T-score) or an age-matched population (Z-score). In most studies, either T- or Z-scores have been used in evaluating predictive factors of low bone density in IBD, making comparison of results difficult. In addition, multivariate analysis has not always been used.

The aim of our study was to compare the results regarding possible risk factors of osteoporosis in IBD patients based on an analysis of T-score and Z-score values. We examined 22 clinical parameters, which were recorded prior to bone density evaluation and analyzed by univariate and multivariate analysis.

Materials and methods

Between June 2003 and June 2005, consecutive patients attending two gastroenterology clinics, who fulfilled the inclusion criteria, were invited to participate in the study. The study was performed according to the Helsinki declaration. All patients were informed about the nature of the study and gave their consent to participate.

The diagnosis of Crohn's disease and ulcerative colitis was established based on endoscopic, histological, radiological and clinical criteria[5]. Patients with indeterminate colitis were excluded from the study. UC patients with colectomy were also excluded from the study since proctocolectomy might diminish the risk of bone disease in these patients[6]. Additional exclusion criteria were: age<18 year, premature menopause, chronic liver disease, chronic renal insufficiency (creatinine>1.5 mg/dl), untreated thyroid disease, diabetes mellitus,

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Variables	All (n=122)	UC (n=56)	CD (n=66)	p
Age (years)	44.8±14.8	49.7±15.5	40.8±12.9	0.001
Sex (male/female)	59/63	30/26	29/37	NS[#]
BMI (kg/m^2)	26±5.4	27.5±4.4	24.9±5.9	0.008
Location of disease	-	P[1]:36, LC[2]:15, Pr[3]:5	SB[4]+C[5]:36, SB:11, C:19	-
Disease duration (months)	90.3±83	100.4±92.1	81.8±74.1	NS
Median	60 (1-343)	63.5 (1-343)	58 (1-264)	
History of resection	15	0	15*	-
Total prednisolone dose (g)	5.3±6.9	5.3±8.1	5.3±5.9	NS
Median	3.2 (0-55.1)	3.2 (0-55.1)	3.2 (0-24)	
Current corticosteroid user	33	14	19	NS
Prednisolone ≥5/<5/0 g	41/63/18	20/27/9	21/36/9	NS
Immunosuppression	49	21	28	NS
Activity index[a] (median)	-	1 (0-10)	4.5 (0-18)	-
Smoking: yes/no/ex-smoker	52/52/18	12/32/12	40/20/6	<0.001
Physical activity 0/I/II/III/IV	104/17/1/0/0	47/8/1/0/0	57/9/0/0/0	NS
Dairy products: free/avoidance	73/49	38/18	35/31	NS
Pre/post-menopausal women	43/20	17/9	26/11	NS
Time after last period (months)	84.2±81.4	123.2±92.3	52.3±57.4	0.05
Age at menopause (years)	49.2±3.1	49.4±3.5	49.0±2.8	NS
Relapse 1/2years prior to DXA	82/94	32/41	40/53	NS
New diagnosis (≤1 year)	20	7	13	NS
Diagnosis at age ≤18 years	7	4	3	NS

Values represent means unless stated otherwise, p denotes difference between patients with ulcerative colitis and Crohn's disease, [#]not significant, [1]pancolitis, [2]left colon, [3]proctitis, [4]small bowel, [5]colon, *small bowel resection, [a]UCSS activity index for ulcerative colitis, Harvey-Bradshaw activity index for Crohn's disease.

Table 1. Clinical characteristics of IBD patients participating in the study.

history of gastrectomy and use of medications known to affect bone mineral metabolism except glucocorticoids.

