Analysis of Risk Factors For Low Bone Mineral Density In Inflammatory Bowel Disease

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Abbreviations: BMD, bone mineral density; BMI, body mass index; CD, Crohn's disease; DEXA, dual energy X-ray absorptiometry; IBD, inflammatory bowel disease; UC, ulcerative colitis

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Abstract

Background/Aims. Several risk factors have been suggested for osteoporosis which frequently occurs in inflammatory bowel disease (IBD) patients. We studied the prevalence and risk factors for reduced bone mineral density (BMD) in IBD patients at the University Hospital Zurich.

Methods. BMD was determined by dual-energy x-ray absorptiometry (DEXA) at the lumbar spine and femoral neck in 88 IBD patients (55 Crohn's disease [CD], 30 ulcerative colitis [UC], 3 indeterminate colitis). Z scores were obtained by comparison with age- and sex-matched normal values, T scores by comparison with sex-matched healthy young adults. Osteopenia and osteoporosis were defined according to the WHO guidelines. Predictive factors for BMD were analyzed by group comparison and stepwise regression analysis.

Results. Osteopenia was present in 43% at the lumbar spine and in 42% at the femoral neck. Osteoporosis was present in 14% at the lumbar spine and in 5% at the femoral neck. At the lumbar spine, stepwise regression analysis showed that body mass index (BMI), age, bowel resections, topic steroids and azathioprine correlated with Z scores. Cumulative steroid dose, topic steroids, age and bowel resection were found to be predictors for a pathological T score. At the femoral neck, regression analysis showed that BMI, age, topic steroids and azathioprine correlated with Z scores. Only low BMI was a significant predictor for a pathological femoral T score.

Conclusions. Osteopenia and osteoporosis are commonly found in IBD patients. Steroid treatment and bowel resection were significant risk factors for osteoporosis of the lumbar spine. However, disease-inherent factors also appear to confer a major risk, indicating that BMD should be determined in all IBD patients irrespective of steroid treatment.

Introduction

Several studies have reported an increased risk of low bone mineral density (BMD) in patients with inflammatory bowel disease (IBD), with a prevalence of osteoporosis reported up to 37% [1]. It is generally accepted that osteoporosis in IBD has a multifactorial pathogenesis, with potential risk factors such as reduced food intake, low body mass index (BMI), malabsorption and vitamin D deficiency, small bowel resection, hypogonadism, corticosteroids [2], smoking [3] and genetic factors [4]. Also Crohn's disease (CD) itself seems to be an important risk factor for low BMD [5]. A low BMD may already be present at the stage of initial diagnosis of CD [6]. CD patients without previous treatment appear to have a significantly lower average density at the lumbar vertebrae when compared to ulcerative colitis (UC) patients [7]. Furthermore, BMD in CD patients increases after induction of remission by azathioprine [8]. These findings suggest that CD itself plays an important role in the development of osteopenia/osteoporosis and that low BMD cannot be attributed solely to treatment with steroids. Corticosteroids have been shown to reduce BMD [9, 10], [2, 11-16], although the data are conflicting [5, 6, 17-21].

IBD patients have up to 40% more fractures than the general population [22], with an increased risk of both vertebral and hip fractures [23]. Analysis of the risk factors for the development of osteoporosis could help to identify those IBD patients who have a higher risk of fracture. We therefore aimed to analyze the risk factors for low BMD in our cohort of unselected IBD patients, so as to optimize BMD monitoring and treatment in patients-at-risk.

Methods

Study design and patients. The study was a cross-sectional analysis of a local IBD cohort. At the time of analysis, 137 patients were registered in the IBD cohort of the University Hospital Zurich. All patients were diagnosed by a combination of radiology, endoscopy and histology. BMD was determined by dual energy X-ray absorptiometry (DEXA) in 88 (64%) patients (55 CD, 30 UC, 3 indeterminate colitis). Demographic and disease data of these patients were obtained by review of the medical records and by a questionnaire sent to all patients. 14 patients were diagnosed with arthritis. There was one case of chronic hepatitis C and one case of primary sclerosing cholangitis, and 6 patients were diagnosed as having liver steatosis. We assessed one patient with a Hashimoto thyreoiditis and one patient with subclinical hyperthyroidism.

