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DENSIDADE MINERAL ÓSSEA E GRAVIDADE DE DOENÇA EM PACIENTES COM DOENÇA INFLAMATÓRIA INTESTINAL

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“A mente que se abre a uma nova ideia jamais volta ao seu tamanho original”

Albert Einstein

DENSIDADE MINERAL ÓSSEA E GRAVIDADE DE DOENÇA EM PACIENTES COM DOENÇA INFLAMATÓRIA INTESTINAL

RESUMO

Introdução: A doença inflamatória intestinal está associada com baixa densidade mineral óssea. Nosso objetivo foi avaliar a associação entre gravidade de doença e DMO em pacientes com DII. **Métodos:** Trata-se de um estudo transversal de prevalência com grupo de comparação, realizado com pacientes com DII. Todos os pacientes e controles realizaram densitometria óssea. Nos pacientes com DII, foram analisados uso de medicações, internação, localização, extensão e fenótipo da doença, de acordo com classificação de Montreal. Atividade de doença foi avaliada de acordo com índices de Harvey Bradshaw e Lichtiger. Análise de correspondência múltipla foi utilizada para avaliar variáveis categóricas. **Resultados:** Foram estudados 68 pacientes com RCU, 60 com DC e 67 pessoas saudáveis. Dentre os pacientes com DC, a maioria teve diagnóstico com idade entre 17 e 40 anos. Doença ileocolônica e não estenosante-não penetrante foi a localização de doença e o comportamento mais frequentes. Em relação a RCU, a colite extensa foi a extensão da doença mais encontrada. Pacientes apresentaram mais osteopenia que os controles. Sexo masculino, doença perianal, doença penetrante e idade de diagnóstico > 40 anos estiveram associados com baixa DMO nos pacientes com DC. Uso de azatioprina e infliximabe foi associado com osteopenia. Nos pacientes com RCU, colite esquerda, uso de corticóides e internação estiveram associados com baixa DMO. Não houve associação entre atividade de doença e osteopenia ou osteoporose. **Conclusion:** Gravidade de doença parece estar associada com osteopenia em pacientes com DII. Devemos estar atentos a alguns fatores que podem estar relacionados com essa perda óssea como doença perianal, comportamento penetrante e uso de azatioprina e infliximabe em pacientes com DC e colite esquerda em pacientes com RCU.

Palavras-chave: Densidade mineral óssea, retocolite ulcerativa, doença de Crohn, doença inflamatória intestinal e osteoporose.

BONE MINERAL DENSITY AND INFLAMMATORY BOWEL DISEASE SEVERITY

ABSTRACT

Background: Inflammatory bowel disease is associated with low bone mineral density. Our purpose was to evaluate the association between disease severity and BMD in patients with IBD and also to identify if there is association between BMD and Montreal classification, disease activity and drug therapy. **Methods:** It is a cross-sectional prevalence study with a comparison group, conducted with IBD patients. All patients and controls had their bone mineral density measured. In IBD patients, current medications, hospitalization, location, extent and phenotype of the disease, according to the Montreal classification, were analyzed. Harvey Bradshaw and Lichtiger indexes were used to measure disease activity. Multiple Correspondence analysis was applied to evaluate the categorical variables. **Results:** We studied 68 patients with UC and 60 with CD. The control group consisted of 67 healthy subjects. In CD group, most of the patients were diagnosed between 17-40 years of age. Ileocolonic and non-stricturing non-penetrating disease were the most frequent disease location and behavior, respectively. In terms of UC, extensive colitis was the most frequent disease location. UC and CD patients were more likely to have osteopenia than control. In CD group, male patients, perianal disease, penetrating behavior and age at diagnosis >40 years were associated with low BMD. Patients taking azathioprine and infliximab also seem to be associated with osteopenia. In UC group, we observed association between low BMD and male patients, left colitis, corticosteroid use and hospitalization. Disease activity was not associated with osteopenia or osteoporosis in CD and UC patients. **Conclusion:** Disease severity seems to be associated with osteopenia in IBD patients, so we should pay attention in some factors that can be related to this loss like perianal disease, penetrating behavior and azathioprine and infliximab use in CD patients and left colitis in UC patients.

Keywords: Bone mineral density, ulcerative colitis, Crohn's disease, inflammatory bowel disease and osteoporosis.

LISTA DE ABREVIATURAS E SIGLAS:

Em língua portuguesa

DC	Doença de Crohn
DII	Doença inflamatória intestinal
DMO	Densidade mineral óssea
RCU	Retocolite ulcerativa

Em língua inglesa

BMD	Bone mineral density
CD	Crohn's disease
CS	Corticosteroids
DEXA	Dual-energy X-ray absorptiometry
DHEAS	Dehydroepiandrosterone sulphate
IBD	Inflammatory bowel disease
IFX	Infliximab
SD	Standard deviation
TNF-α	Tumor necrosis factor alpha
UC	Ulcerative colitis

SUMÁRIO:

1 INTRODUÇÃO

A doença inflamatória intestinal (DII) compreendida, sobretudo, pela Retocolite Ulcerativa (RCU) e pela Doença de Crohn (DC) é caracterizada por um quadro inflamatório do trato gastrointestinal, porém está associada com diversas manifestações extra-intestinais (MEI).

As MEI podem acometer vários órgãos e sistemas, sendo os principais a pele, o fígado e vias biliares e as articulações. A DII também está relacionada com alterações no metabolismo ósseo. Sabe-se que pacientes com DII têm maior risco de perda de massa óssea que a população geral.

A inflamação crônica tem sido relacionada com redução da densidade mineral óssea (DMO) causando osteopenia e osteoporose. A principal complicação relacionada à osteoporose nesses pacientes é o surgimento de fraturas, sobretudo fraturas não traumáticas. Acredita-se que pacientes com DII tenham um risco 40% maior de fraturas que a população geral.

Diversos fatores de risco têm sido relacionados com perda óssea na DII. Alguns relacionados à população geral, como idade, sedentarismo, mulheres na pós-menopausa, desnutrição, dentre outros. Fatores de risco relacionados especificamente com a DII também têm sido identificados como a inflamação, composição corporal, uso de medicações e cirurgias intestinais.

Alguns elementos associados a DII ainda não estão claramente definidos se interferem na densidade mineral óssea desses pacientes. A atividade de doença parece causar redução na massa óssea, porém os resultados são conflitantes. Não sabemos também se a gravidade da doença inflamatória interfere na DMO, como também não temos definição se algumas medicações usadas no tratamento da DII podem ter fator de proteção.

Além disso, a prevalência de osteopenia e osteoporose na DII é bastante variável, pois depende do desenho de estudo realizado, da localização e do tipo de população estudada. A maior parte das publicações foi realizada na Europa e na América do Norte que apresentam condições climáticas e populações bem diferentes. No Brasil, temos alguns estudos publicados, porém realizados na região sudeste e sul.

Esse estudo foi realizado com pacientes de dois centros de referência no tratamento das DII na Bahia, estado localizado no nordeste brasileiro. Não há, até então, publicações na literatura internacional que avaliem a DMO desses pacientes.

2 OBJETIVOS

2.1 OBJETIVO GERAL

- Avaliar associação entre gravidade de doença e densidade mineral óssea em pacientes com DII.

2.2 OBJETIVOS ESPECÍFICOS:

- Realizar revisão da literatura sobre os fatores de risco associados a osteoporose na DII
- Avaliar associação entre densidade mineral óssea e atividade de doença em pacientes com DII
- Avaliar associação entre densidade mineral óssea e terapêutica medicamentosa em pacientes com DII.

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Risk factors for osteoporosis in Inflammatory Bowel disease patients

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ABSTRACT

It has been demonstrated that inflammatory bowel disease (IBD) patients have higher risk for reduction in bone mineral density (BMD) and osteopenia / osteoporosis. The major complication of osteoporosis is the increased risk of fracture. In this article, we reviewed each risk factor for osteoporosis in IBD patients. The inflammation is one of the factors that contribute to osteoporosis in IBD and the main system involved in bone loss seems to be the RANK/RANKL/osteoprotegerin. Smoking has been recognized as a risk factor for bone loss and fractures and many mechanisms have been proposed to explain this loss. Body composition also seems to interfere in bone metabolism and increasing muscle mass may have a positive effect on BMD. It is known that corticosteroid use is frequent in IBD patients and it stimulates osteoclastogenesis. IBD patients are also associated with vitamin D deficiency which contributes to bone loss. However, infliximab therapy has been associated with improvement in bone metabolism although it's not clear if it is because of inflammation improvement or infliximab use. Ulcerative colitis patients with proctocolectomy and ileal pouch and CD patients with ostomy seem to be in risk for bone loss and should be monitored closely.

Key words: Inflammatory bowel disease, Bone mineral density, Ulcerative colitis, Crohn’s disease, Osteoporosis, Risk factors.

INTRODUCTION

Inflammatory bowel disease (IBD) comprising mainly by ulcerative colitis (UC) and Crohn's disease (CD) is associated with various systemic complications such as extra-intestinal manifestations (EIM) [1]. These complications are found in about 40% of the patients. The most widely known EIM are skin lesions (erythema nodosum and pyoderma gangrenosum), articular manifestations and liver diseases (primary sclerosing cholangitis and primary biliary cirrhosis) [2, 3].

IBD patients have higher risk for bone loss than the general population. It is known that chronic inflammation causes a reduction in bone mineral density (BMD) leading to osteopenia and osteoporosis. Cross-sectional studies have reported highly variable prevalence of low BMD in IBD patients. The prevalence of osteopenia and osteoporosis varies significantly depending on the study population, location, and design, but ranges from 22%-77% and 17%-41%, respectively [4].

Dual-energy X-ray absorptiometry (DXA) is the current gold standard technique for measuring bone mass. Measurements are usually obtained at the femoral neck and lumbar spine. The DXA results are typically expressed as the number of standard deviations (SD) above or below the mean expected for individuals of the same age, ethnicity and gender (Z-score) or the mean of peak bone mass in young adults (T-score) [5-7].

The World Health Organization has reported formulated diagnostic ranges for osteoporosis based on T score. Osteoporosis and osteopenia are defined by a T-score below -2.5, and between -1 and -2.5, respectively. These recommendations were derived from postmenopausal Caucasian females. Therefore, caution must be exercised when extrapolating these data to other groups [7, 8].

The current guidelines recommend DXA screening in IBD patients with one or more risk factors: history of vertebral fractures, postmenopausal, male > 50 years of age, chronic corticosteroid therapy, or hypogonadism [7 - 9].

The major complication of bone loss and osteoporosis is the increased risk of fracture, especially nontraumatic fractures [10, 11]. Bernstein et al. have demonstrated that the incidence of fracture among persons with IBD is 40% greater than in the general population [12]. Other authors also showed similar findings [13 – 15].

It is unknown if there are differences between the IBD type (CD or UC) and BMD. A cross sectional population based study, published by Janhsen et al. have found that CD patients had significantly reduced BMD compared with UC patients and healthy controls[16]. However, this result is not in agreement with other reports.