Patients' data were collected from both medical records and personal interviews. The following clinical parameters were recorded prior to bone density measurement: age, sex, height, weight, disease diagnosis, location and duration, history of newly diagnosed disease, history of diagnosed disease at puberty, history of resection in CD patients, current corticosteroid use, cumulative lifetime corticosteroid dose, azathioprine or other immunosuppressive medication use, smoking, physical activity, consumption of dairy products (free or avoidance), menstrual pattern in women, including age at menopause and time elapsed after the last menstruation, history of relapse during the last one or two years before entry and activity index at the time of DXA. Body mass index (BMI) was calculated as weight/height^2 (kg/m^2). Duration of disease was estimated from its diagnosis and not from the beginning of the symptoms. Disease was defined as newly diagnosed, if diagnosis was made during the last year prior to DXA. Cumulative lifetime steroid dose was expressed in grams of prednisolone. Current corticosteroid user was defined as a patient who has used corticosteroids for at least one month during the past 3 months before entry, independently of the dose. Other therapies such as azathioprine use were documented. Physical activity during the month before the entry was classified as 0=fully active, I=ambulatory, capable of light work, II=in bed less than 50% of time, capable of self-care but not of work activities, III=in bed more than 50% of time, capable of only limited self-care, and IV=completely bedridden[7]. The consumption of dairy products was classified as free if daily consumption included at least a glass of milk (250 ml), a yoghurt (200 g) and/or 30 g of cheese. Menopause was defined as amenorrhea for more than six months. Relapse during the last one or two years before entry was defined as one or more bowel motions mixed with blood per day and confirmed inflammation with rigid sigmoidoscopy, treatment with oral or rectal corticosteroids, treatment with metronidazole, ciprofloxacin, or infliximab, change of mesalazine dose and/or presence of a fistula. Patients with Crohn's disease or ulcerative colitis were in clinical remission or had active disease according to the Harvey-Bradshaw index of Crohn's disease activity[8] and ulcerative colitis scoring system (UCSS)[9], respectively.

Bone mineral density was measured by dual energy X-ray absorptiometry (DXA-Norland XR-26 Fort Atkinson, WI, USA) at the spine (L2-L4) and the neck of the left proximal femur. Results were expressed as absolute BMD values (g/cm^2), Z-scores and T-scores obtained by comparison with values of age- and young sex-matched persons, respectively, of the healthy Hellenic population[10].

Statistics

Differences between groups means were evaluated by the Student's unpaired t-test and the Mann Whitney U rank test for normally and non-normally distributed data, respectively. Comparison of T-scores and Z-scores in the lumbar spine and femoral neck in each patient was assessed by paired t-test. A comparison of incidences was performed using X^2 statistics or Fischer's exact test, as appropriate. Pearson's correlation coefficients were calculated for the continuous variables. Stepwise linear regression analysis was used to identify factors significantly related with low bone mineral density. Variables were included in the analysis either because they achieved a level of significance on univariate analysis or because they were considered of major importance for evaluating bone density, i.e., age, sex, type of disease, duration of disease, cumulative corticosteroid dose and BMI. Significance was defined as $p<0.05$. Statistical analyses were made with the Statistical Package for Social Sciences (SPSS 10.0).

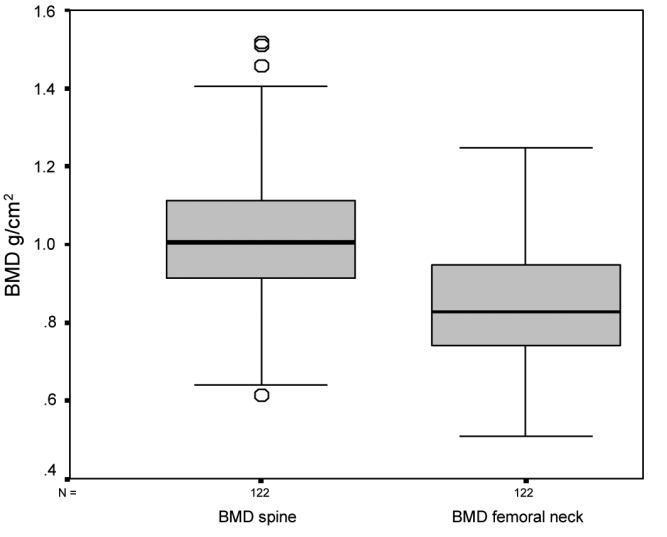

Figure 1. Mean bone mineral density (BMD) of the lumbar spine and femoral neck in all patients.