Bone density measurement. BMD of lumbar L2-L4 vertebrae and the femoral neck was determined by standard DEXA at the Department of Rheumatology, University Hospital Zurich. The results are expressed as either Z scores or T scores. Z scores indicate the number of standard deviations (SD) from the normal sex and age specific mean value. T scores were calculated in relation to sex-matched healthy young adults at the age of peak bone mass as reference group. According to the World Health Organization (WHO) criteria, osteoporosis was defined as a T score below -2.5 SD and osteopenia was defined by a T score below -1 SD but not more than 2.5 SD below the average. Data from the reference groups were supplied by the manufacturer.

Statistical analysis. The two-tailed Mann-Whitney U test was used to study the relationship between Z scores and the following potential individual risk factors: diagnosis, sex, involvement of small bowel, weight loss, anemia, bowel resection, topic steroid treatment, azathioprine and methotrexate treatment, alcohol and nicotine consumption and family history. Other risk factors were not studied because subgroups were too small for a meaningful analysis. To determine factors predictive for Z scores, stepwise regression with backward selection was performed with the following independent variables: diagnosis (CD versus UC), sex, age, BMI, involvement of small bowel, bowel resection, family history of IBD, steroids (daily

steroid dose, cumulative steroid dose and topic steroid treatment), azathioprine treatment, methotrexate treatment, as well as alcohol and nicotine consumption. The two-tailed Mann-Whitney U test was used to study the relationship between T scores and individual risk factors. To determine factors predictive for T scores, patients were divided into two groups (normal BMD with T scores above - 1 SD versus pathological BMD with T scores below -1 SD) and stepwise logistic regression with backward selection was performed. P values < 0.05 were considered as statistically significant.

Results

Characteristics of patients assessed by DEXA. BMD was measured by DEXA in 88 IBD patients. DEXA was performed in 55 CD patients (30 male, 25 female, mean age 39.0) and in 30 UC patients (19 male, 11 female, mean age 44.2) with a disease duration of 8.5 ± 7.2 and 8.7 ± 7.4 years, respectively (Table 1). BMD was additionally measured in 3 patients with indeterminate colitis. As expected, small bowel was more often affected in CD than UC patients (62% and 10%, respectively), making small bowel resections necessary in one third of CD patients. Nearly all IBD patients had been treated with steroids at some stage of their disease (90% in CD and 97% in UC patients) with a higher cumulative systemic steroid dose in UC than in CD patients (32.6 g and 20.6 g, respectively).

Prevalence of osteopenia and osteoporosis in IBD patients. Pathological BMD (osteopenia or osteoporosis) was more frequently observed at the lumbar spine than at the femoral neck (57% and 47% of IBD patients, respectively) (Fig. 1). Osteoporosis, defined as a T score below -2.5 SD, was found in 14% of IBD patients (18% of CD and 10% of UC patients) at the lumbar spine and in 5% of IBD patients (4% of CD and 7% of UC patients) at the femoral neck. Osteopenia, defined as a T score between -1 SD and -2.5 SD, was present in 40% of IBD patients.

Assessment of risk factors for low Z scores. Distribution of Z scores at the lumbar spine and femoral neck among CD und UC patients is shown by box plot in Fig. 2. Median values for CD patients were -1.15 at the lumbar spine and -0.6 at the femoral neck. Median values for UC patients were -0.8 at the lumbar spine and -0.2 at the femoral neck. To analyze the contribution of individual potential risk factors to low BMD, we performed Mann-Whitney U tests. Patients who had undergone bowel resection showed a significantly lower lumbar Z score than patients without bowel resections (Table 2). Other statistically significant individual risk factors were not found, neither at the lumbar spine nor at the femoral neck. We next performed stepwise regression analysis to identify predictive factors for low Z scores. Patients who had undergone bowel resections or had been treated with topic steroids and azathioprine had a significantly increased risk of low lumbar Z score. Additionally, patients with low BMI and younger patients had a significantly increased risk of

having low lumbar Z scores. The same predictive factors were found for femoral Z scores except bowel resection which did not reach statistical significance (p=0.18) (Table 3).