It is also not clear if gender interferes with BMD in IBD patients. Ardizzone et al. showed that among UC patients, spine and femur BMD Z-scores and T-scores were significantly lower in men than in women, however this has not demonstrated in CD patients [17]. A case control cross-sectional study with 113 CD patients found that female patients had significantly decreased BMD of the femoral neck and the trochanteric region but in male patients, BMD was not significantly different from that of healthy controls [18].

Apart from chronic inflammation, some risk factors associated to IBD or general population are also related to loss of bone mass as older age, postmenopausal status, smoking, malnutrition, physical inactivity, use of corticosteroids for more than three months and vitamin D deficiency[19].

The aim of this review was to describe the specific risk factors for osteoporosis in IBD patients.

INFLAMMATION

Many factors have important effect on bone metabolism, but there is increased evidence that inflammation per se may contribute to osteoporosis in IBD. Some studies in patients with newly diagnosed IBD have shown reduction of BMD, even without the use of medications such as corticosteroids [20, 21].

Several chronic inflammatory disorders are associated with osteoporosis and increased number of fractures. Inflammation is characterized by production of cytocines that have been associated with increased bone resorption and reduced bone formation. The main system involved in the development of osteoporosis in IBD and other inflammatory diseases seems to be the RANK/RANKL/osteoprotegerin [22].

The receptor activator of nuclear factor-κB (RANK) is a transmembrane protein expressed on the surface of cells of hematopoietic origin and that belongs to TNF receptor family. It is the primary cytokine receptor in the development of osteoclastogenesis [23-26].

The ligand for RANK receptor (RANKL) is expressed on the surface of osteoblasts, mesenchymal cells and other cells such as T and B-lymphocytes. When the RANKL binds to RANK differentiation of osteoclast precursors occurs. Furthermore, RANKL also promotes increased resorptive activity of osteoclasts and prolong their survival, by supressing apoptosis [23-26].

As a control, to maintain balance, osteoblasts produce osteoprotegerin (OPG), which is a decoy receptor molecule that naturally binds to RANKL to inhibit osteoclast activation and thus protect against bone loss [23-26].

Chronic inflammatory state has effects on osteoblasts and osteoclasts mediated by T cell-produced cytokines. Activated T cells produce RANKL and its soluble form (sRANKL) and therefore directly trigger bone loss by inducing and activating osteoclasts via RANK [27].

Several pro-inflammatory cytokines are involved in the activation of osteoclasts, such as IL-1, tumor necrosis factor alpha (TNF-α), IL-6, IL-11, IL -15 and IL-17[28].

IL-6 appears to have an important role in mediating inflammatory osteoporosis, and it may also be involved in pathways leading to osteoporosis that are not elicited by inflammation [29].

A study by Turk et al. showed that patients with newly diagnosed and untreated CD had elevated levels of proinflammatory cytokines (IL-6, TNF-α, IL-1β) and increased free sRANKL and OPG activity. The authors also observed a positive correlation between TNF-alpha and sRANK [30].

Disease activity appears to interfere with bone metabolism. Some studies have shown that patients with disease in remission have an increase in BMD. Reffiti et al. analyzed 137 IBD patients and showed that patients with longer disease in remission had higher BMD [31].

SMOKING

Smoking has been recognized as a risk factor for both bone loss and fractures many years ago. Several mechanisms have been proposed to explain the differences in BMD between smokers and non-smokers. However, the pathophysiologic mechanisms underlying osteoporosis in cigarette smokers have not been fully explored [32, 33].

Some studies have demonstrated that the effect of smoking on bone may be influenced by dose and duration of smoking [33, 34].

Smoking seems to be related to vitamin D deficiency, and one possible explanation is that smoking may alter hepatic metabolism of vitamin D by influencing 25 hydroxylase in the liver, lowering serum 25-hydroxyvitamin D [32, 33].

There is also evidence that smoking alters gastrointestinal calcium absorption. Smokers also have an unhealthy lifestyle such as low calcium/vitamin D intake, lack of exercise and alcohol ingestion that affect bone health [32, 33].

Although there are controversies if smoking is associated with estradiol levels, some studies have demonstrated that smoking changes estrogen production and its metabolism. There are some possible mechanisms such as nicotine may reduce estrogen production, smoking enhances the hepatic metabolism of estradiol and smokers have higher serum sex-hormone binding globulin (SHBG) levels, reducing free estradiol concentration [32, 33].

Few studies have investigated the relationship between smoking and the RANK–RANKL–OPG system. Some reports have demonstrated that smokers have lower OPG levels without difference in RANKL levels [33].

A cross-sectional study of Iranian IBD patients with a total of 126 UC and 39 CD patients demonstrated that femoral neck T score was predicted by age, BMI, smoking, and corticosteroid use. However, in this study the association between smoking and BMD was not observed in the lumbar spine [35].

Silvennoinen et al. evaluated the effect of smoking on BMD in 152 IBD patients (67 UC, 78 CD, 7 indeterminate colitis) and 73 controls. They found that IBD female current smokers or with

previous history of smoking had lower Z-scores on lumbar spine and femoral neck than the female patients who had never smoked [36].

Smoking is also associated with relapses and disease activity (especially CD) with the need for steroids, which also interferes negatively in bone metabolism. Despite suspension of smoking being associated with more flare-ups in UC, smoking cessation should be encouraged in all IBD patients because it reduces other complications such as cardiovascular disease, lung cancer and changes in bone health [37].

BODY COMPOSITION

Low body mass index (BMI) is a well-documented risk factor for low BMD and fracture [38].

Azzopardi et al. have analyzed the risk factors for osteoporosis in 83 CD patients and found a significant association between BMI and BMD [39]. Many others studies have also identified a positive association between BMD and BMI [40-42]. Atreja et al. also considered BMI as a strong risk factor for altered bone metabolism and a way to identify osteoporotic patients missed by current guidelines [43].

Leslie et al. studied 388 IBD patients and found that greater weight, height, and body mass measurements were positively correlated with bone density at all sites. In this study, both fat tissue and lean tissue showed positive relationship with BMD, but lean tissue showed a much stronger correlation than fat tissue, especially for the total hip [44].

Although low BMI has been considered a risk factor for fractures, it is not so clear if obesity can be considered as a protective factor, once it has shown to increase the risk of some osteoporotic fractures [45, 46]. Johansson et al. have published a recent meta- analysis of the association of fracture risk and BMI in women and concluded that there is a slight increase in osteoporotic fracture risk with increasing BMI after adjustment for BMD [47]. Thus, body composition appears to be more important than the BMI in bone metabolism.

The mechanical loading of the muscles acting on the bone causes an anabolic effect and results in osteogenesis [48, 49]. Many IBD patients have their muscle (lean mass) reduced due to nutritional

factors, sedentary lifestyle or medications, and this may lead to a reduced bone mass secondary to the decrease of mechanical stimulation of the skeleton by loads [50].

A Canadian study has analyzed the bone mass (bone mineral content) and muscle mass (lean mass) in 65 CD patients. In multiple regression analysis, only total lean mass was independently associated with lumbar bone mineral content (BMC), BMC in both hips and total BMC [50].

Similar findings were demonstrated by Lee et al. in a cohort of 61 CD patients. In this study they found that both lean mass and muscle strength, but not fat mass, were significantly correlated with regional and whole body BMD, but after multiple regression analysis, lean mass was the only independent predictor of hip BMD. They concluded that maintaining or increasing muscle mass may have a positive effect on BMD and prevent the development of osteopenia and osteoporosis [51].

GLUCOCORTICOID USE

Glucocorticoids (GCs) are frequently used in the treatment of inflammatory conditions, such as rheumatoid arthritis, systemic lupus erythematous, asthma and IBD. Glucocorticoid (GC) exposure is common in IBD patients, with over 50% of patients having been exposed to systemic GCs within 5 years of diagnosis, and 20% having used at least 3 g of prednisone in any 1-year period [52].

Many studies have consistently identified systemic GC usage as a risk factor for osteoporosis and for bone mineral loss in IBD patients [52, 53]. Abraham et al. studied 166 IBD patients and showed that the risk of osteoporosis was twice as high in those who used corticosteroids [OR 2,4 (1,5-3,4) p=0,001][54].

Osteoporosis attributed to GC exposure is the most common etiology of drug-induced osteoporosis. Almost 50% of patients receiving chronic GC therapy will develop osteopenia and fractures while 17% of these patients will develop fractures within the first year of GC therapy [55].

Some risk factors for the development of fractures after steroid exposure have been identified as age older than 65 years, cumulative steroid dose (high GC dose and duration of treatment >3 months), positive family history of osteoporosis, low calcium intake, female sex, low bodyweight (BMI <24 kg/m^2) and low BMD [55, 56].

The mechanism of this loss is not fully understood. It is known that GC exposure alters the balance between osteoclast and osteoblast activity in bone metabolism. An important mechanism for GC effects on bone is osteoblastic dysfunction. GC inhibits stem cell differentiation into osteoblasts and induces osteoblasts apoptosis, thereby decreasing the secretion of osteoid matrix and new bone formation [55, 57].

GCs increase the expression of receptor activator of nuclear fator κB ligand (RANK-L) and decrease the expression of its soluble decoy receptor osteoprotegerin (OPG) in stromal and osteoblastic cells, which causes a greater differentiation of precursors into osteoclasts and increases their resorptive activity, thereby enhancing bone resorption. There is also evidence that GCs directly prolong the lifespan of mature osteoclasts [55, 57, 58].

The increase in RANKL is only transient. Therefore, failure of bone formation rather than increased bone resorption seems to be the main mechanism underlying glucocorticoid-associated bone loss [56].

GCs also have a negative effect on the sex hormones status as they reduce estrogen and testosterone production. This negative effect of oral GCs on the gonadal function may increase bone resorption [50, 52].

GCs reduce intestinal calcium absorption while inhibiting calcium reabsorption in the kidney, which indirectly leads to a negative net calcium balance, stimulates an increase in parathyroid hormone (PTH), further increasing the number of osteoclasts and stimulating bone resorption [55, 56].

THE ROLE OF VITAMIN D

In recent years, much has been studied about the role of vitamin D in IBD. The main actions of this vitamin are to increase serum levels of calcium and phosphate and to promote bone mineralization.

Vitamin D is available in two forms: vitamin D3 (cholecalciferol), produced in the skin by exposure to sunlight and obtained from animal sources, and vitamin D2 (ergocalciferol) obtained from plant sources. It is metabolized in the liver to 25-hydroxyvitamin D (25-(OH) D), circulates in the blood plasma and is stored in the fat tissue and muscles. The metabolites of vitamin D are transported

bound to albumin binding protein or vitamin D. This protein has the ability to regulate the effects of the metabolites in the target organs [59].

A study of 49 healthy young men showed that free and bioavailable 25 (OH) D were positively correlated with BMD, suggesting a possible benefit of vitamin D supplementation when it is deficient. [60].

Vitamin D exerts its biological effects through the vitamin D receptor (VDR) [61]. Multiple tissues and immune cells express this receptor and have the enzyme responsible for the conversion of vitamin D into its active metabolite. Thus, vitamin D appears to influence both the innate immune response by inhibiting the maturation of dendritic cells and IL-12, as in the adaptive immune response by inhibiting the production of IFN-γ, IL-17 and IL-21[61, 62].