Results

Study population

A total of 160 patients were invited to participate in the study. Twenty-one patients did not fulfil the inclusion criteria. Four patients were <18-years-old, one patient had chronic liver disease, two patients had diabetes mellitus and five patients were using medications known to affect bone mineral metabolism. Six patients with indeterminate colitis and three UC patients with colectomy were also excluded from the study. Seventeen patients (median age 41, range 20-65) declined the invitation to participate. Of these 8 patients had ulcerative colitis and 9 had Crohn's disease. Therefore, one hundred and twenty-two patients (59 men, 63 women) with inflammatory bowel disease were, finally, recruited into the study. Sixty-six patients had Crohn's disease and 56 had ulcerative colitis. The clinical characteristics of the study population are shown in Table 1. At the time of the study, 23 patients had active Crohn's disease (Harvey-Bradshaw activity index>5) and 10 patients had active ulcerative colitis (UCSS>2).

Comparison of bone density at the spine and femoral neck

The mean bone mineral density (BMD) of the lumbar spine and femoral neck in all patients was 1.020 ± 0.18 g/cm^2 and 0.840 ± 0.15 g/cm^2, respectively (Figure 1). The mean T-score was -0.56 ± 1.47 SD at the lumbar spine and -1.13 ± 1.37 SD at the femoral neck. The mean Z-score was 0.08 ± 1.47 SD at the lumbar spine and -0.22 ± 1.14 SD at the femoral neck. Femoral neck T-score and Z-score were significantly lower than lumbar spine (paired $t=4.4$, $p<0.001$/paired $t=2.5$, $p=0.01$, respectively).

According to the 1994 WHO criteria[11], thirty-two (26.2%, 19 CD and 13 UC) of our IBD patients had osteopenia at the lumbar spine (mean BMD 0.896 ± 0.05) and 12 (9.8%, 9 CD and 3 UC) had spine osteoporosis (mean BMD 0.713 ± 0.06). At the femoral neck, 47 (38.5%, 22 CD and 25 UC) of the patients had osteopenia (mean BMD 0.782 ± 0.06) and 19 (15.6%, 11 CD and 8 UC) had osteoporosis (mean BMD 0.623 ± 0.07). Significantly, more patients had osteopenia or osteoporosis at the femoral neck compared to the spine ($p=0.01$). When Z-score<-1 SD and Z-score<-2 SD were used to define osteopenia and osteoporosis, respectively, the prevalence of spine and femoral neck osteopenia was 12.3% (15 patients, 8 CD and 7 UC) and 18.9% (23 patients, 11 CD and 12 UC), respectively, and spine and femoral neck osteoporosis were 8.2% (10 patients, 9 CD and 1 UC) and 7.4% (9 patients, 8 CD and 1 UC), respectively (p=ns).

There was a significant correlation of T-score ($r=0.491$, $p<0.001$) and Z-score ($r=0.509$, $p<0.001$) between the spine and femoral neck, suggesting that low bone density at one site was predictive of low bone density at the other. Because of these data and since larger number of patients had osteopenia or osteoporosis at the femoral neck compared to the spine, it was decided to present only the data of the femoral neck.

BMD values of the femoral neck expressed as T-score and Z-score in UC and CD patients are shown in Table 2.

Univariate and multivariate analysis of risk factors

On univariate analysis of all variables listed in Table 1, there was a negative correlation of femoral neck T-score with age ($r=-0.509$, $p<0.001$), disease duration ($r=-0.202$, $p=0.03$) and cumulative steroid dose ($r=-0.404$, $p<0.001$). Low physical activity ($p=0.008$), menopause in women ($p=0.005$), immunosuppressive therapy ($p=0.02$) and current steroid use ($p=0.003$) were statistically significant predictive factors of low T-score.

