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*Observational Study*

Overweight and abdominal fat are associated with normal bone mineral density in patients with ulcerative colitis

fat body and bone mineral density in ulcerative colitis

Mirella Brasil Lopes, Andre Castro Lyra, Raquel Rocha, Fernanda Gomes Coqueiro, Carla Andrade Lima, Carolina Cunha de Oliveira, Genoile Oliveira Santana

## Abstract

### BACKGROUND

Low bone mineral density (BMD) is common in patients with inflammatory bowel disease (IBD). However, nutritional risk factors for low BMD in the ulcerative colitis (UC) population are still poorly understood.

### AIM

To investigate the association between anthropometric indicators, body composition and BMD in patients with UC.

### METHODS

Cross-sectional study with UC patients, adults, of both genders, followed up on an outpatient basis and control group. The nutritional indicators evaluated were body mass index (BMI), total body mass (TBM), waist circumference (WC), body fat in kg (BFkg), body fat in percentage (BF%), trunk body fat (TBF) and also lean mass (LBM). Body composition and BMD assessments were performed by dual-energy X-ray absorptiometry (DXA).

### RESULTS

The sociodemographic characteristics of patients with UC ( $n = 68$ ) were similar to healthy volunteers ( $n = 66$ ) ( $p > 0.05$ ). Most patients (97.0%) were in remission of the disease, 58.8% were eutrophic, 33.8% were overweight, 39.0% high WC and 67.6% excess BF%. However, the means of BMI, WC, BFkg and TBF of UC patients were lower when compared to the control group ( $p < 0.05$ ). Reduced BMD was present in 41.2% of patients with UC (38.2% with osteopenia and 2.9% with osteoporosis) and 3.0% control group ( $p < 0.001$ ). UC patients with low BMD had lower BMI, TBM and BFkg values than those with normal BMD ( $p < 0.05$ ). Male patients are more likely to have low BMD (PR = 1.86; 95%CI: 1.07–3.26). Those with excess weight (PR = 0.43; 95%CI: 0.19–0.97) and high WC (PR = 0.44; 95%CI = 0.21–0.94) are less likely to have low BMD.

## CONCLUSION

Patients with UC in remission have a high prevalence of metabolic bone diseases. Body fat appears to protect against the development of low BMD in these patients.

**Key Words:** ulcerative colitis; bone mineral density; body composition; fat body; abdominal fat.

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**Core Tip:** here is a high prevalence of osteopenia/osteoporosis in adult, outpatients with ulcerative colitis in remission. Patients with ulcerative colitis had 22.4 times greater chance of developing reduced bone mineral density than healthy individuals. Lower values of body mass index and body fat indicators were identified in patients with ulcerative colitis with low bone mineral density. Low bone mineral density was associated with males and those without excess weight and with normal waist circumference.

## INTRODUCTION

Low bone mineral density (BMD) is often seen in patients with inflammatory bowel disease (IBD)<sup>[1,2]</sup>. Patients with Crohn's disease and ulcerative colitis (UC), the main types of IBD, are at increased risk of fracture compared to healthy controls, with an osteoporotic fracture risk around 32%<sup>[3-6]</sup>. In patients with UC, the prevalence of osteoporosis varies between 2% to 9%<sup>[7]</sup>.

The cause of osteoporosis in patients with IBD is multifactorial. Most studies involving patients with UC demonstrate that the main risk factors for this disease are

related to genetics, chronic inflammatory status, treatment with steroids and low weight<sup>[8-10]</sup>.

Nutritional status appears to influence the BMD of patients with IBD. The inflammatory process and complications of the disease in the active phase can lead to compromised nutritional status, with reduced body mass and muscle mass reserves and micronutrient deficiency, and consequently to low BMD and increased risk of osteoporotic fractures<sup>[11,12]</sup>. Although the increased prevalence of overweight/obesity is evident in patients with UC, studies explaining the relationship between abdominal fat and disease complications in this group of patients are limited<sup>[13]</sup>.

Studies that demonstrate the relationship between nutritional risk factors for low BMD are more frequent among patients with CD considering the extension and severity of the disease, which can compromise the main sites of nutrient absorption. Thus, there is little evidence that brings the relationship of nutritional risk factors for the development of reduced BMD in patients with UC. The aim of the present study was to investigate the association between indicators of total body mass, body composition and BMD in patients with UC.

## **MATERIALS AND METHODS**

### *Study design and patients*

Cross-sectional study, involving adult outpatients with UC, from two reference centers in the treatment of IBD. Consecutive patients with a diagnosis of UC confirmed by clinical, endoscopic, radiological and histological criteria were included<sup>[14]</sup>. The control group consisted of healthy volunteers, family members and close people with the same sociodemographic characteristics and lifestyle compared to the UC group. Volunteers recruited were matched for gender and age, with no history of bowel surgery or taking medications known to affect bone turnover.