Several studies have demonstrated a high prevalence of vitamin D deficiency in IBD patients. Many factors have been attributed to this deficiency, some common to the general population as low sun exposure, inadequate intake and inactivity and others related to inflammatory disease, such as terminal ileum resection and low absorption due to the inflammatory process [62]. Disease activity also appears to be associated to low levels of vitamin D both in CD and in UC [63, 64].

Vitamin D deficiency leads to reduction of calcium, causing secondary hyperparathyroidism, which in turn stimulates osteoclastogenesis, increasing bone resorption, resulting in osteopenia and osteoporosis [62].

DOES ANTI-TNF IS A PROTECTIVE FACTOR?

Elevated TNF-α concentration may play a role in dysfunctional bone metabolism in IBD. The tumor necrosis factor alpha (TNF-α) is a major factor in activation of osteoclasts. It is known that this cytokine induces osteoclast differentiation, increases osteoclast bone resorption and protects them against apoptosis, while sensitize osteoblasts to apoptosis, thus diminishing bone formation [65].

Infliximab (IFX) is a monoclonal antibody having high affinity and specificity for TNF-α. The use of anti-TNF therapy is an important IBD treatment, as it allows remission induction, relapse prevention and decrease in corticosteroids usage [66]. Some studies have shown benefits of using

IFX in BMD. However, the exact mechanism of action of this anti-TNF in bone metabolism is not clear yet.

Miheller et al. studied the effects of infliximab on bone metabolism by measuring biochemical parameters in 29 CD patients and found it was responsible for increased levels of osteocalcin (marker of bone formation) and reduced levels of beta-CrossLaps (marker of bone resorption) [67].

In a study of 38 CD patients, Abreu et al. observed increased bone alkaline phosphatase (bone formation marker) in all patients treated with IFX and no significant change in the dose of N-telopeptide of type I collagen (NTX - marker of bone resorption) [68].

Franchimont et al. also studied the evolution of biochemical markers of bone metabolism after first treatment with IFX in 71 CD patients. In this study, the authors detected normalization of bone markers after 08 weeks of treatment with IFX, with a median increase in formation markers of 14–51%, according to marker, and reduction of about 10% in bone resorption [69].

A retrospective study by Mauro et al. in 15 CD patients treated with IFX, showed significant increase in BMC and BMD at the lumbar spine compared with control group [70].

The benefit of using IFX in BMD has also been demonstrated with its association with bisphosphonates, as noted by Pazianas et al. in a retrospective cohort. They studied 61 CD patients, and those who used bisphosphonates plus IFX had experienced a greater increase in BMD than those using only bisphosphonate (+ 6.7% / year x 4.46% / year, $p < 0.05$) [71].

While the mechanism of action of IFX on bone metabolism is not well established, its benefits in BMD may occur by alteration of bone markers, as shown, but also by the reduction of GC utilization and by the induction of clinical and endoscopic remission (Table 1).

Adalimumab is a human monoclonal IgG1 antibody specific for human TNF. It is also used in the treatment of IBD and other inflammatory diseases such as rheumatoid arthritis and spondyloarthritis [72].

Studies have shown benefits in BMD in some patients using this therapy. Durnez et al. studied 59 patients with spondyloarthropathy during a follow up of 6.5 years treated with anti-TNF

(infliximab, adalimumab or etarnecept) and found an increase in BMD of 11.8% at the lumbar spine and the trochanteric 3.6%[73].

Wijbrandts et al. conducted a prospective, open-label study involving 50 patients with rheumatoid arthritis. They analyzed the mineral density of the lumbar spine and femoral neck before and 1 year after treatment with adalimumab. The authors observed no significant changes in BMD in lumbar spine (+ 0.3%) or femoral neck (+ 0.3%) and concluded that therapy with this anti-TNF does not increase BMD, but it can stop bone loss [74].

Another study by Krieckaert et al. evaluated the effect of long-term use of adalimumab in BMD of the lumbar spine, hip and hands of patients with rheumatoid arthritis. One hundred eighty four patients were studied, and after 1 year of treatment hip and lumbar spine BMD remained stable, while hands BMD significantly decreased by -1.41%. After a mean follow-up of 4.0 years, mean BMD change per year was - 0.58% and 0.07% for hip and lumbar spine, respectively (overall P-value of hip was <0.0001 and spine was 0.67). The authors considered BMD changes associated to disease activity [75].

However, there are currently no published data investigating the effect of adalimumab on bone metabolism in IBD patients. There are also no data with certolizumab pegol.

THE EFFECT OF SURGERY

Proctocolectomy with ileal pouch-anal anastomosis (IPAA) has been the procedure of choice for treatment of most patients with refractory UC, UC with dysplasia and familial adenomatous polyposis [76-78].

Some studies have shown an increase in long-term BMD after total colectomy with IPAA [77]. This surgery may improve BMD in UC patients, possibly due to discontinuation of corticosteroids, improvement of nutritional status and decreased production of cytokines by the diseased colon [76, 77].

However, it is unclear whether total colectomy with ileal pouch provides benefits or causes detriment in relation to BMD. In a study of 327 UC patients who underwent this surgery, 32% had low BMD 4 years after surgery, suggesting that bone loss continues after colectomy [76].

Possible risk factors and mechanisms of bone loss are considered. Ileal pouch changes the anatomy and function of the small intestine, reducing absorption of bile salts, which contributes to reduce the absorption of vitamin D. It has been shown that stasis of stool in the ileum in UC patients with IPAA promotes bacterial overgrowth which causes deconjugation of bile salts, leading to malabsorption of vitamin D [77]. Another mechanism is inflammation of the ileal pouch which increases inflammatory cytokines levels such as IL-1, IL-6 and TNF-α stimulating osteoclast activity and promoting bone loss [77].

Although Navaneethan et al. have also found a lower BMD in UC patients undergoing total proctocolectomy and ileal pouch when compared with control group (31.1% vs. 15.1% - $p < 0.001$), they also found that in 13 patients BMD was already low before surgery and in 7 (53.8%) of these patients had an increase in BMD after surgery [79].

Anyway, some studies have shown a higher incidence of fractures in UC patients with IPAA, ranging 7-15% [76, 79].

IBD patients, particularly CD, are at increased risk of surgery according to the severity and duration of disease. The most common surgery for CD involves the removal of the terminal ileum, which is associated to vitamin D deficiency and consequent secondary hyperparathyroidism, promoting bone mass reduction. However, their relationship with osteoporosis in CD is not well defined [52].

A study by Gupta et al. analyzed 126 patients with ostomy, of which 95% had CD and ileostomy. This study also showed a high frequency of fractures (9.5%) in CD patients after ostomy, with significantly higher rates in those with low BMD. IBD patients with ostomy and with low BMD also had low BMI. In addition, fractures were five times more frequent in IBD patients with ostomy and with low BMD [80].

IBD patients with ostomy can be considered at higher risk for bone loss and thus should be monitored closely, especially those with risk factors such as low BMI and previous history of fractures.

CONCLUSIONS

IBD is associated with bone loss and patients are at increased risk of developing fractures. Many risk factors are associated with reduction in BMD in this population including inflammation, smoking, body composition, glucocorticoids use, vitamin D deficiency and surgery. Infliximab seems to increase BMD but the exact mechanism is not well established. More studies are needed to analyze the effect of others anti-TNF in BMD.

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Table 1- Infliximab effects on bone mineral density

Authors (year)	Study design[a]	Participants no.	Endpoints	Results
Miheller (2007)	Prospective	29 CD patients	Determine the effects of IFX on bone metabolism in CD patients	IFX improves bone metabolism in CD independently from the behavior of the disease
Abreu (2006)	Prospective	38 CD patients	Assess the ability of IFX to increase bone formation measured by markers of bone turnover in active CD patients	Treatment with IFX was associated with increased markers of bone formation
Franchimont (2004)	Prospective	71 CD patients 68 controls	Assess the evolution of markers of bone turnover after IFX treatment for active CD	IFX induces improvement in biochemical markers of bone turnover.
Mauro (2007)	Retrospective	15 CD patients 30 controls	Assess whether treatment with infliximab had a beneficial effect on lumbar bone mass	Treatment with IFX was associated with significant increases in lumbar bone area, BMC and BMD in CD patients

(continued)

Table 1 – Infliximabe effects on bone mineral density (continued)

Authors (year)	**Study design**[a]	**Participants no.**	**Endpoints**	**Results**
Pazianas (2006)	Retrospective	61 CD patients	Evaluate the effects of IFX administration on BMD in patients with CD	IFX may work in synergy with bisphosphonates to provide additional **i**ncreases in BMD in **CD patients**

Abbreviations: CD, Crohn disease; UC, Ulcerative colitis; IFX, Infliximab; BMC, bone mineral content; BMD, bone mineral density.

[a] All were cohort study.

4 RESULTADOS

4.1 ARTIGO ORIGINAL: BONE MINERAL DENSITY AND INFLAMMATORY BOWEL DISEASE SEVERITY. BMC RESEARCH NOTES (SUBMETIDO)

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Original Article

Bone mineral density and inflammatory bowel disease severity

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ABSTRACT

Background: Inflammatory bowel disease is associated with low bone mineral density. Our purpose was to evaluate the association between disease severity and BMD in patients with IBD, identifying if there is association between BMD and Montreal classification, disease activity and drug therapy in these patients.

Methods: It is a cross-sectional prevalence study with a comparison group, conducted with IBD patients. All patients and controls had their bone mineral density measured. In IBD patients, current medications, hospitalization, location, extent and phenotype of the disease, according to the Montreal classification, were analyzed. Harvey Bradshaw and Lichtiger indexes were used to measure disease activity. Multiple Correspondence analysis was applied to evaluate the categorical variables.

Results: We studied 128 patients, 68 patients with UC and 60 with CD. The control group consisted of 67 healthy subjects. In CD group, most of the patients were diagnosed between 17-40 years of age. Ileocolonic and non-stricturing non-penetrating disease were the most frequent disease location and behavior, respectively. In terms of UC, extensive colitis was the most frequent disease location.

UC and CD patients were more likely to have osteopenia than controls (OR: 14.93 / OR: 24.38, respectively). In CD group, male patients, perianal disease, penetrating behavior and age at diagnosis >40 years were associated with low BMD, but no association was found between BMD and disease location. Patients taking azathioprine and infliximab also seem to be associated with osteopenia. In UC group, we observed association between low BMD and male patients, left colitis, corticosteroid use and hospitalization. Disease activity was not associated with osteopenia or osteoporosis in CD and UC patients.

Conclusion: Disease severity seems to be associated with osteopenia in IBD patients, so we should pay attention in some factors that can be related to this loss like perianal disease, penetrating behavior and azathioprine and infliximab use in CD patients and left colitis in UC patients.

Keywords: Bone mineral density, ulcerative colitis, Crohn's disease, inflammatory bowel disease and osteoporosis.

INTRODUCTION

Inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), is associated with low bone mineral density (BMD). The prevalence of osteopenia and osteoporosis in patients with IBD ranges from 22-77% and 17-41%, respectively, depending on the study population, study design and disease location [1].