On univariate analysis using Z-score, there was a negative correlation of femoral neck Z-score with cumulative steroid

	Ulcerative colitis (n=56)	Crohn's disease (n=66)	p
T-score (SD) Femoral ne.ck	-1.19±1.34	-1.07±1.42	NS*
Z-score (SD) Femoral neck	0.03±1.07	-0.37±1.18	NS

* We found no significant difference of mean T-score between UC and CD patients although there was a difference in mean age of 9 years between CD and UC patients. Z-score is corrected for age.

Table 2. T-score and Z-score of femoral neck in patients with ulcerative colitis and Crohn's disease.

Variables	T-score	Z-score
Age	p<0.001	NS#
BMI	NS	p=0.03
Cumulative dose of prednisolone	p<0.001	p=0.001

#non significant

Table 3. Significant independent risk factors of low femoral neck T-score and Z-score values on multivariate analysis in all patients.

dose (r=-0.377, p<0.001) and a positive correlation with BMI (r=0.216, p=0.02). Immunosuppressive therapy (p=0.007) and current steroid use (p=0.007) were statistically significant predictive factors of low Z-score.

The type of disease and disease activity (active versus non-active according to UCSS and Harvey-Bradshaw activity index) were not being proved statistically significant predictive factors of either T-score or Z-score. In CD patients, history of bowel resection was not a predictive factor of either T-score or Z-score. Overall, ten variables (those statistically significant on univariate analysis and of great importance as stated in statistics) were included on multivariate analysis using T-score and eight variables in the analysis using Z-score. Significant independent risk factors on multivariate analysis using T-score and Z-score are shown in Table 3.

Odds ratio

We calculated the risk of developing low femoral T-score (T-score>-1SD) when one of the independent factors was present. Patients aged ≥55-years-old were at increased risk of low femoral neck T-score (OR 5.08, CI 1.90-13.57, p=0.001) as well as those who had received ≥5 g of prednisolone as a cumulative lifetime dose (OR 3.41, CI 1.50-7.73, p=0.004). When we calculated the risk of low Z-score (Z-score>-1SD), none of the factors examined reached statistical significance.

Discussion

Reduced bone density and fractures are reported complications from inflammatory bowel disease, though the magnitude of the problem, major risk factors, and therapeutic approach remain controversial. Furthermore, the data in the literature are conflicting as to what variables correlate with bone measurements in IBD patients, either because different variables have been examined in each study or only T-score or Z-score values have been used in analysis. In our study, we evaluate 22 clinical parameters, which could affect bone density in IBD patients, and compare the results of T- and Z-score values in predicting possible risk factors of low bone density in 122 patients.

Our data show a discrepancy of results regarding risk factors of osteoporosis in IBD patients, depending on whether we have used T-scores or Z-scores. Nevertheless, the discrepancy is small, showing that both T-score and Z-score measurements are suitable for evaluating risk factors of low bone density in IBD patients. On multivariate analysis, a cumulative lifetime dose of prednisolone was a predictive factor of femoral neck T-score and Z-score values. Age was a predictive factor of femoral neck T-score, but not of Z-score, this was an expected finding since Z-score is corrected for age. BMI was a predictive factor of femoral neck Z-score, but not of T-score. Although the discrepancy is small, we believe that this discordance must be taken into consideration, as there is no uniformity in published studies, which discuss low bone density in association with IBD.

We identified three studies where both T-scores and Z-scores were evaluated. In the study of Martin et al.[12], which included 91 IBD patients, on multivariate analysis of Z-scores, disease type (Crohn's disease) and BMI were significant factors, whereas none of the variables tested was a predictive factor of T-score. Therefore, it was concluded that the Z-score is a more reliable indicator in evaluating bone density in IBD. This is not confirmed by our study, where significant results were reached with both T- and Z-score. Unlike our study, de Jong et al.[13] evaluated 91 CD patients and showed that history of bowel resection was an independent predictive factor of low T-score and Z-score both in the spine and the femoral neck. A larger number of CD patients had a history of bowel resection in the study of de Jong et al. (59/91) compared to our study (15/66), which might explain the above discrepancy. Similarly to Pollak et al.[14], who studied 59 IBD patients, we found a positive correlation of femoral Z-score and BMI and an inverse correlation of femoral neck T-score and disease duration, although the latter was not a significant factor on multivariate analysis. Unlike these studies, we have shown that cumulative steroid dose was a predictive factor of low T-score and Z-score at the femoral neck.