Elderly people, pregnant women, patients with diseases that cause changes in bone metabolism (chronic renal failure, chronic obstructive pulmonary disease, thyroid disease, liver disease, systemic lupus erythematosus), malignant diseases, diabetes

mellitus, celiac disease and **menopausal, post-menopausal** or in use of estrogen therapy women were not included in the study.

#### *Clinical data*

The clinical criteria of patients with UC evaluated were activity index and disease duration, past history of intestinal resection, accumulated dose of glucocorticoids in the last year, use of glucocorticoids for 3 mo or more, extent of disease according to Montreal classification<sup>[15]</sup>, serum calcium, albumin and CRP levels, in addition to smoking, regular physical activity<sup>[16]</sup> and use of calcium and vitamin D supplements.

Disease activity was assessed by the Lichtiger index<sup>[17]</sup>, considering activity when a score  $\geq 10$  points. Calcium (mmol/L) and serum albumin (g/dL), C-reactive protein (CRP) (mg/L) were collected on the same day as the BMD evaluation and performed in the same laboratory. **Calcium and albumin were measured using the dry chemical method and C-RP (C-reactive protein) was measured by the turbidimetry method.**

#### *Anthropometric assessment and body composition*

Anthropometric measurements were performed by a trained and standardized team. Height (in centimeters) and body weight (in kg) were measured in duplicate, wearing light clothing and without shoes, using a scale (**Filizola®, São Paulo, Brazil**), 150 kg capacity and 100g interval, with an attached stadiometer with a 0.5cm scale. The body mass index (BMI) was obtained using the formula  $\text{weight/height}^2$  and classified according to the World Health Organization<sup>[18]</sup>. **For statistical analysis, two groups were considered, those with excess weight ( $\text{BMI} \geq 25.0 \text{ kg/m}^2$ ) and those without excess weight ( $\text{BMI} < 25.0 \text{ kg/m}^2$ ).**

Waist circumference (WC) was measured with the individual in an upright position, with feet together and without shoes. The measurement was taken with an inelastic measuring tape, which circled the individual at the midpoint between the iliac crest and

the last rib<sup>[18]</sup>. High WC was considered when  $\geq 80$  cm for women and  $\geq 90$  cm for men<sup>[19]</sup>.

The evaluation of body composition was performed by dual-energy X-ray absorptiometry (DXA) of the total body using a Prodigy Lunar Bone Densitometer (GE Medical Systems®, USA). The equipment calibration followed the manufacturer's recommendations and both the calibration and the analyzes were performed by a single technician with experience in this type of assessment. The values of total body fat in percentage (BF%), total body fat in kilograms (BFkg), trunk body fat in kg (TBF) and lean mass in kilograms (LBM) were obtained. The percentage of body fat (BF%) was considered high when  $\geq 25\%$  for men and  $\geq 32\%$  for women<sup>[18]</sup>.

#### *Bone mineral density assessment*

BMD was determined by DXA in the whole body, lumbar spine (L1-L4) and femoral neck. Results da DMO were expressed in g/cm<sup>2</sup> and also presented as T-score or Z-score. The BMD classification was based on the T-score for men 50 years of age and older and patients with UC and the Z-score for those younger than 50 years of age for men and premenopausal women. For patients with UC, the T-score was used regardless of age, considering the possibility of secondary loss of bone mass determined by the underlying disease or by the therapies used. According to the T-score the BMD was normal up to 1 standard deviation (SD), with osteopenia values below -1 and above -2.5 SD and with osteoporosis  $\leq -2.5$  SD. For the Z-score, BMD  $\leq -2.0$  SD was considered below the estimated for the age group (BMD reduced for age). In the osteopenia/osteoporosis classification, the bone sites of the femoral neck or lumbar spine were used<sup>[20]</sup>.

#### *Statistical analysis*

Results were expressed as proportions for categorical variables, mean and SD for continuous variables with normal distribution, and median and interquartile range (IIQ) for variables without normal distribution. Mann-Whitney test was used to compare continuous variables and the chi-square test or Fisher's exact test to compare



categorical variables. Poisson regression analysis with robust variance was used to obtain estimates of the prevalence ratio and the respective 95% confidence intervals. For all tests, a p-value <0.05 was considered statistically significant. The Statistical Package for Social Science program (SPSS, Chicago, IL, USA, version 21.0) was used for data tabulation and analysis.