The reduction in BMD is associated with increased risk of fractures. It is estimated that patients with IBD reach up to 40% more fractures than the general population, which contributes to increased morbidity and reduced quality of life [2]. Some studies have shown a higher BMD prevalence in CD patients than in those with UC [3], but this difference was not observed in others.

The exact mechanism that bone loss occurs is not well established. Initially, it was believed that this loss was due to the use of medications such as corticosteroids, but studies in IBD patients without any treatment have already shown low BMD in these patients as well, suggesting that the inflammatory process contributes to this mechanism [4]. Several proinflammatory cytokines such as IL-1, tumor necrosis factor alpha (TNF-α), IL-6, IL-11, IL -15 and IL-17 are elevated in IBD and have been identified as stimulators of osteoclastogenesis [5].

Older age, smoking, physical inactivity and menopause are some known risk factors for osteoporosis in the general population and they may also be present in IBD patients. Others characteristics specific for IBD may increase the likelihood of osteoporosis and fractures like malnutrition, vitamin D deficiency, intestinal resection, and corticosteroids use [6].

The time from diagnosis and disease activity may be associated with lower BMD values [7]. Some medications used to treat IBD seem to interfere with BMD. The use of corticosteroids is well established as a risk factor for osteoporosis, while azathioprine and anti-TNF therapy appear to contribute to increase bone mass [8, 9].

Our purpose was to evaluate the association between disease severity and BMD in IBD patients as well as to identify if there is an association between BMD and Montreal classification, disease activity and drug therapy in these patients.

METHODOLOGY

This is a cross-sectional prevalence study with a comparison group, conducted with patients from two IBD treatment referral centers in Bahia, Brazil both of which are located in the city of Salvador.

IBD patients, aged between 18 and 60 years, were included. The diagnosis of CD or UC was based on clinical, endoscopic, radiological and histological data [10, 11].

Exclusion criteria were pregnancy, diseases that cause changes in bone metabolism (such as chronic renal failure, chronic obstructive pulmonary disease, thyroid disease, liver disease and systemic lupus erythematosus), cancer, diabetes mellitus, and women after menopause or use of estrogen therapy.

The control group was matched according to age and gender of UC and CD patients and comprised healthy volunteers recruited from the hospital staff, medical and nutrition students and

patient's relatives. The same exclusion criteria were used. None of them was taking medications known to affect bone turnover, and none had metabolic bone disease or had undergone intestinal resection.

Gender and age (years) from all participants were analyzed at the time of inclusion. Time of IBD diagnosis, previous history of intestinal resection, current or last year of steroid use and cumulative dose, current medications, hospital admission in the previous year, location, extent and phenotype of the disease, according to the Montreal classification [12] (Table 1) were also analyzed. Disease activity was assessed by the activity index Harvey Bradshow [13] (Table 2) for CD and index Lichtiger [14] for UC (Table 3).

Informed consent was obtained from all patients and controls.

Measurement of Bone Mineral Density

Bone mineral density was measured by dual-energy X-ray absorptiometry (DEXA) using a Hologic QDR1000 densitometer. The measurement sites were the femoral neck and the lumbar spine. The results were expressed in g / cm2 and presented either as Z-score or as a T-score.

According to the Guideline of World Health Organization (WHO), T-score was used to determine low bone mineral density. Values were considered to be normal when they reached up to 1 standard deviation (SD), while osteopenia was defined as -1 SD below and above -2.5 SD and osteoporosis was defined as values below or equal to -2.5 SD comparing with normal population (WHO 1994) [15].

Statistical analysis

Data were analyzed using the statistical package R (version 3.1.1) [16]. The population was characterized using descriptive statistics. Because the population of two reference centers was examined (rather than a random sample) statistical inference was not performed [17]. For the multivariate analysis, considering the level of measurement of variables and the multifactorial

context, we chose the multiple correspondence analysis technique with eigenvalues decomposition Burt matrix adjusted for inertia and the standard coordinates multiplied by the masses for the evaluation of geometrical relationships in chi-square distances from the contingency of the variables studied in the multidimensional context [18] built from prior knowledge of literature and experience of the researcher, separately for ulcerative colitis and Chron's disease considering its severity criteria.

ETHICAL CONSIDERATIONS

The study was approved by the ethics committee of the University Hospital Professor Edgard Santos.

RESULTS

We studied 128 patients, 68 patients with UC (53.1%) and 60 with CD (46.9%). Age ranged from 19 to 56 years, mean 37.8 years (SD 8.65). Most patients were female (72/ 56.3%). The control group consisted of 67 healthy subjects. No significant differences were found between patients and controls with respect to age and sex.

Regarding the CD patients group of most patients (47/ 78.3%) were diagnosed between 17-40 years of age, ileocolonic disease (L3 of the Montreal classification) was present in 32 patients (53.3%) and 29 patients (48.3%) had non stricturing non-penetrating disease (B1 of the Montreal classification). The perianal disease was present in 20 patients (33.3%).

Most CD patients had not undergone surgery (34/ 64.2%). In those operated (19 /60), partial colon resection was the most frequent surgery (12/ 63.2%), followed by small intestine and colonic resection (5/ 26.3%) and finally only small intestine resection (2/ 10.5%). Perianal surgery has not been evaluated.

Twenty-nine patients (44.6%) had extensive UC according to the Montreal classification. Only 2 patients (2.9%) had undergone surgery, one of whom underwent to total proctocolectomy with ileal pouch. Baseline characteristics of patients and controls are reported in Table 4.

Most of CD patients were taking azathioprine (37 /61.7%), 11 patients were taking Infliximab (18.3%) and only 8 patients received corticosteroid therapy in the past year (13.6%) with a mean cumulative dose of 1890 mg (± 1017), ranging from 330 to 3285mg, and average duration of 4.5 months (± 3.2), ranging from 2 months to 12 months. In UC patients, sixty patients (88.2%) were taking aminosalicylates, 8 patients were taking azathioprine (11.8%) and 12 (17.6%) used corticosteroid in the past year with a mean cumulative dose of 2072 mg (±1437).

Most UC patients (66/ 97.1%) and CD patients (44/ 73.3%) were in clinical remission.

Among the total sample 28 UC patients (41.2%) and 32 CD patients (53.3%) had abnormal BMD, and osteoporosis was found in 2 UC patients (2.9%) and 7 CD patients (11.7%). In the control group, no one presented osteoporosis and osteopenia was present in only 3 subjects (4.5%).

UC and CD patients were more likely to have osteopenia than controls (OR:14.93 / OR:24.38, respectively).

In CD group, male patients, perianal disease, penetrating behavior and age at diagnosis >40 years were associated with low BMD. Patients taking azathioprine and infliximab also seem to be associated with osteopenia. However, there was no association between BMD and hospitalization in the last year, neither surgery and disease activity (Figure 1).

In UC group, we observed association between low BMD and male patients, left colitis, corticosteroid use and hospitalization. Extensive colitis and disease activity were not associated with osteopenia and osteoporosis (Figure 2).

DISCUSSION

It is known that IBD is associated with low bone mineral density. In this study we found a frequency of approximately 40% for osteopenia and 7% for osteoporosis among our patients. Many deleterious factors are associated with bone loss in IBD patients. However, the exact mechanism associated with bone loss is not yet fully understood, as well as its associated risk factors. The study of the real variables involved in this complication is crucial to prevent disabling diseases.

We observed similar frequencies of low BMD between UC and CD patients, unlike Janhsen et al that showed that CD patients had lower BMD than UC patients and controls [3]. Ezzat et al also demonstrated a higher frequency of low BMD in CD patients than UC patients [19]. However, in these 2 studies, CD patients had lower BMI, and had used higher doses of corticosteroids than UC patients, which may have affected the results. As our results, other authors have not demonstrated this difference [4, 20].

There is still no definition whether gender affects BMD in IBD patients. Ardizzone et al studied 91 IBD patients and showed that in UC patients was observed that the BMD of the spine and femur, T-score and z-score were significantly lower in men than in women, but in the group of CD patients no difference was observed [21]. Andreassen et al have shown that the female sex was a predictor of low BMD in CD patients [22]. Our results were similar to the ones from the Italian study that observed low BMD in male UC patients, but in our study male CD patients were also associated with low BMD. One possible reason for this find is that IBD patients have lower dehydroepiandrosterone sulphate (DHEAS) levels which may have contributed to bone loss in those patients. Szathmári et al have studied 45 men with IBD and they evidenced that 23 patients had low levels of DHEAS and that there is a correlation between DHEAS levels and the BMD in lumbar spine and femoral neck [23].

There is a lack of consistent definition of aggressive and disabling UC. Some authors have defined aggressive UC as those patients who need immunosuppressive therapy or surgery. Some factors have been related with an aggressive course of UC like age at diagnosis, corticosteroid use at diagnosis, disease extension, history of hospitalization and infliximabe therapy [24 -26]. Extent of the disease and history of hospitalization were the 2 factors used in this study to identify aggressive UC patients. There is also no definition of disabling CD. It is known that stricturing or penetrating disease behavior is considered as complicated disease. Age below 40 years, perianal disease, initial requirement for steroids and ileal disease are considered as predictors of disabling CD by some authors [27, 28]. In our study, we considered aggressive CD patients as those with age at diagnosis below 40 years, presence of fistulizing or stricturing behavior, perianal disease, ileal involvement and history of hospitalization.

Among UC patients, a higher frequency of extensive colitis and left colitis was found, while in CD patients, we found that most of them (51.7%) had more severe disease phenotype (stricturing and penetrating CD). These findings may have occurred since the survey was conducted in 02 centers of excellence in IBD. In the group of CD patients, no association between low BMD and disease location was observed. However, penetrating disease and age at diagnosis > 40 years were associated with osteopenia. Vázquez et al conducted a prospective case-control study of 107 IBD patients and showed that neither the extent nor the location of the disease had interfered significantly with BMD and the presence of fractures, both in UC and CD patients [29]. Cravo et al have observed that stricturing and penetrating phenotype, small bowel disease, older age, history of surgery, and duration of illness over 15 years were associated with osteoporosis in CD patients [8]. In the group of UC patients, we found association between left colitis and low BMD, but no association was evidenced between extensive colitis and osteopenia/osteoporosis. A study by Jahnsen et al, with 60 UC patients, did not demonstrate interference of disease extension in BMD

[3]. Thirty five UC patients were studied by Bjarnason et al and no difference in T-score was observed between proctosigmoiditis and extensive colitis [20].

