https://doi.org/10.31925/farmacia.2022.2.23 **ORIGINAL ARTICLE**

THERAPIES AND BONE IMPAIRMENT IN INFLAMMATORY BOWEL DISEASE YOUNG ADULTS

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Abstract

Low bone mineral density (BMD) and fractures are well-known complications associated with inflammatory bowel disease (IBD). The most incriminated causes are the exposure to high doses of glucocorticoids, chronic inflammation, and malabsorption; however, the impact of biologic therapy on bones' mass is still under debate. The objective of this study was to evaluate the prevalence of low BMD and the impact of different therapies on bone impairment in IBD young patients. A total of 52 premenopausal women and men (under 50 years old) IBD patients and 53 healthy subjects (matched for age, gender, and body mass index (BMI) were included in this study. Dual energy X-ray assessment (DXA) was performed in all the subjects. DXA parameters of 38 well-controlled patients (of which 24 on biologic agents and 14 with previous exposure to high doses of glucocorticoids) were compared with those of healthy controls. Low BMD status was more prevalent in IBD patients when compared to healthy subjects (32.6% *vs* 9.4 %, $\chi = 8.5$, $p = 0.003$). Lumbar spine BMD was significantly higher in healthy controls than in IBD patients on biologic therapies (1.2 ± 0.11 *vs* 1.09 ± 0.17, $p = 0.002$). Both lumbar spine and hip BMD were significantly lower in patients with previous exposure to long-term glucocorticoids when compared to controls (0.94 ± 0.13 *vs* 1.22 ± 0.11, $p < 0.001$; 0.85 ± 0.11 *vs* 0.95 ± 0.14, $p = 0.04$), and also when compared to patients on biologic agents (0.94 ± 0.13 *vs* 1.09 ± 0.17, $p = 0.01$; 0.85 ± 0.11 *vs* 0.95 ± 0.14, $p = 0.04$ respectively). Our study showed that low BMD is a frequent complication in young adults with IBD. Although long-term exposure to glucocorticoids has a deleterious impact on bone loss, this effect is also observed in patients on biologic therapy. Hence, an early diagnosis, as well as a long term follow–up, are required for these patients.

Rezumat

Densitatea minerală osoasă (DMO) scăzută și fracturile sunt complicații importante care apar în boala inflamatorie intestinală (BII). Ele sunt datorate tratamentului cu glucocorticoizi în doze crescute, inflamației cronice și malabsorbției. Cu toate acestea, efectele terapiei biologice asupra masei osoase sunt încă incomplet descrise. Studiul de față și-a propus evaluarea prevalenței DMO scăzute și impactul diferitelor tipuri de tratamente asupra osului la pacienții tineri cu BII. Au fost incluși în studiu 52 femei în premenopauză și bărbați cu vârsta sub 50 ani cu BII și 53 de subiecți sănătoși cu vârste și indice de masă corporală (IMC) asemănătoare. Parametrii osteodensitometrici ai pacienților cu un control bun al bolii (24 pe terapie biologică și 19 cu istoric de glucocorticoizi în doză crescută) au fost comparați cu cei ai subiecților. Rezultatele obținute au arătat o prevalență crescută a DMO la pacienții cu BII, comparativ cu subiecții din lotul control (32,6% *vs* 9,4 %, $\chi = 8,5$, $p = 0,003$). DMO de la nivelul coloanei lombare a fost semnificativ mai mare la subiecții control față de pacienții aflați în tratament biologic ($1,2 \pm 0,11$ *vs* $1,09 \pm 0,17$, $p = 0,002$). Pacienții cu tratament cu glucocorticoizi în doze crescute au avut DMO la nivelul coloanei lombare, dar și a șoldului semnificativ mai mici atât față de subiecții sănătoși ($0,94 \pm 0,13$ *vs* $1,22 \pm 0,11$, $p < 0,001$; respectiv $0,85 \pm 0,11$ *vs* $0,95 \pm 0,14$, $p = 0,04$), cât și față de cei în tratament biologic ($0,94 \pm 0,13$ *vs* $1,09 \pm 0,17$, $p = 0,01$; $0,85 \pm 0,11$ *vs* $0,95 \pm 0,14$, $p = 0,04$). Studiul prezent arată că DMO scăzută este o complicație frecventă la pacienții tineri cu BII. Atât pacienții aflați în tratament cu doze crescute de glucocorticoizi, cât și cei cu terapie biologică au modificări ale masei osoase. Screeningul precoce și urmărirea pe termen lung este recomandată în cazul acestor pacienți.