Assessment of risk factors for low T scores. For analysis of risk factors for low T scores, patients were divided into two groups according to the WHO guidelines: (i) patients with normal T scores (above – 1 SD), and (ii) patients with osteopenia or osteoporosis (T score below – 1 SD). Patients with a pathological lumbar T score were significantly younger, had a lower BMI and had received more corticosteroid treatment (longer duration of steroid therapy and higher cumulative steroid dose). These results are shown in Table 4 and Fig. 3. Table 4 shows median values of these risk factors in patients with normal and pathological BMD, respectively. The box plot in Fig. 3 shows the distribution of the cumulative steroid dose in patients with normal and pathological lumbar BMD. Stepwise regression analysis with backward selection revealed that a pathological lumbar T score in IBD patients was significantly correlated with a high cumulative steroid dose, treatment with topic steroids, younger age and bowel resection (Table 5). At the femoral neck, only low BMI was significantly related to a pathological T score (Table 4). In stepwise regression analysis, pathological femoral T scores were significantly correlated with low BMI, topic steroids and azathioprine treatment (Table 5).

Discussion

The chief findings of this study can be summarized as follows: (i) osteopenia and osteoporosis show a high prevalence in IBD patients, with more than 50% of IBD patients being affected; (ii) major risk factors for the development of osteopenia/osteoporosis are corticosteroid treatment and bowel resections; however, after exclusion of all other variables, disease activity per se appears to confer a relevant independent risk.

We found a 14% prevalence of osteoporosis at the lumbar spine in our cohort of Swiss IBD patients. This is comparable with another Swiss study that recently reported a 9.7% prevalence of osteoporosis in IBD patients seen in specialist gastroenterology practice [24]. Earlier studies reported an even higher prevalence of osteoporosis in IBD patients of around 30% [1, 18, 25]. The reason for this is not clear, since more patients were excluded in these studies compared to our investigation (one study excluded patients with bowel resections or lifetime steroid dose higher than 25 g [25], whereas another excluded patients receiving treatment for osteoporosis or patients with severe malabsorption [1]). Of note, however, the percentage of IBD patients with osteopenia was 40% in our study; this underlines the importance of carefully assessing all IBD patients for bone mineral density and initiating appropriate treatment in patients with a pathological BMD. The relevance and efficiency of bisphosphonates in the treatment of these patients is a subject of continued debate [26-30]. Until further studies have clearly shown the clinical benefit of biphosphonates in osteoporosis associated with IBD, calcium and vitamin D should remain the baseline treatment in osteopenic and osteoporotic patients.

In our IBD cohort, both in CD and UC patients, the lumbar spine was found to be affected more often by a pathological BMD than the femoral neck. This finding is surprising, because most studies have found a higher prevalence of osteoporosis at the femoral neck [5, 18, 25, 31-33]. There is no obvious reason for this discrepancy. It has been reported that treatment with corticosteroids results in bone loss especially at trabecular bone sites [34], such as the lumbar spine. There was, however, no evidence for excessive steroid treatment in our cohort compared to the other studies.

Multivariate regression analysis identified several predictive variables of reduced BMD at the lumbar spine. Besides BMI, which has been found as a predictive factor of BMD in various studies [17, 18, 20, 35], young age was identified as a predictive variable for both low Z and T scores. This suggests that, at least in our cohort, younger IBD patients had a mildly elevated risk of osteoporosis than older patients. This could be due to a more active disease in young patients, leading to osteoporosis via circulating cytokines [36] which affect osteoclast [37] and osteoblast function [38]. This observation is in agreement with a study showing that IBD patients younger than 18 years at diagnosis are at risk for osteoporosis [32].

The hypothesis that disease activity is an independent risk factor for the development of osteoporosis is supported by the finding that topic steroids and azathioprine were significant predictors of BMD. So far, no detrimental effect of azathioprine on BMD has been shown. We assume that azathioprine is negatively correlated with BMD because it is used in IBD patients with high inflammatory activity requiring additional immunosuppressive medication. The negative correlation of topic steroid treatment and BMD might, however, also be caused by a systemic effect of local steroids.

The deleterious effect of systemic steroids on BMD is supported by the finding that patients with a pathological BMD had received a more intense steroid treatment (higher cumulative steroid dose and longer duration of steroid therapy). This confirms previous observations showing that systemic corticosteroids are a risk factor for osteoporosis in CD patients [2]. In particular, high lifetime systemic steroid doses greater than 10 g have been reported to be correlated with low BMD [12, 14].

Multivariate analysis further revealed a history of bowel resections as a significant predictive variable of low BMD, as described by others [14, 18]. Patients with a history of bowel resection had a threefold increased risk of having a pathological BMD at the lumbar spine. One possible explanation for this relationship is that bowel resections lead to a malabsorptive state, e.g. for vitamin D [39] or vitamin K [40]. An alternative explanation, however, is that bowel resections are a sign of severe disease leading to systemic inflammation and to complications which necessitate a surgical intervention.