In our study we did not find association between BMD and hospitalization in the previous year in CD patients. However hospitalization was associated with low BMD in UC patients. Azathioprine and infliximab (IFX) use was associated with low BMD in CD patients. A Canadian study published by Targownik et al also found no association between history of hospitalization, duration of illness and use of medications with low T-score or risk of osteoporosis in IBD patients compared with controls [30]. Florén et al have analyzed the effect of azathioprine on bone density in a retrospective study with 59 CD patients. They found that azathioprine does not seem to affect bone mineral density by itself, however it seems to conserve bone mineral mass in CD patients by reducing corticosteroid use [31]. However, Cravo et al studied mild to moderate CD patients and had been demonstrated that azathioprine was considered a protective factor. In relation to infliximab use no association was observed in this study, although the number of patients using this medication was small [8]. A retrospective study by Mauro et al showed significant increase in BMD at the lumbar spine in CD patients treated with IFX [32]. Pazianas et al had also shown benefit of using IFX in BMD in a retrospective cohort. They studied 61 CD patients and those who used bisphosphonates plus IFX had experienced a greater increase in BMD than those using only bisphosphonate [33]. In our study few patients were on infliximab therapy, which may have interfered in our results. Furthermore, we did not evaluate how long the patients were taking azathioprine and if their disease was really on remission, once the criteria used were those of Harvey and Bradshaw for CD and Lichtiger for UC, that assess the clinical remission, but not endoscopic remission.

Many studies have identified association between the use of systemic corticosteroids (CS) with osteoporosis and bone loss in IBD patients. It is known that the use of CS alters the balance

between osteoblasts and osteoclasts. It is believed that this medication stimulates osteoclast differentiation and activation and induces osteoblasts apoptosis, reducing bone formation [34, 35]. Abraham et al studied 166 IBD patients and showed that CS use more than doubled the risk of low BMD [36]. Ezzat et al also observed a negative correlation between low BMD and cumulative CS dose and duration of its use [19]. However, others authors have found no clear association of low BMD with CS use. One hundred and thirteen CD patients were studied by Andreassen et al, and no correlation between BMD and cumulative dose of CS was found [22]. Miznerova et al studied 76 IBD patients and also found no negative relationship between the corticosteroids use and BMD. Indeed, a positive correlation between the mean prednisone dose and BMD of the femur was observed, which may be due to the improvement of inflammation [37]. In our study we demonstrated an association between corticosteroids use and low BMD in UC patients, but not in CD patients. However, only 8 CD patients received corticosteroids in the previous year and had low cumulative dose (average of less than 02g of prednisone).

It is well known that inflammation per si contributes to reduction of BMD. A number of inflammatory diseases have been associated with osteoporosis. A cross-sectional study by Bjarnason et al evaluated 79 IBD patients and it was observed that patients with newly diagnosed UC or CD and who had never used corticosteroids also had low BMD [20]. It is believed that the main system involved in bone loss in IBD is RANK / RANKL / Osteoprotegerin, which promotes osteoclastogenesis [5, 6]. Several proinflammatory cytokines such as IL-1, IL-6, TNF-α, IL-11, IL-15 and IL-17 are associated with activation of osteoclasts and are also high in IBD [6]. In our study, no association was found between disease activity and reduction in BMD. However, only 2 UC patients and 16 CD patients presented active disease at the time that DEXA was performed, which may have affected the results as remission disease can be associated with increase in BMD. Reffiti et al. conducted a study of 137 IBD patients and demonstrated a correlation

between z-score increase and time of the disease in remission in both UC and CD patients [38]. Although it was a cross-sectional study and the results are limited, this study provides evidence of an association between disease remission and greater bone density in both the lumbar spine and femoral neck.

Some studies have shown that surgery may be related to greater bone loss in IBD patients. Gupta et al studied a total of 126 IBD patients with ostomy, and most had CD and ileostomy. A prevalence of 29% of low BMD was found and the presence of fractures was 05 times more common in these patients [39]. Shen et al have conducted a case-control study of 327 UC patients who had undergone total proctocolectomy with ileal pouch. They found a prevalence of 32% of low BMD in these patients [40]. In our study, no association was found between history of surgery and change in BMD. However, this result may be due to the small number of patients undergoing surgery and the type of surgery. Only one UC patient had undergone complete colectomy with ileal pouch and no CD patient had ostomy when DEXA was performed.

Lora et al have published a study in 2005 in southern Brazil with a total of 76 IBD patients and 40 controls. It was a cross-sectional study, similar to ours, and they found that low BMD was observed in patients, especially in CD patients, but no association was identified between BMD and corticosteroids use, surgery and disease activity [41]. Although this study has been done with a population in a different location from ours and with a less number of patients, similar results between the two studies were found. We also did not find association between some of these clinical criteria and low BMD.

CONCLUSIONS

In our study, we found a higher prevalence of low BMD in IBD patients compared with controls, although most of patients was on clinical remission. Disease severity seems to be

associated with osteopenia in IBD patients, so we should pay attention in some factors that can be related to this loss like perianal disease, penetrating behavior and azathioprine and infliximab use in CD patients and left colitis in UC patients.

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Table 1- Montreal Classification

Age at diagnosis		
A1 – 16 years or younger		
A2- 17 – 40 years		
A3- over 40 years		
Location (L)	**Upper GI modifier (L4)**	
L1- terminal ileum	L1+ L4	Terminal ileum + Upper GI
L2- colon	L2+ L4	Colon + Upper GI
L3- ileocolon	L3+ L4	Ileocolon + Upper GI
L4- Upper GI	-	-
Behaviour (B)	**Perianal disease modifier**	
B1 – Nonstricturing, non penetrating	B1p	Nonstricturing, non penetrating + perianal
B2- Stricturing	B2p	Stricturing + perianal
B3- Penetrating	B3p	Penetrating + perianal

GI: gastrointestinal

Table 2- Harvey-Bradshaw Index (Simplified CD Activity Index)

Score	0	1	2	3	4
General well-being	Well	Slightly poor	Poor	Very poor	Extremely poor
Abdominal pain	None	Mild	Moderate	Severe	
Diarrhea	1 for each liquid stool per day				
Abdominal mass	None	Dubious	Definite	Definite and with tenderness	
Complications	1 for each item: arthralgia, uveitis, erythema nodosum, pyoderma gangrenous, aphthous ulcer, anal fissure, new fistula or abscess				

Total disease activity score (sum of the item scores): ≤4 - remission; 5-8 - moderately active; 9≤ - markedly active.

Table 3- Lichtiger Index

Symptom	Score
Diarrhea (no. of daily stools)	
0-2	0
3 or 4	1
5 or 6	2
7-9	3
10	4
Nocturnal diarrhea	
No	0
Yes	1
Visible blood in stool (% of movements)	
0	0
< 50	1
≥ 50	2
100	3
Fecal Incontinence	
No	0
Yes	1
Abdominal pain or cramping	
None	0
Mild	1
Moderate	2
Severe	3
General well-being	
Perfect	0
Very good	1

Table 3- Lichtiger Index (continued)

Sympton	**Score**
Good	2
Average	3
Poor	4
Terrible	5
Abdominal tenderness	
None	0
Mild and localized	1
Mild to moderate and diffuse	2
Severe or rebound	3
Need of anti-diarrheal drugs	
No	0
Yes	1

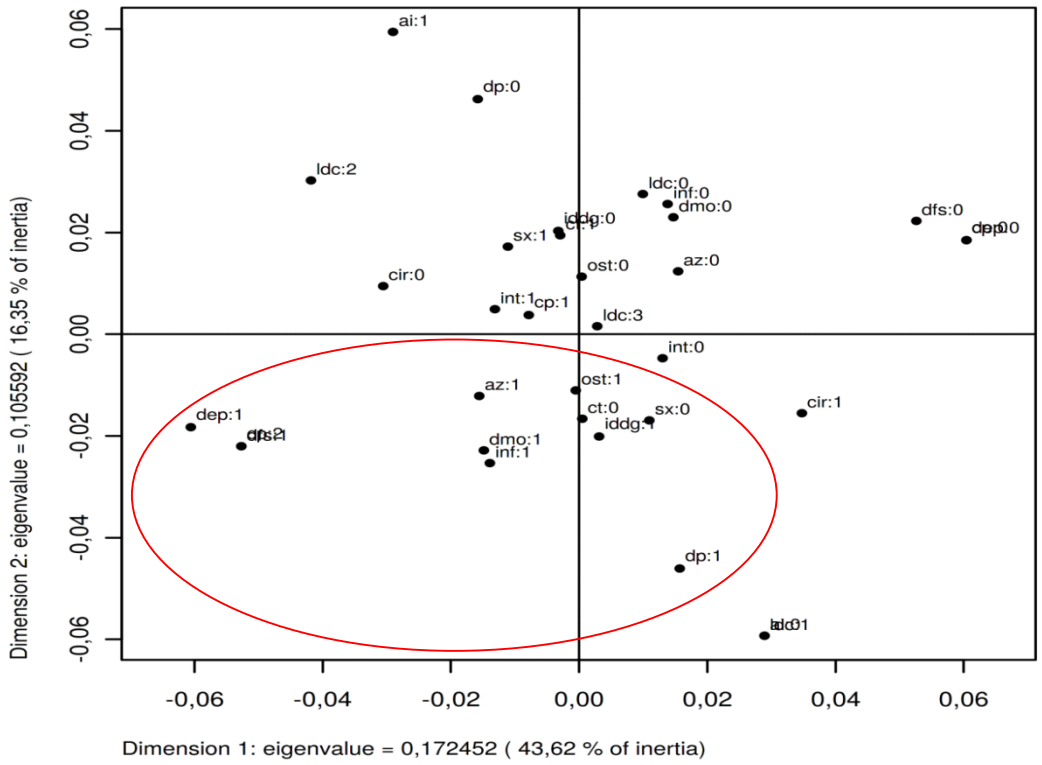
A score of less than 10 on two consecutive days was considered to indicate a clinical response

Table 4 – Baseline characteristics of patients and controls

	Crohn's Disease (n= 60)	Ulcerative Colitis (n= 68)	Controls (n= 67)
Sex (female/male)	30/30 (50/50%)	42/26 (61.8/38.2%)	40/27 (59.7/40.3%)
Age (mean ±SD)	37.4 ±8,3	38.2 ±9.0	36.3 ±8.67
Active disease	16 (26.7%)	2 (2.9%)	
Surgery	19 (35.8%)	2 (2.9%)	
Corticosteroid use	8 (13.3%)	12 (17.6%)	
Age at diagnosis			
< 17 years	4 (6.7%)		
17 - 40 years	47 (78.3%)		
> 40 years	9 (15%)		
Location			
L1- ileal	8 (13.3%)		
L2- colonic	19 (31.7%)		
L3- ileocolonic	32 (53.3%)		
L4- Upper GI	1 (1.7%)		
Behavior			
B1- Non stricturing-non penetrating	29 (48.3%)		
B2- Stricturing	13 (21.7%)		
B3- Penetrating	18 (30%)		
p- perianal disease	20 (33.3%)		
Ulcerative proctitis		12 (17.6%)	
Left-sided UC		27 (39.7%)	
Extensive UC		29 (42.6%)	