#### *Ethical considerations*

Informed consent was obtained from all participants and the Ethics Committee of the University Hospital Professor Edgar Santos approved the study protocol (n°117/2011).

## **RESULTS**

#### *Clinical and nutritional characteristics*

In this study, 68 patients with UC and 66 people in the control group were included. In both groups, the majority were female and demographics, lifestyle and use of nutritional supplements were similar ( $p > 0.05$ ) (Table 1).

Most patients (97.0%) were in remission of the disease, only 2.9% had a previous history of intestinal resection and extensive colitis was present in 44.1%. The use of steroids in the last year occurred in 17.6% of the patients, and of these, 66.7% used it for three months or more (Table 1).

Regarding the anthropometric nutritional status, it was observed that the majority of UC patients had normal weight (58.8%), however the frequency of overweight was high (33.8%), with six (8.8%) had grade I obesity and one (1.5%) had grade II obesity. Women had a higher concentration of BF% (37.3% vs 19.7%;  $P = 0.00$ ), BFkg (22.5kg vs 12.7 kg;  $P = 0.00$ ) and TBF (10.8kg vs 7.3 kg;  $P = 0.00$ ) than men. BFkg and TBF of UC patients were statistically lower compared to the control group ( $p < 0.05$ ) (Table 1).

#### *BMD Characteristics*



Low BMD was present in 41.2% ( $n = 28$ ) of patients with UC (38.2% with osteopenia and 2.9% with osteoporosis) and in 3.0% ( $n = 2$ ) in the control group ( $p < 0.001$ ). It was observed that UC patients have a 22.4 times greater chance of developing reduced BMD than healthy individuals (OR: 22.4; 95%CI: 5.06 – 99.19). The majority (71.4%; 20/28) of UC patients with low BMD were younger than 45 years of age. The BMD of total body in UC patients was statistically lower compared to the control group ( $p < 0.05$ ) (Table 1).

UC patients who had low BMD were mostly male, without regular physical activity and had left colitis compared to those with normal BMD ( $p < 0.05$ ) (Table 2). Serum calcium had a lower concentration in those with low BMD, although with a clinically irrelevant difference (Table 2). Low BMD occurred equally at both sites, spine and femur.

Individuals in the control group who had low BMD (3.0%; 2/66) had osteopenia located in the lumbar spine, all were female and without regular physical activity.

#### *Anthropometric indicators and body composition vs BMD*

Male patients with UC are more likely to have low BMD (PR = 1.86; 95%CI: 1.07 – 3.26) and those with excess weight (PR = 0.29; 95%CI: 0.13–0.66) and high WC (PR = 0.36; 95%CI = 0.17–0.75) are less likely to have low BMD (Table 3). Patients with UC with low BMD had a lower BMI value than those with normal BMD (22.8 [20.5–24.4] vs 25.6 [21.9–28.4] kg/m<sup>2</sup>;  $P = 0.02$ ), TBM (58.5 [52.7–65.7] vs 67.4 [59.1–76.8] kg;  $P = 0.02$ ) and BFkg (17.2 [9.9–21.3] vs 21.2 [15.4–28.4] kg;  $P = 0.01$ ) (Figure 1).

No significant differences were found in anthropometric nutritional characteristics and body composition between those with UC with low and normal BMD when stratified by sex.

## **DISCUSSION**

Our data demonstrate that in a sample of patients with UC, predominantly in remission, with reduced frequency of glucocorticoid use and excess body fat, low BMD

had a high prevalence, in patients under 45 years of age, being that excess weight and abdominal fat are associated with normal BMD.

It is recommended that patients with IBD should be screened based on established guidelines for the general population (pre-existing fragility fracture, women aged 65 years and older and men aged 70 years and older, and those with risk factors that increase probability of detecting low bone mass)<sup>[21]</sup>. However, this is a matter of concern considering that in this sample the majority of patients with UC with reduced BMD are younger than 45 years of age, with reduced frequency of glucocorticoid use and in remission.

Bone mass loss is a frequent complication in patients with UC<sup>[22-24]</sup> and with a higher prevalence when compared to healthy controls<sup>[25]</sup>. Greater bone fragility increases the risk of fractures, and consequently morbidity and reduced quality of life for patients. The mechanisms reported in the literature associated with bone loss in UC patients are mainly related to the UC itself, the use of steroids, hospitalization<sup>[25-27]</sup> and low BMI values<sup>[28-31]</sup>.