One limitation of our study is that we did not apply strict exclusion criteria, in order to include a broad spectrum of IBD patients in our analyses. Moreover, this study cannot prove that corticosteroids or bowel resections are causes of osteoporosis in IBD patients. The performed regression analyses are only able to provide correlative evidence for the involvement of different risk factors in the development of osteoporosis in IBD patients.

In summary, our results show that the prevalence of osteopenia and osteoporosis is high in a Swiss cohort of IBD patients. Major risk factors for low BMD were corticosteroid treatment and a history of bowel resection, although a relevant risk is conferred by disease activity per se, irrespective of other variables analyzed. Moreover, the high prevalence of osteopenia reported in this study underlines the importance of monitoring not only high-risk but all IBD patients by DEXA, and of initiating appropriate treatment in patients with low BMD. Whether antiresorptive therapy with bisphosphonates in addition to calcium and vitamin D helps to prevent fractures in IBD patients with low BMD remains to be evaluated.

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Figure legends

Fig. 1: Prevalence of osteopenia and osteoporosis in 88 IBD patients, determined by DEXA at the lumbar spine and femoral neck

Fig. 2: Bone mineral density expressed as Z score in CD and UC patients

Fig. 3: Cumulative steroid dose in patients with normal and pathological BMD

Table 1: Characteristics of 88 IBD patients assessed by DEXA (patients with indeterminate colitis not shown)

	IBD (n=88)	**CD** (n=55)	**UC** (n=30)
Male (%)	**50** (57%)	**30** (55%)	**19** (63%)
Age (Mean ± SD)	**40.6** ± 15.3	**39.0** ± 14.7	**44.2** ± 16.3
BMI [kg/m^2] (Mean ± SD)	**23.1** ± 4.5	**22.6** ± 3.9	**23.6** ± 5.0
Disease duration (Mean ± SD)	**8.3** ± 7.2	**8.5** ± 7.2	**8.7** ± 7.4
Flares (Mean ± SD)	**9.3** ± 10.0	**9.3** ± 11.0	**9.2** ± 8.2
Small intestine involved	**38** (43%)	**34** (62%)	**3** (10%)
Bowel resection Small bowel resection	**25** (28%) **18** (20%)	**24** (44%) **17** (31%)	**1** (3%) **0** (0%)
Steroid therapy	**82** (93%)	**50** (90%)	**29** (97%)
Cumulative steroid dose (Mean ± SD)	**26.7** ± 46.8	**20.6** ± 38.8	**32.6** ± 56.7
Duration of steroid therapy [months] (Mean ± SD)	**40.8** ± 65.8	**32.6** ± 61.9	**47.9** ± 69.7

Table 2: Relationship between individual risk factors and Z scores, assessed by Mann-Whitney U test. * indicates a statistically significant p value.

	P values	
	Lumbar spine	**Femoral neck**
Diagnosis (CD vs. UC)	.31	.21
Sex	.13	.58
Small intestine involved (y/n)	.33	.56
Weight loss (y/n)	.57	.16
Anemia (y/n)	.55	.72
Bowel resection (y/n)	.04 *	.08
Topic steroids (y/n)	.24	.23
Azathioprine (y/n)	.16	.36
Methotrexate (y/n)	.36	.18
Nicotine (y/n)	.99	.99
Alcohol (y/n)	.82	.16
Family history of IBD (y/n)	.37	.19

Table 3: Predictive factors for Z scores, assessed by stepwise regression analysis

Lumbar spine Z score			**Femoral neck Z score**		
Significant predictors	B regression coefficient	p	Significant predictors	B regression coefficient	p
BMI [kg/m^2]	.084	.013	BMI [kg/m^2]	.130	.000
Age [y]	.025	.005	Age [y]	.020	.009
Bowel resection (y/n)	-.580	.026	Topic steroids (y/n)	-.393	.046
Topic steroids (y/n)	-.531	.028	Azathioprine (y/n)	-.551	.012
Azathioprine (y/n)	-.685	.010			