Keywords: collagen, minocycline, spongious delivery systems, freeze-drying

Introduction

Low bone mineral density (BMD) is a frequent complication that can occur in inflammatory bowel disease (IBD), even in younger patients [4]. Its pathogenesis is multifactorial, with risk factors such as low body mass index (BMI), a previous high–dose exposure to glucocorticoids, systemic inflammation, malnutrition, and malabsorption being commonly incriminated. Local and systemic production of

inflammatory cytokines (TNFα, IL6) negatively affects bone metabolism, and is linked to the pathogenesis of bone loss through t RANKL activation, resulting in osteoclastogenesis induction [9, 10, 16]. Anti-TNFα therapy was shown to have a good impact on bone metabolism, with increased bone formation and improved BMD dual energy X-ray assessment (DXA) measurements [11]. A recent prospective study showed that osteoblast differentiation and functionality were affected in IBD patients and the use of biologic therapy could reverse these interferences [17]. Crohn`s disease (CD) has been associated with low BMD, leading to osteopenia and osteoporosis, as it was reported by a previous study [5]. However, the reported data involved both young and old adults, which might have influenced the results. The majority of the patients were diagnosed at a young age and required multiple treatments, with impact on their bone mass. Aside from the high dose exposure to glucocorticoids, a well-known parameter that could aggravate bone loss, studies on the impact of biologic therapy are still under debate.

The aim of the study was to assess the prevalence of low BMD in IBD premenopausal women and men under 50 years old, with special focus on well-controlled disease receiving high doses of glucocorticoids or biologic therapy.

Materials and Methods

A total of 52 IBD patients and 53 healthy subjects were evaluated in a research study conducted by the Department of Endocrinology, Elias Hospital, Bucharest, Romania. All participants were premenopausal women and men under 50 years old. IBD patients were diagnosed according to ECCO guidelines [7] We also studied two subgroups with a good control of the disease, as appreciated by the Harvey-Bradshaw index (HBI) for Crohn`s disease (CD) and the partial Mayo score for ulcerative colitis (UC) [2, 12]. HBI takes into account general wellbeing, abdominal pain, number of liquid stools, abdominal mass, and complications, whereas the partial Mayo score considers stool frequency, rectal bleeding, and physician global assessment. A disease score of HBI equal or under 4 and partial Mayo score under 1 is considered as clinical remission, while a higher score represents an active disease [2, 12].

Group 1 (corticoids treated patients) comprised patients on high doses long term glucocorticoids (2 - 4 sequences of more than 7.5 mg prednisone for more than three months or under continuous exposure to glucocorticoids for six months). Group 2 (biologics treated patients) included patients on biologic therapy (anti–TNFα) with no exposure or only short-term use of high doses of glucocorticoids (more than 7.5 mg prednisone and less than three months). A control group of 29 BMI, age and gender matched subjects was selected and a comparative analysis of DXA parameters of the two subgroups was performed. Demographic characteristics, medical history, previous and current treatments were documented. Patients' and subjects' assessments included anthropometric measurements (height and weight) and the calculation of BMI and DXA.

The BMD of the lumbar spine and hip were assessed for all subjects included in the study using DEXA Prodigy®, GE Healthcare. The trabecular bone score (TBS) was analysed using DEXA images of the lumbar spine (L1 - L4), employing TBS iNight software version 3.0.2.0, calculated for the same region as lumbar BMD assessment.

We expressed DXA results using Z-score as this is the standard approach as for the assessment of BMD in premenopausal women and men under 50 years old and we considered low BMD, according to the International Society of Clinical Densitometry, as Z-score <- 2SD [15].

All subjects were provided and signed an informed consent for the inclusion in the study. The study protocol was conducted in accordance with the DoH (Declaration of Helsinki) and the protocol was approved by the Hospital Ethics Committee.

None of the patients or the controls received anti-osteoporotic treatment, vitamin D or calcium supplementation at the time of the evaluation.