It has been suggested that IBD patients aged >60 years old have an increased risk of fractures[1] and that the frequency of osteopenia in patients receiving >5 mg cumulative dose of prednisolone equivalents is higher compared to

patients who received a lower dose[15]. In accordance to these observations, our study has identified a group of patients who are at increased risk of low bone density; patients older than 55 years are at increased risk of low femoral neck T-score (OR 5.08, 95% CI 1.90-13.57, p=0.001), as are those who received more than 5 g of prednisolone as a cumulative lifetime dose (OR 3.41, 95% CI 1.50-7.73, p=0.004). We suggest that patients who fulfil any of the above criteria should be definitely followed by DXA measurements.

Cumulative steroid dose was the only variable proved to be a risk factor of both low T-score and Z-score, in our IBD patients. Corticosteroids are the most efficient first line therapy for active IBD and the finding that diminished bone density was related to corticosteroid use is confounded by the fact that patients with more severe disease are usually treated with corticosteroids. We acknowledge that since patients were recruited from specialty clinics, individuals with more severe disease, greater steroid exposure, and probably more severe bone disease might have entered the study. In order to examine if activity of disease plays an independent significant role on bone loss, we included in the analysis the history of recent relapse (one or two years prior to DXA) and the activity of disease during DXA according to the Harvey-Bradshaw score for CD patients and UCSS for UC patients. None of either factor proved statistically significant. From experimental animal data it appears that inflammation-associated bone loss is reversible[16-18]. It may, therefore, be speculated that also in humans, periods of active disease lead to bone loss and that in periods of remission bone mass may recover. This may partially explain why patients with a history of a relapse during one or two years prior to DXA did not have lower bone density than patients with negative history of relapse. In addition, the number of relapses and their duration throughout out the whole of the disease duration could be an important factor of low bone density, but this has not been studied so far. Furthermore, active disease duration over the one-year prospective study by Motley et al.[19] was not correlated with bone loss rate. On the contrary, Reffitt et al.[20] showed that patients with IBD in remission for more than three years have greater bone density relative to patients with active disease.

Our results suggest that bone loss occurs not only on both the trabecular and the cortical skeleton but probably it is more prominent at the cortical skeleton. Previous studies have also reported the same result[21,22]. This is possibly an indicator that factors other than corticosteroid use (which affect mainly the trabecular zone) play a significant role in bone loss in IBD.

Malabsorption has been suggested to be an important determinant of bone loss. Our data do not support the theory that small bowel dysfunction necessarily contributes to the diminished bone density seen in patients with Crohn's disease. Involvement of the small bowel was not found as a predictive factor of low bone mineral density in patients with Crohn's disease. In addition, small bowel resection played no role regarding bone loss. In previous studies, no correlation was found between BMD and surgery history[23,24]. Vitamin D status measured at patients with small bowel disease and osteopenia was found within normal range in all patients but one (a woman with Crohn's disease and hip osteoporosis). Sunshine in Greece probably plays a significant role in reserving normal vitamin D levels even in patients with small bowel disease.

Conclusions

We have shown that there is a small discrepancy between results, regarding risk factors of osteoporosis in IBD patients, depending on whether T-score or Z-score values are used in analysis. Among twenty-two clinical parameters examined, cumulative steroid dose and age proved the most important factors. Patients who have received a lifetime dose of prednisolone over 5 g and/or are older than 55 years of age have at least a triple risk of having diminished bone density relative to other IBD patients.

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