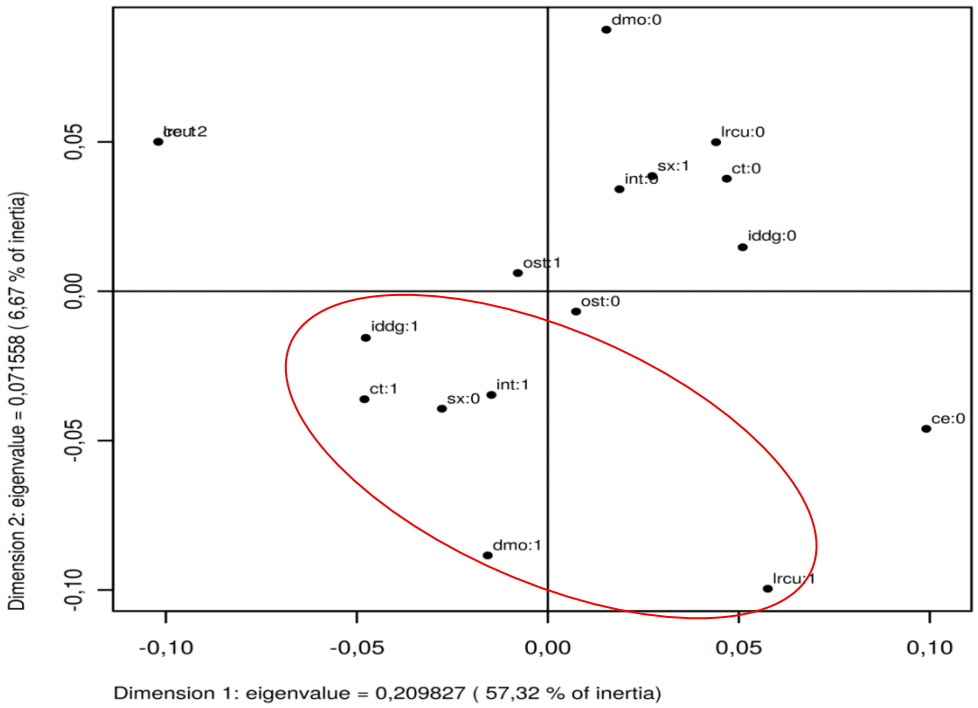
GI: gastrointestinal; UC: ulcerative colitis

Figure 1- Multiple correspondence analyses for categorical variables in CD patients.



LEGEND:	
Ai: 1 - active disease	Cp: 0 - non penetrating non stricturing CD
Ai: 0 – remission	Cp:1 – stricturing CD
Dp: 1- with perianal disease	Cp: 2 – penetrating CD
Dp: 0- without perianal disease	Dmo: 0- normal bone mineral density
Ldc: 0 - ileal CD	Dmo: 1 – low bone mineral density
Ldc: 1- colonic CD	Ost: 0 – without osteoporosis
Ldc: 2 - ileocolonic CD	Ost: 1 – with osteoporosis
Ldc: 3 - Superior gastrointestinal tract CD	Iddg: 0 - age at diagnosis < 40 years
Cir: 0 – without surgery	Iddg: 1 – age at diagnosis >40 years
Cir: 1 – with surgery	Inf: 0 - no infliximab use
Sx: 0 - male	Inf: 1 – infliximab use
Sx:1 - female	Az: 0 - no azathioprine use
Int: 0 – no hospitalization in the last year	Az: 1 – azathioprine use
Int: 1 – hospitalization in the last year	Ct: 0 – no corticosteroid use
	Ct: 1 – corticosteroid use

Figure 2 - Multiple correspondence analyses for categorical variables in UC patients.



LEGEND:	
Ct: 0 – no corticosteroid use	Int: 0 – no hospitalization in the last year
Ct: 1 – corticosteroid use	Int: 1 – hospitalization in the last year
Sx: 0- male	Dmo: 0- normal bone mineral density
Sx: 1- female	Dmo: 1 – low bone mineral density
Lrcu: 0 - proctitis	Ost: 0 – without osteoporosis
Lrcu: 1- left colitis	Ost: 1 – with osteoporosis
Lrcu: 2 – extensive colitis	Iddg: 0 – age >30 years
Ce: 0 - no extensive colitis	Iddg: 1- age < 30 years
Ce: 1 – extensive colitis	

Eigenvalues and dimensional statistics for CD

Eigenvalues:

	1	2	3	4	5	6	7
Value	0,02974	0,01115	0,004379	0,001946	0,00051	0,000311	0,000101
Percentage	43,62%	16,35%	6,42%	2,85%	0,75%	0,46%	0,15%

Columns:

	iddg:0	iddg:1	sx:0	sx:1	dfs:0	dfs:1	dp:0
Mass	0,057130	0,010099	0,033464	0,033765	0,047106	0,020124	0,044769
ChiDist	0,124013	0,700456	0,285805	0,281112	0,283336	0,664596	0,234948
Inertia	0,000879	0,004955	0,002733	0,002668	0,003782	0,008888	0,002471
Dim. 1	-0,056840	0,309144	0,327291	-0,328986	1,116916	-2,618317	-0,353060
Dim. 2	0,355568	-1,990325	-0,506014	0,510057	0,472881	-1,094232	1,032467

	dp:1	inf:0	inf:1	az:0	az:1	ct:0	ct:1
Mass	0,022460	0,054944	0,012285	0,025776	0,041453	0,057281	0,008894
ChiDist	0,466560	0,149008	0,667940	0,365338	0,227459	0,123667	0,813226
Inertia	0,004889	0,001220	0,005481	0,003440	0,002145	0,000876	0,005882
Dim. 1	0,698806	0,251382	-1,133252	0,599375	-0,375724	0,008737	-0,331643
Dim. 2	-2,050720	0,465968	-2,062168	0,479911	-0,292910	-0,290101	2,186772

	ldc:0	ldc:1	ldc:2	ldc:3	ai:0	ai:1	int:0
Mass	0,008894	0,021330	0,035876	0,001131	0,021330	0,045900	0,056075
ChiDist	0,827270	0,584888	0,345728	2,116789	0,584888	0,272882	0,134916
Inertia	0,006087	0,007297	0,004288	0,005066	0,007297	0,003418	0,001021
Dim. 1	1,117573	1,356242	-1,165879	2,499988	1,356242	-0,632486	0,232271
Dim. 2	3,099418	-2,779094	0,842924	1,394278	-2,779094	1,294921	-0,084047

	int:1	dep:0	dep:1	cp:0	cp:1	cp:2	dmo:0
Mass	0,011155	0,032484	0,034745	0,032484	0,014622	0,020124	0,031278
ChiDist	0,682828	0,455811	0,426544	0,455811	0,596878	0,664596	0,327256

Inertia 0,005201 0,006749 0,006322 0,006749 0,005209 0,008888 0,003350

Dim. 1 -1,177114 1,860360 -1,743249 1,860360 -0,536755 -2,618317 0,470123

Dim. 2 0,441866 0,569276 -0,525834 0,569276 0,258367 -1,094232 0,735399

dmo:1 ost:0 ost:1 cir:0 cir:1

Mass 0,035951 0,059466 0,007763 0,021405 0,038438

ChiDist 0,284318 0,106289 0,820583 0,470186 0,272446

Inertia 0,002906 0,000672 0,005227 0,004732 0,002853

Dim. 1 -0,413234 0,006703 -0,067436 -1,427515 0,904204

Dim. 2 -0,634988 0,190403 -1,422519 0,442138 -0,403749

Principal inertias (eigenvalues):

dim	value	%	cum%	scree plot
1	0,029740	43.6	43.6	**********
2	0,011150	16.4	60.0	*********
3	0,004379	6.4	66.4	****
4	0,001946	2.9	69.2	**
5	0,000510	0.7	70.0	
6	0,000311	0.5	70.4	
7	0,000101	0.1	70.6	
	--------	-----		
Total: 0.068186				

Columns:

	name	mass	qlt	inr	k=1 cor	ctr	k=2 cor	ctr
1	iddg:0	57	400	6	-10	26	0	37
2	iddg:1	10	391	34	53	24	1	-209
3	sx:0	33	425	19	56	224	4	-53

	ctr
1	374
2	367
3	200

1	iddg:0	57	400	6	-10	26	0	37
2	iddg:1	10	391	34	53	24	1	-209
3	sx:0	33	425	19	56	224	4	-53

	ctr
1	374
2	367
3	200

4 | sx:1 | 34 438 19 | -57 231 4 | 54 207 9 |

5 | dfs:0 | 47 712 26 | 192 667 59 | 50 45 11 |

6 | dfs:1 | 20 711 62 | -450 667 138 | -115 43 24 |

7 | dp:0 | 45 674 17 | -61 161 6 | 108 513 48 |

8 | dp:1 | 22 674 34 | 120 160 11 | -215 514 94 |

9 | inf:0 | 55 554 8 | 43 243 3 | 49 311 12 |

10 | inf:1 | 12 553 38 | -195 247 16 | -216 305 52 |

11 | az:0 | 26 486 24 | 103 392 9 | 50 94 6 |

12 | az:1 | 41 483 15 | -65 394 6 | -31 89 4 |

13 | ct:0 | 57 184 6 | 2 0 0 | -30 184 5 |

14 | ct:1 | 9 244 41 | -57 14 1 | 230 230 43 |

15 | ldc:0 | 9 565 42 | 192 146 11 | 325 419 85 |

16 | ldc:1 | 21 658 51 | 233 256 39 | -292 402 165 |

17 | ldc:2 | 36 737 30 | -200 617 49 | 88 120 25 |

18 | ldc:3 | 1 313 35 | 430 280 7 | 146 32 2 |

19 | ai:0 | 21 658 51 | 233 256 39 | -292 402 165 |

20 | ai:1 | 46 656 24 | -109 256 18 | 136 400 77 |

21 | int:0 | 56 323 7 | 40 308 3 | -9 15 0 |

22 | int:1 | 11 322 36 | -202 306 15 | 46 16 2 |

23 | dep:0 | 32 728 47 | 320 703 112 | 60 25 11 |

24 | dep:1 | 35 728 44 | -300 704 106 | -55 24 10 |

25 | cp:0 | 32 728 47 | 320 703 112 | 60 25 11 |

26 | cp:1 | 15 74 36 | -92 69 4 | 27 6 1 |

27 | cp:2 | 20 711 62 | -450 667 138 | -115 43 24 |

28 | dmo:0 | 31 398 23 | 81 208 7 | 77 190 17 |

29 | dmo:1 | 36 392 20 | -71 208 6 | -67 184 14 |

30 | ost:0 | 59 148 5 | 1 0 0 | 20 147 2 |

31 | ost:1 | 8 142 36 | -12 1 0 | -149 141 16 |

32 | cir:0 | 21 678 33 | -245 654 44 | 46 23 4 |

33 | cir:1 | 38 755 20 | 155 703 31 | -42 52 6 |

Eigenvalues and dimensional statistics for UC

Eigenvalues:

	1	2	3
Value	0,044028	0,005121	0,003611
Percentage	57,32%	6,67%	4,7%

Columns:

	iddg:0	iddg:1	sx:0	sx:1	ct:0	ct:1	lrcu:0
Mass	0,095328	0,026192	0,048372	0,078103	0,103115	0,022180	0,022652
ChiDist	0,222717	0,790870	0,479416	0,297020	0,194884	0,923282	0,891711
Inertia	0,004729	0,016382	0,011118	0,006890	0,003916	0,018908	0,018012
Dim. 1	0,534705	-1,821074	-0,574043	0,349263	0,453799	-2,166483	1,942032
Dim. 2	0,154890	-0,594055	-0,811949	0,494126	0,365835	-1,627534	2,204259

	lrcu:1	lrcu:2	dmo:0	dmo:1	ost:0	ost:1	ce:0
Mass	0,049788	0,054035	0,074328	0,052147	0,122699	0,003775	0,069608
ChiDist	0,557385	0,615122	0,331524	0,473566	0,067065	2,144162	0,461895
Inertia	0,015468	0,020445	0,008169	0,011695	0,000552	0,017357	0,014851
Dim. 1	1,155637	-1,888138	0,205672	-0,302708	0,059994	-2,090947	1,422808
Dim. 2	-1,999334	0,926757	1,178423	-1,695093	-0,055014	1,627038	-0,661068

	ce:1	int:0	int:1
Mass	0,054035	0,116092	0,007551
ChiDist	0,615122	0,106706	1,526406

Inertia 0,020445 0,001322 0,017593

Dim. 1 -1,888138 0,161129 -1,962449

Dim. 2 0,926757 0,294573 -4,590963

Principal inertias (eigenvalues):

dim	value	%	cum%	scree plot
1	0,044028	57.3	57.3	**********
2	0,005121	6.7	64.0	*
3	0,003611	4.7	68.7	
	--------	-----		
Total: 0.076812				

Columns:

	name	mass	qlt	inr	k=1 cor	ctr	k=2 cor	ctr
1	iddg:0	95	821	23	112	813	27	11	8	2
2	iddg:1	26	858	79	-380	848	87	-42	10	9
3	sx:0	48	628	53	-120	512	16	-57	115	32
4	sx:1	78	607	33	73	495	10	35	111	19
5	ct:0	103	780	19	95	727	21	26	53	14
6	ct:1	22	767	91	-452	721	104	-114	46	59
7	lrcu:0	23	718	87	405	627	85	154	91	110
8	lrcu:1	50	611	74	241	457	66	-140	154	199

9 | lrcu:2 | 54 669 98 | -394 651 193 | 65 18 46 |

10 | dmo:0 | 74 369 39 | 43 79 3 | 82 291 103 |

11 | dmo:1 | 52 364 56 | -63 80 5 | -119 284 150 |

12 | ost:0 | 123 260 3 | 13 238 0 | -4 22 0 |

13 | ost:1 | 4 305 84 | -436 286 17 | 114 19 10 |

14 | ce:0 | 70 689 71 | 297 673 141 | -46 16 30 |

15 | ce:1 | 54 660 98 | -394 643 193 | 65 17 46 |

16 | int:0 | 116 455 6 | 34 331 3 | 21 124 10 |

17 | int:1 | 8 612 85 | -409 379 29 | -321 233 159 |

5 CONCLUSÕES

- Pacientes com DII apresentaram menor densidade mineral óssea que os controles.
- Frequências semelhantes de alterações na DMO foram encontradas nos pacientes com RCU e DC.
- Pacientes do sexo masculino tanto com DC quanto com RCU foram associados com baixa densidade mineral óssea.
- A maioria dos pacientes, tanto com DC quanto com RCU, encontrava-se em remissão clínica, não sendo dessa forma encontrada associação entre atividade de doença e baixa DMO.
- Gravidade da DII parece estar associada com osteopenia/osteoporose.
- Devemos ficar alertas com os pacientes com DC que apresentem doença perianal, comportamento penetrante e idade de diagnóstico acima de 40 anos devido a associação com baixa densidade mineral óssea.
- Da mesma forma, maior atenção deve ser dada aos pacientes com RCU que tenham colite esquerda, estejam em uso de corticosteroide ou tenham histórico de internação hospitalar no último ano, pois também estão associados com osteopenia/osteoporose.
- A associação encontrada do uso de azatioprina e de infliximabe com osteopenia difere de dados da literatura, demonstrando a necessidade de estudos prospectivos para melhor definir a relação entre essas drogas e a densidade mineral óssea.

6 CONSIDERAÇÕES FINAIS

Os casos de DII têm crescido nos últimos anos, sobretudo nos países em desenvolvimento como o Brasil. Com isso, têm-se observado também uma maior identificação de manifestações extra intestinais e de suas complicações, dentre elas as alterações do metabolismo ósseo como osteopenia e osteoporose.

Identificação precoce e instituição de tratamento podem ser fundamentais nesses pacientes, pois os mesmos estão associados com maior risco de fraturas, inclusive fraturas não traumáticas. Além disso, é importante disseminar essa preocupação, pois grande parte dos pacientes com DII são jovens, sem outras comorbidades, tornando mais difícil associá-los ao risco de osteoporose.

Muitos estudos vêm sendo realizados no intuito de entender melhor os mecanismos relacionados com a redução da DMO nos pacientes com DII. Entretanto, os resultados vêm se mostrando divergentes em alguns aspectos devido à diferença de população e de sua localização.

No Brasil, existem poucos estudos publicados sobre esse tema e até o momento, nenhum realizado com pacientes do nordeste. Com esse estudo, pudemos evidenciar que também os nossos pacientes apresentam maior perda óssea, com prevalência semelhante à da literatura internacional, apesar de a maioria deles estar com doença em remissão. Gravidade de doença e uso de medicações como azatioprina e infliximabe estiveram associados com perda óssea. Isso demonstra o quanto é importante estarmos atentos a esses riscos, para que possamos aumentar a identificação de pacientes com osteopenia ou osteoporose e instituirmos tratamento adequado, antes da ocorrência de complicações.

Esse estudo contribuiu para um melhor conhecimento sobre a nossa população de pacientes, além de aumentar o entendimento sobre alguns fatores relacionados com perda óssea na DII.

7 PERSPECTIVAS DE ESTUDOS

O grupo de estudos em doenças inflamatórias intestinais do HUPES/UFBA tem se empenhado em manter, com regularidade, uma produção científica. Além dos artigos, cartas e casos clínicos já publicados, têm sido apresentados trabalhos nos últimos congressos nacionais e internacionais voltados para o público interessado nas DII.

Assim como esse trabalho, que avaliou a associação entre gravidade da DII e a DMO, anteriormente já havia sido publicado artigo que avaliava características nutricionais e DMO em pacientes com doença de Crohn, acompanhados no serviço de gastroenterologia do HUPES / HGRS. O grupo realizou também pesquisas sobre polimorfismos genéticos na doença de Crohn e sobre perfil epidemiológico da RCU.

Pretendemos continuar essa linha de pesquisa com esses pacientes avaliando outros fatores que possam estar contribuindo para redução da DMO.

Projeto 1: Dosagem de vitamina D nos pacientes com DII e baixa DMO e nos controles.

Projeto 2: Concentração sérica de OPG e RANKL nos pacientes com DII e baixa DMO e sua relação com fenótipos da doença e uso de medicações

8 ANEXO

8.1 ANEXO A – PARECER DO COMITÊ DE ÉTICA EM PESQUISA

Parecer Consubstanciado de Projeto

Título do Projeto: CARACTERÍSTICAS NUTRICIONAIS X CONDIÇÕES CLÍNICAS EM PACIENTES COM DOENÇA INFLAMATÓRIA INTESTINAL

Pesquisador Responsável Genoile Oliveira Santana

Data da Versão 09/11/2011 | **Cadastro 117** | **Data do Parecer 23/04/2012**

Grupo e Área Temática III - Projeto fora das áreas temáticas especiais

Objetivos do Projeto
Avaliar a frequência da intolerância à lactose e osteoporose/osteopenia e a associação destas com as características nutricionais nos pacientes portadores de DII em nosso meio

Sumário do Projeto
O grupo caso será formado por pacientes com diagnóstico de Doença Inflamatória Intestinal (DII), acompanhados no Ambulatório de Gastroenterologia do Pavilhão Professor Francisco Magalhães Neto – Complexo Hospitalar Universitário Professor Edgard Santos / UFBA (C-HUPES), com idade superior a 18 anos. Serão excluídos pacientes gestantes, portadores de doenças que causem alterações do metabolismo ósseo (como insuficiência renal crônica, doença pulmonar obstrutiva crônica, tireoidopatias, hepatopatias, lúpus eritematoso), com câncer, ressecção intestinal prévia, mulheres na pós menopausa ou em uso de terapia estrogênica.
Os controles serão os pacientes atendidos no mesmo espaço físico e período, no Ambulatório de Dermatologia, que apresentem características homogêneas de sexo e idade com os pacientes estudados e que não possuam nenhum dos critérios de exclusão.
Serão avaliados 50 pacientes com DII, sendo 25 pacientes com Doença de Crohn (DC) e 25 pacientes com Retocolite Ulcerativa Inspecífica (RCUI), atendidos no período de desenvolvimento do estudo que preencherem os critérios de inclusão e aceitarem participar da presente pesquisa. O grupo controle será composto por 50 pacientes atendidos no ambulatório de dermatologia, no período de estudo, que não apresentem sintomatologia ou história de DII.
Para verificar se as variáveis apresentam distribuição normal será realizado o teste de Kolmogorv-Smirnov. A análise descritiva da amostra estudada será então procedida. Utilizaremos proporções para variáveis categóricas e a média com desvio-padrão para variáveis contínuas. As variáveis categóricas serão analisadas por meio do teste quiquadrado ou teste Exato de Fisher. Variáveis contínuas serão analisadas utilizando o teste T student ou o teste de Mann-Whitney, quando a variável não tiver distribuição normal.

Aspectos relevantes para avaliação	*Situação*
Título	Adequado
Relação dos Pesquisadores	Adequada
Local de Origem na Instituição	Adequado
Projeto elaborado por patrocinador	Não
Local de Realização	Própria instituição
Outras instituições envolvidas	Não
Condições para realização	Adequadas
Introdução	Adequada
Objetivos	Adequados
Método	
Tipo de projeto	Pesquisa em Seres Humanos
Delineamento	Adequado
Tamanho de amostra	Total 100 Na instituição 100
Cálculo do tamanho da amostra	Adequado
Participantes pertencentes a grupos especiais	Não
Seleção eqüitativa dos indivíduos participantes	Adequada
Critérios de inclusão e exclusão	Adequados
Relação risco- benefício	Adequada

Uso de placebo	Não utiliza
Período de suspensão de uso de drogas (wash out)	Não utiliza
Monitoramento da segurança e dados	Adequado
Armazenamento de material biológico	Adequado
Instrumentos de coleta de dados	Adequados
Avaliação dos dados	Adequada - quantitativa
Privacidade e confidencialidade	Adequada
Termo de Consentimento	Adequado
Adequação às Normas e Diretrizes	Sim
Cronograma	Adequado
Data de início prevista	jan-11
Data de término prevista	dez-12
Orçamento	Adequado
Solicita recursos à instituição	Não
Fonte de financiamento externa	Agência de fomento
Referências Bibliográficas	Adequadas

Recomendação

Aprovar

Comentários Gerais sobre o Projeto

Parecer Aprovado

As correções e os esclarecimentos foram feitos.