Statistical analysis

Statistical analyses were performed using SPSS (version 21.0; SPSS Inc.). Descriptive data were expressed as average SD and interquartile range (IQR) according to their distribution. Normally distributed variables were compared using an independent t-test, and non-parametrically distributed variables using the Mann-Whitney U-test. In the case of categorical variables, we used chi-squared test. In order to analyse the differences between the studied groups we used one-way ANOVA test. $p < 0.05$ was considered statistically significant. Type I collagen of bovine origin was extracted by the currently

Results and Discussion

Demographic characteristics and comparative analysis of DXA parameters between IBD patients and controls

A total of 52 IBD patients were included in the study, 33 Crohn`s disease (CD) CD and 19 ulcerative colitis (UC), 29 men and 23 women, median BMI 22.2 (5.4) kg/m^2, median age 33 (17) years and disease duration 5 (7) years, mean age at the time of diagnosis 26.9 ± 10.3 years. A total of 53 BMI, age, gender matched healthy subjects were enrolled in the study.

Overall, a total of 17 of the patients (32.69 %) were diagnosed with low BMD, of whom 14 with CD and 3 - UC (42.4 % *vs* 15.7 %, $\chi = 3.88$, $p = 0.04$). In the control group 5 were diagnosed with low BMD (32.6% *vs* 9.4 %, $\chi = 8.5$, $p = 0.003$). Among the IBD patients,

two were diagnosed with vertebral fractures, while none were identified from the healthy subjects' group. When compared to healthy controls, all DXA parameters were significantly lower in IBD patients: LS BMD (1.07 ± 0.17 *vs* 1.16 ± 0.16, p = 0.005), hip BMD (0.91 ± 0.13 *vs* 0.98 ± 0.13, p = 0.014) and TBS (1.40 ± 0.1 *vs* 1.45 ± 0.099, p = 0.011) as seen in Table I.

Table I

Demographic, clinical, DXA parameters and low BMD in case and control groups

Parameter	All patients (105)	IBD patients (52)	Healthy controls (53)	p-value
Age (years) (IQR)	33 (16)	33 (17)	32 (16)	NS
BMI (kg/m^2) (IQR)	23.1 (5.6)	22.2 (5.4)	23.8 (5.9)	NS
LS BMD (g/cm^2) (SD)	1.11 ± 0.17	1.07 ± 0.17	1.16 ± 0.16	0.005
Z-score LS BMD (SD)	-0.73 ± 1.3	-1.09 ± 1.2	-0.38 ± 1.2	0.006
Hip BMD (g/cm^2) (SD)	0.95 ± 0.12	0.91 ± 0.13	0.98 ± 0.13	0.014
Z-score hip BMD (SD)	-0.64 ± 0.92	-0.91 ± 0.93	-0.37 ± 0.85	0.002
TBS (SD)	1.43 ± 0.11	1.40 ± 0.1	1.45 ± 0.099	0.011
Low BMD (%)	20.9%	32.69%	9.4%	0.003

Values are presented as mean ± SD, IQR, according to the type of variable and the normality of distribution. p-value presented statistically significant differences p < 0.05. BMI=body mass index, LS BMD = lumbar spine bone mass density, TBS = trabecular bone score

Comparative analysis of DXA parameters according to different types of treatment

Group 1 (corticoid treated patients) included 14 patients, median age 33 (9) years, BMI 21.6 (4.1) kg/m^2 and group 2, 24 patients, median age 31 (13) years, BMI 22.3 (6) kg/m^2. These patients' DXA parameters were compared to 29 healthy subjects with matched age, sex, and BMI.

Patients in group 1 had significant lower LS and hip BMD as compared to group 2 (0.94 ± 0.13 *vs* 1.09 ± 0.17, p = 0.01, respectively 0.85 ± 0.11 *vs* 0.95 ± 0.14, p = 0.04). Moreover, all DXA parameters were more impaired than in the control group: LS BMD (0.94 ± 0.13 *vs* 1.22 ± 0.11, p < 0.001), Z-score LS BMD (-2.2 ± 1.1 *vs* 0.03 ± 0.98, p < 0.001), hip BMD 0.85 ± 0.11 *vs* 0.99 ± 0.1, p < 0.001), TBS (1.34 ± 0.14, 1.49 ± 0.06, p < 0.001).

When compared to the control group, patients in group 2 (biologics treated patients) had significant lower values of all significant bone parameters: (LS BMD 1.2 ± 0.11 *vs* 1.09 ± 0.17, p = 0.002), LS Z-score (0.03 ± 0.98 *vs* -0.8 ± 1.1, p = 0.003), hip BMD (0.99 ± 0.1 *vs* 0.95 ± 0.14, p = 0.188), TBS (1.49 ± 0.06 *vs* 1.42 ± 0.08, p = 0.003). Data are presented in Figure 1.