The role of obesity in patients with IBD is still uncertain, although initially it is believed that the greater inflammatory potential of adipose tissue could have a negative impact on the evolution of the disease in these patients<sup>[32,33]</sup>. The effect of body weight on bone mass can be attributed to the mechanical compression of weight on the skeleton, and in response, it increases bone mass to accommodate greater load<sup>[34]</sup>. In UC patients, obesity appears to be associated with a lower risk of low BMD<sup>[35]</sup>, with a 5 kg/m<sup>2</sup> increase in BMI decreasing by 57% the chance of having low BMD in 327 patients with UC and ileo-anal anastomosis with pouch illegitimate<sup>[29]</sup>.

The effects that body fat plays on BMD in patients with IBD have been discussed<sup>[36]</sup>, considering the increase in the prevalence of overweight individuals diagnosed with UC<sup>[37,38]</sup>. Although there is no clear consensus in the literature, body fat seems to have a positive effect on bone mass, as a result of the anabolic effect of mechanical tension of the fat mass on bone, in addition to the action of hormones released by adipocytes, which influence the activities of bone cells, both osteoblasts and osteoclasts<sup>[34]</sup>.

The influence of gender on the BMD of patients with IBD is discordant<sup>[1,4]</sup>. In our study, male patients were more likely to have reduced BMD, we suppose that at the expense of lower body fat compared to females.

No studies were found evaluating the association between WC/abdominal fat and BMD in patients with IBD. It is known that the relationship between abdominal fat and BMD is quite complex and the results of studies in the general population are conflicting<sup>[39,40]</sup>. The two adipose tissues present in the abdominal region (subcutaneous and visceral) are highly metabolic, with the production of adipokines, estrogens and metabolic factors derived from bones, with feedback mechanisms that affect bone remodeling and body composition<sup>[40]</sup>.

Our article has some limitations, serum levels of alkaline phosphatase, parathyroid hormone and vitamin D. On the other hand, it has the advantage of assessing body mass by DXA. More robust, prospective studies with larger samples and techniques for more accurate quantification of adipose tissues are needed to better explain the relationship between total and abdominal body fat and BMD.

## **CONCLUSION**

In conclusion, we observed that male UC patients, in remission have a high prevalence of metabolic bone diseases, and nutritional parameters related to body fat seem protects against the development of low BMD. Understanding the protective effect that each nutritional component exerts on the bone mass of patients with IBD is important to assist in the development of strategies that can provide the control of metabolic bone diseases in these patients.

## **ARTICLE HIGHLIGHTS**

### ***Research background***

Inflammatory bowel disease is associated with complications such as low bone mineral density and increased risk of fracture compared to healthy controls. In patients with ulcerative colitis, the prevalence of osteoporosis varies between 2% to 9% and the main

risk factors are related to genetics, chronic inflammatory status, treatment with steroids and low weight.

### ***Research motivation***

There is little that brings the relationship of nutritional risk factors for the development of reduced bone mineral density (BMD) in patients with ulcerative colitis, despite the studies demonstrating the relationship between nutritional <sup>9</sup> risk factors for low BMD are more frequent in patients with Crohn's disease, considering evidence the extension and severity of factors the disease, which can compromise the main sites of nutrient absorption

### ***Research objectives***

We aim to investigate the association between indicators of total body mass, body composition and BMD in patients with UC.

### ***Research methods***

This cross-sectional study with ulcerative colitis patients, adults, of both genders, followed up on an outpatient basis and control group. The nutritional indicators evaluated were <sup>8</sup> body mass index (BMI), total body mass (TBM), waist circumference (WC), body fat in kg (BFkg), body fat in percentage (BF%), trunk body fat (TBF) and also lean mass (LBM). Body composition and BMD assessments were performed by dual-energy X-ray absorptiometry (DXA).

### ***Research results***

Most ulcerative colitis (UC) patients (97.0%) were in remission of the disease, 58.8% were eutrophic, 33.8% were overweight, <sup>5</sup> 39.0% high WC and 67.6% excess BF%. However, the means of BMI, WC, BFkg and TBF of UC patients were lower when compared to the control group (p <0.05). Reduced BMD was present in 41.2% of patients with UC (38.2% with osteopenia and 2.9% with osteoporosis) and 3.0% control

group ( $p < 0.001$ ). UC patients with low BMD had lower BMI, TBM and BFkg values than those with normal BMD ( $p < 0.05$ ). Male patients are more likely to have low BMD (PR = 1.86; 95%CI: 1.07–3.26). Those with excess <sup>1</sup>weight (PR = 0.43; 95%CI: 0.19–0.97) and high WC (PR = 0.44; 95%CI = 0.21–0.94) are less likely to have low BMD.

### *Research conclusions*

Patients with ulcerative colitis in remission have a high prevalence of metabolic bone diseases and body fat appears to protect against the development of low BMD in these patients

### *Research perspectives*

The future perspective is to evaluate other nutritional characteristics such as food consumption.

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