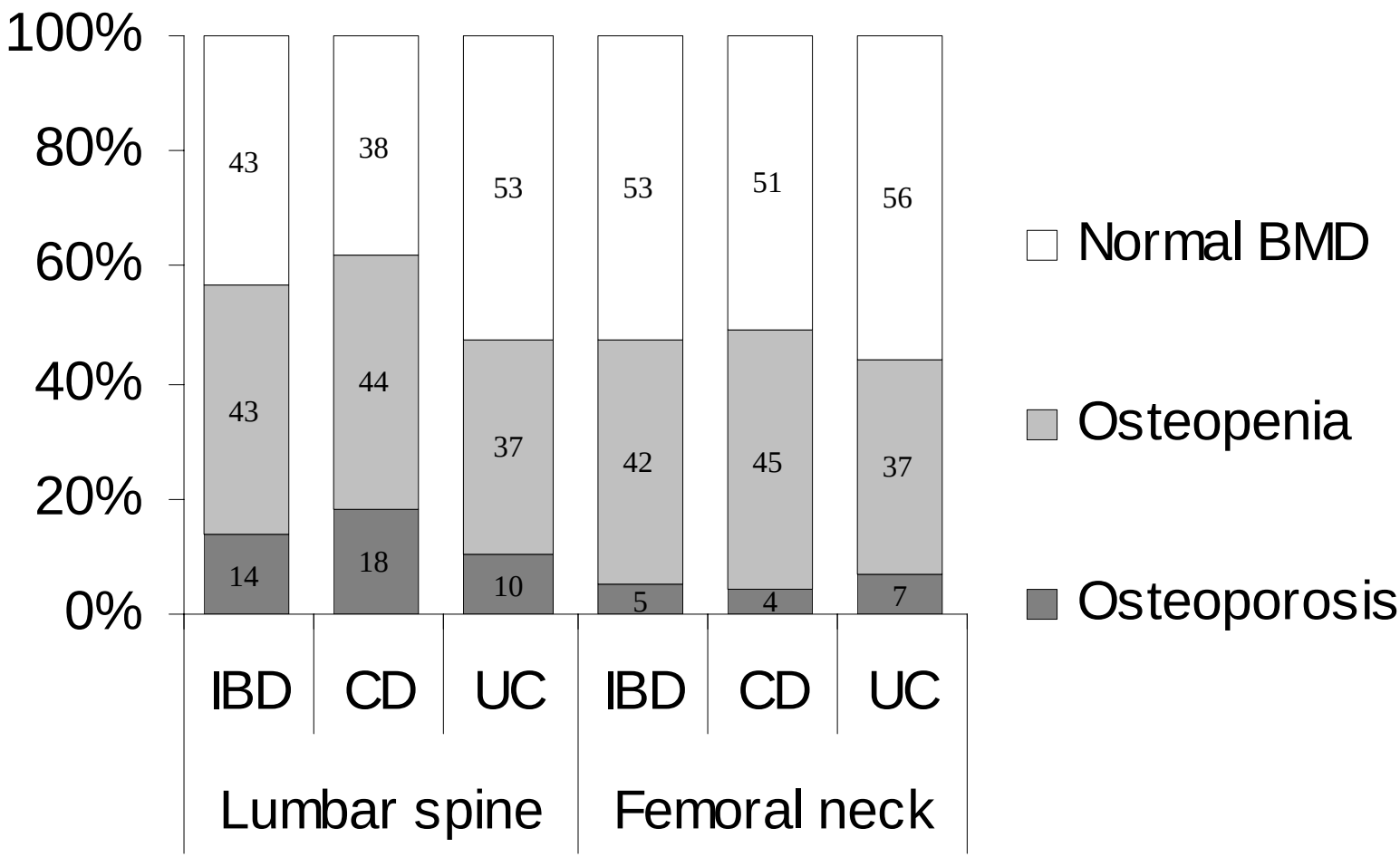
Table 4: Relationship between individual risk factors and T scores > 1 SD below mean, assessed by Mann-Whitney U test

Lumbar spine				**Femoral neck**			
Significant risk factors	T score > - 1 SD	T score < - 1 SD	p	Significant risk factors	T score > - 1 SD	T score < - 1 SD	p
BMI [kg/m^2]	23.1	21.4	.048	BMI [kg/m^2]	23.6	20.8	.005
Age [y]	40.4	34.9	.027				
Duration of steroid therapy [mo]	9.0	18.5	.034				
Cumulative steroid dose [g]	4.0	7.2	.031				

Table 5: Predictive factors for T scores > 1 SD below mean, assessed by stepwise logistic regression. Exp (B) indicates the fold increase in risk to have a T score < -1 that is conferred by the respective parameter (this can be interpreted as an Odds Ratio). In the case of the cumulative steroid dose, the Exp(B) value indicates a 1.022 greater risk to have a T score < -1 with a cumulative steroid dose of 1 g; for 10 g cumulative steroids this risk increases to 1.022^{10} (= 1.24), for 40 g 1.022^{40} (= 2.38), for 100 g 1.022^{100} (= 8.8).