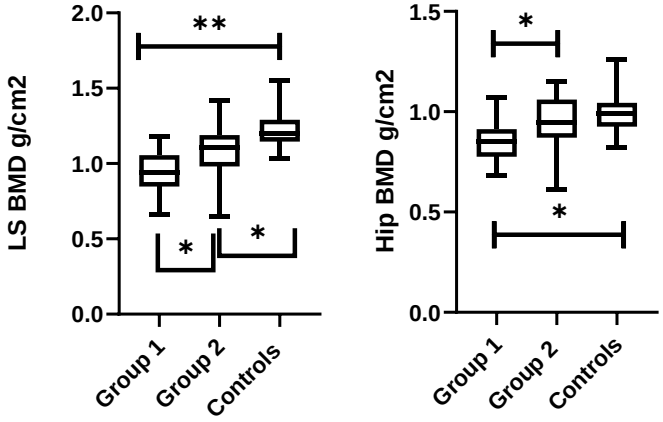

Figure 1.

Differences between DXA parameters in groups 1, 2 and controls;
Group 1 – Corticoids treated patients; Group 2 – Biologics treated patients. ** p < 0.005, * p < 0.05

Although often neglected, low BMD is a frequent complication associated with IBD. Our study showed that approximately one third of the young IBD patients (32.69%) have low BMD. This result correlates to previous research stating that osteopenia and osteoporosis may affect between 20% [13] and 40% [3] of IBD patients. However, data regarding the prevalence of low BMD in young adults has not been yet reported. Our data are similar to a study that included only young adults, but low BMD was appreciated as Z-score < -1 SD and included Asian patients newly diagnosed with IBD [4]. Moreover, our study showed that there is a significant difference in both lumbar spine and hip BMD, when compared with healthy subjects, as described in previous studies [14].

Several research studies suggested that CD is usually associated with a higher risk for low BMD, due to its more profound inflammation and involvement of the small intestine leading to malabsorption, and our study showed similar results [6]. However, glucocorticoids

are still an important factor affecting bone mass in young patients and our data show that BMD is lower in both lumbar and spine in these patients, when compared to patients receiving immunologic therapy. Over the last decades, the introduction of biologic therapies with anti-inflammatory activity has been emphasized as a treatment that could lead to a better control of the disease, alongside the improvement of bone loss associated with chronic diseases. However, our study showed that even in a well-controlled disease state on biologic agents, bone parameters are significantly lower when compared to healthy controls. The fact that biologic therapy is reserved for patients with adverse outcomes and the increased time between first symptoms and diagnosis, could be some of the explanations for enhanced bone loss. Moreover, the patients' age at diagnosis, before achieving peak bone mass, could represent another factor contributing to a decreased BMD. Although both BMD at the lumbar spine and at the hip were lower than that in healthy controls, only LS BMD was statistically significant, suggesting that changes could appear faster in trabecular bones. Further longitudinal studies should be conducted to assess the evolution over time.

Several studies have assessed the impact of anti-TNFα drugs on bone changes. A longitudinal study conducted by Bernstein showed increased bone mass after one year of treatment with anti-TNF medication [1]. Another study showed that after seven years of longitudinal follow–ups, even though there was an increase in bone mineral density, it did not reduce the risk of vertebral fractures in these patients [8].

The strength of our study is the population included in the research. We focused on pre-menopausal women and men under 50 years old, whereas prior observations focused on both old and young patients. Since BMD is influenced by age, decreases in sex hormones levels, changes in lean mass and sarcopenia, we excluded these confounding factors.

However, we are aware of some limitations in our study such as the small number of patients included in the study and the lack of prospective information. Also, it would have been interesting to screen newly diagnosed patients with IBD, in order to assess existing bone changes compared to healthy subjects at diagnosis.

Conclusions

Low BMD remains an important complication that can affect young IBD patients with precocious screening being the key in this process. Although glucocorticoids therapy is a well-known risk factor for bone loss, low BMD was also observed in well-controlled patients under biologic therapy. Long-term prospective studies should be conducted in order to further validate the perceived results.

Conflict of interest

The authors declare no conflict of interest.

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