Lumbar spine Z score			**Femoral neck Z score**		
Significant predictors	Exp (B)	p	Significant predictors	Exp (B)	p
Cumulative steroid dose	1.022	.042	BMI	0.818	.003
Topic steroids	2.917	.038	Topic steroids	2.679	.051
Age	0.955	.010	Azathioprine	3.792	.018
Bowel resection	3.088	.059			

Figure 1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IBD
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Lumbar spine
Femoral neck
Normal BMD
Osteopenia
Osteoporosis

Figure 2

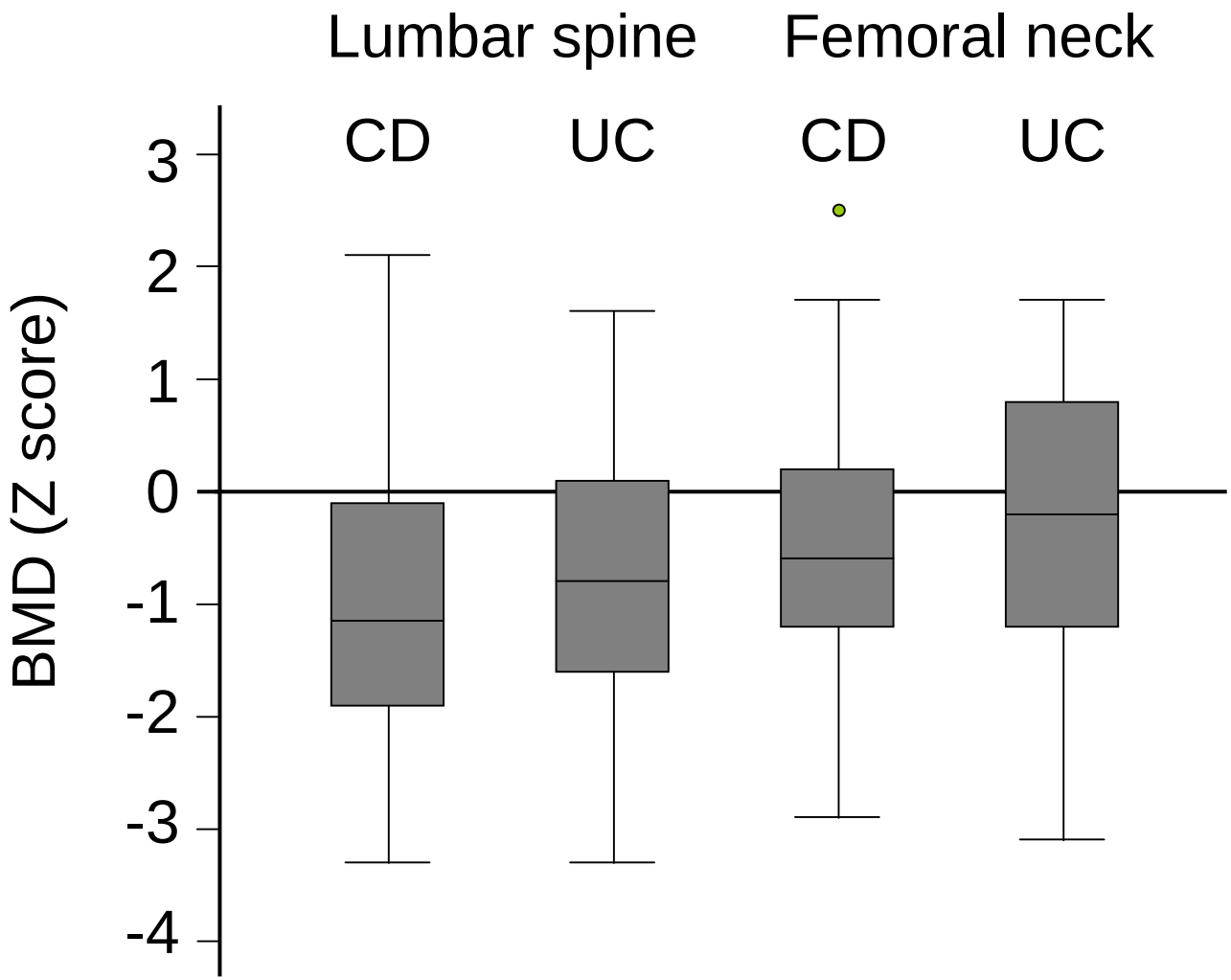
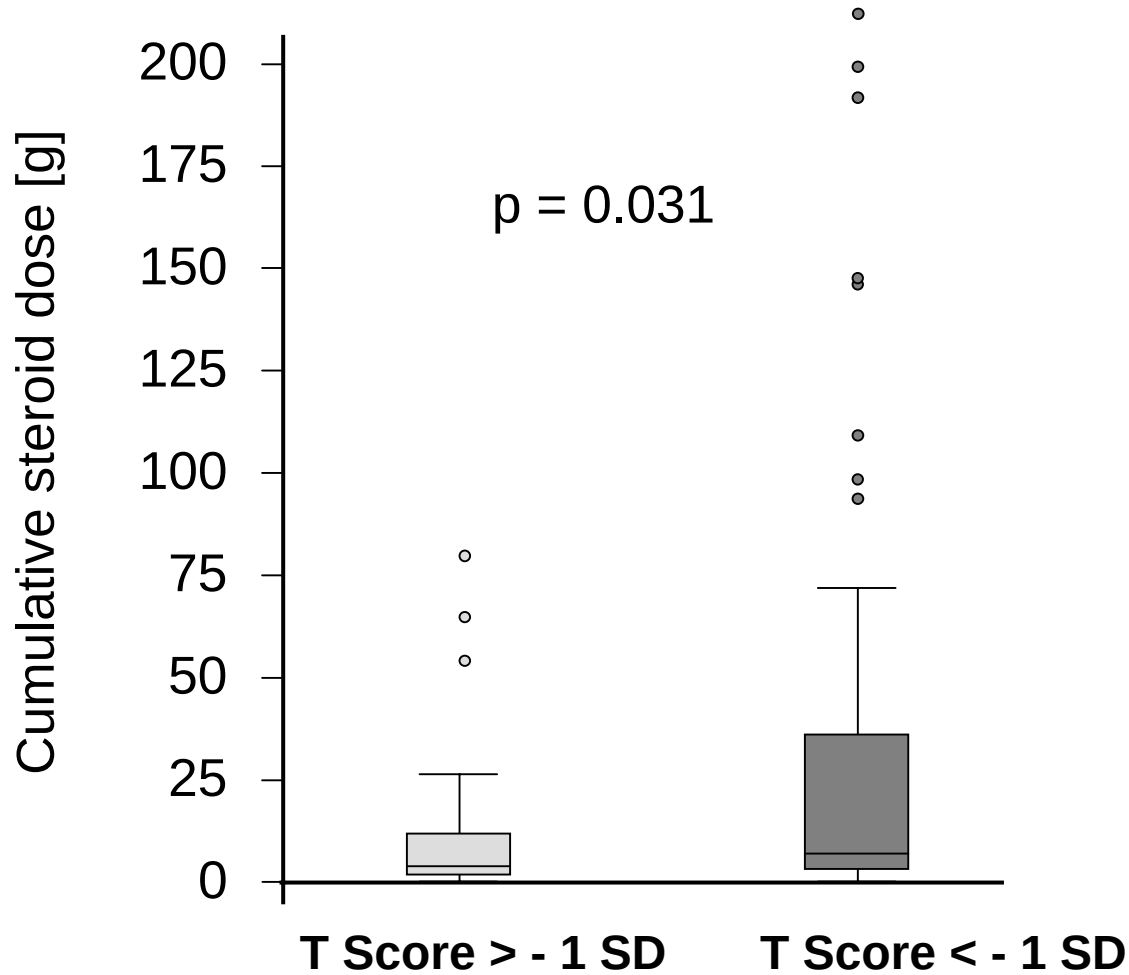


Figure 3


Cumulative steroid dose [g]
200
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p = 0.031
T Score > - 1 SD
T Score < - 1 SD