• O sujeito da pesquisa tem a liberdade de recusar-se a participar ou de retirar seu consentimento em qualquer fase da pesquisa, sem penali¬zação alguma e sem prejuízo ao seu cuidado (Res. CNS 196/96 - Item IV.1.f) e deve receber uma cópia do Termo de Consentimento Livre e Esclarecido, na íntegra, por ele assinado (Item IV.2.d).

• O pesquisador deve desenvolver a pesquisa conforme delineada no protocolo aprovado e descontinuar o estudo somente após análise das razões da descontinuidade pelo CEP que o aprovou (Res. CNS Item III.3.z), aguardando seu parecer, exceto quando perceber risco ou dano não previsto ao sujeito participante ou quando constatar a superioridade de regime oferecido a um dos grupos da pesquisa (Item V.3) que requeiram ação imediata.

• O CEP deve ser informado de todos os efeitos adversos ou fatos relevantes que alterem o curso normal do estudo (Res. CNS Item V.4). É papel do pesquisador assegurar medidas imediatas adequadas frente a evento adverso grave ocorrido (mesmo que tenha sido em outro centro) e enviar notificação ao CEP e à Agência Nacional de Vigilância Sanitária – ANVISA – junto com seu posicionamento.

Relatórios parciais e final devem ser apresentados ao CEP, inicialmente em _____/_____/_____ e ao término do estudo.

Para projetos do Grupo 1 do fluxograma acrescentar:

Seu projeto (Registro 117/2011 Grupo III Área temática especial NÃO) está sendo encaminhado a CONEP e só poderá ser iniciado após parecer aprovatório desta.

ROBERTO BADARÓ, MD PHD
Coordenador CEP
CHUPES

Bahia

HGRS HOSPITAL GERAL ROBERTO SANTOS

HOSPITAL GERAL ROBERTO SANTOS

Salvador, 26 de junho de 2012.

DECLARAÇÃO

Declaro que o projeto de pesquisa intitulado "**CARACTERISTICAS NUTRICIONAIS EM PACIENTES COM DOENÇA INFLAMATÓRIA INTESTINAL**", que tem como pesquisador responsável RAQUEL ROCHA DOS SANTOS tem inclusão autorizada para realização no ambulatório de GASTROENTEROLOGIA DO HOSPITAL GERAL ROBERTO SANTOS conforme parecer emitido pelo Comitê de Ética em Pesquisa do Complexo hospitalar prof. Edgard Santos.

Delvone Freire G. Almeida
Diretora Geral

8.2 ANEXO B- TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Você está sendo convidado (a) a participar da pesquisa "**Características Nutricionais X Condições Clínicas em Pacientes com Doença Inflamatória Intestinal**", que tem o objetivo de avaliar a relação entre consumo alimentar e composição corporal com presença de osteoporose e/ou intolerância a lactose em pacientes com doença inflamatória intestinal. A pesquisa é coordenada pela nutricionista Dra. Raquel Rocha dos Santos, professora da Escola de Nutrição da Universidade Federal da Bahia.

A pesquisa inclui diversas fases. Será realizada coleta de dados do prontuário médico, aplicação de questionário sobre os hábitos alimentares e avaliação da composição corporal, utilizando medidas de peso, altura, circunferência do braço, dobras cutâneas e exame de bioimpedância. Esse exame será feito para avaliar a quantidade de gordura e de massa muscular do corpo, em posição deitada e relaxada, sendo colocados 2 eletrodos (objetos metálicos) na mão e no pé, por onde passa uma corrente elétrica de baixa intensidade que não irá causar nenhum desconforto ou dor. Também serão realizados: exame de densitometria óssea para avaliar presença de osteoporose, que também não causa dor e é feito com o paciente deitado; exames de sangue, onde os riscos que podem existir são os de uma coleta comum de sangue, como hematoma (mancha roxa na pele) e dor no local da punção; e avaliação da intolerância à lactose, que é o açúcar do leite. Para essa avaliação será realizado o teste de hidrogênio expirado e será necessário um período de 12 horas de jejum. No local do exame, você será orientado a beber uma solução contendo lactose e, logo após, respirar com a boca conectada a um tubo. A mesma medida será repetida 1 hora após a administração da dose e a cada 30 minutos até completar 3 horas. Podem ocorrer sintomas como gases, diarréia, distensão e dor na barriga. Todos os exames serão pagos pela pesquisa.

Para participação em todas as etapas do estudo, será necessário comparecer ao Complexo Hospitalar Universitário Professor Edgard Santos / UFBA (C-HUPES) para realização da bioimpedância, do exame de sangue e do teste de hidrogênio expirado; e em um laboratório de referência indicado pelos pesquisadores para realização da densitometria óssea.

A participação é voluntária e você não receberá benefícios financeiros. Da mesma forma, a qualquer momento, mesmo após assinar este termo, você poderá desistir de participar da pesquisa, sem que isso signifique prejuízo ou custo. Se este termo não for assinado, isso também não vai causar nenhum tipo penalização a você. É um direito seu recusar este convite. Você também terá o direito de saber os resultados encontrados nos seus exames. Sua identidade ficará em sigilo e não será divulgada, mesmo que esses estudos sejam publicados em revistas científicas.

Os pesquisadores comprometem-se com o mínimo de riscos, garantindo que quaisquer danos previsíveis serão evitados.

Você pode tirar qualquer dúvida que tenha sobre a pesquisa. Para isso, poderá entrar em contato com a pesquisadora Raquel Rocha dos Santos, por meio dos contatos descritos no final desta folha ou pessoalmente no ambulatório de Nutrição no Pavilhão Professor Francisco Magalhães Neto às segundas feiras a partir das 13 horas. Também poderá entrar em contato com o Comitê de Ética em Pesquisa do Hospital Universitário Professor Edgard Santos no endereço Rua Augusto Viana, S/N, Canela, CEP: 40.110-060 – Salvador – Bahia, pelo telefone 3283-8043, e via e-mail: cep.hupes@gmail.com.

Se você leu este termo, ou se ele foi lido para você por algum representante legal, e você entendeu e aceita participar da pesquisa, assine nos campos indicados, para permitir sua participação. Não se esqueça de assinar e colocar a data em todas as páginas. Este documento tem duas vias, ficando uma com você e outra com o nosso grupo de pesquisa.

Contatos dos pesquisadores:
Raquel Rocha dos Santos: raquelrocha2@yahoo.com.br/ Tel.: (71) 9974-9964.

Paciente: _____

_____

Assinatura do Paciente

_____

Assinatura da Pesquisadora Responsável

Contatos: 9974.9964 – raquelrocha2@yahoo.com.br

Endereço: Av. Araújo Pinho, 32 Canela, CEP: 40.110-150 - Salvador – Bahia.

Salvador_____ de _____ de 20___.

8.3 ANEXO C- FICHA UTILIZADA NA COLETA DE DADOS

Características Nutricionais X Condições Clínicas em Pacientes com Doença Inflamatória Intestinal

Nome: **Registro:** **( ) HUPES ( ) HGRS**

Endereço: **Telefone:**

1- GÊNERO: (1) Masculino (2) Feminino
2- TIPO DE DOENÇA: (1) RCUI (2) DC
3- IDADE: (anos)
4- TEMPO DE DIAGNÓSTICO DA DOENÇA (DC): (em anos) (9) Não se aplica
5- IDADE AO DIAGNÓSTICO (DC): (1) < 17 anos (2) 17 a 40 anos (3) > 40 anos (9) Não se aplica
6- USO REGULAR DAS MEDICAÇÕES: (1) Não (2) Sim
7- USO DE AMINOSSALICILATOS: (1) Não (2) Sim
8- USO DE CORTICÓIDE: (1) Não (2) Sim
9- USO DE CORTICÓIDE NO ÚLTIMO ANO: (1) Não (2) Sim
10- DOSE ACUMULADA DO CORTICÓIDE: (convertido em mg de Prednisona) (9) Não se aplica
11- TEMPO DE CORTICÓIDE (EM MESES): (9) Não se aplica
12- USO DE AZATIOPRINA: (1) Não (2) Sim
13- USO DE METOTREXATE: (1) Não (2) Sim
14- USO DE INFLIXIMABE: (1) Não (2) Sim
15- USO DE ADALIMUMABE: (1) Não (2) Sim
16- ATIVIDADE DE RCUI: (1) Não (2) Sim (9) Não se aplica
17- ÍNDICE DE ATIVIDADE (Escore de Litgher): (9) Não se aplica
18- RESSECÇÃO INTESTINAL NA RCU: (1) Não (2) Sim
19- TIPO DE RESSECÇÃO: (9) Não se aplica
20- LOCALIZAÇÃO DA RCUI: (1) Proctite (2) Colite esquerda (3): Colite extensa (9) Não se aplica
21- PRATICA ATIVIDADE FÍSICA REGUÇAR: (1) Não (2) Sim
22- QUAL/FREQUÊNCIA/semana: (9) Não se aplica
23- IMC:
24- LOCALIZAÇÃO DA DC: (1) ileal (2) Colônica (3)ileocolônica (4)TGS (9) Não se aplica
25- COMPORTAMENTO DA DC: (1) Não estenosante não penetrante (2) estenosante (3) penetrante (9) Não se aplica
26- DOENÇA PERIANAL: (1) Não (2) Sim (9) Não se aplica
27- RESSECÇÃO INTESTINAL NA DC: (1) Não (2) Sim (9) Não se aplica
28- TIPO DE RESSECÇÃO INTESTINAL NA DC: (1) delgado (2)cólon (3)delgado+cólon (9) Não se aplica
29- ÍNDICE DE ATIVIDADE DE DC (Harvey-Bradshow): (9) Não se aplica
30- CLASSIFICAÇÃO DA ATIVIDADE: (1) Não (2) Sim (9) Não se aplica
31- INTERNAÇÃO HOSPITALAR NO ÚLTIMO ANO: (1)Não (2)Sim

AVALIAÇÃO DA DENSITOMETRIA ÓSSEA E DE BIOQUÍMICOS		
Nome		Data:
Registro/ Hospital:		Peso:
Data de Nascimento:	Idade:	Altura:
Sexo: ( ) Masculino ( ) Feminino		IMC:

Densitometria de Coluna	Densitometria de Fêmur
DMO (g/cm2):	DMO (g/cm2):
T-score:	T-score:
Z- score:	Z- score:
Conclusão: ( ) Normal ( ) Osteopenia ( ) Osteoporose	

Densitometria de Corpo Total
Braço:
Massa Magra (g): _____ Tecido Adiposo (g):_____ % tecido adiposo: _____
Perna:
Massa Magra (g): _____ Tecido Adiposo (g):_____ % tecido adiposo: _____
Tronco:
Massa Magra (g): _____ Tecido Adiposo (g):_____ % tecido adiposo: _____
Corpo Total
Tecido Total (g): _____ Tecido Adiposo (g): _____
Massa Magra (g): _____ % tecido adiposo: _____
DMO (g/cm2): T- score: Z-score:

QUESTIONÁRIO - GRUPO CONTROLE DEXA

DADOS DE IDENTIFICAÇÃO				
NOME:			DATA:	Nº DO REGISTRO:
SEXO:	DATA DE NASCIMENTO:	IDADE:	NATURALIDADE:	TELEFONE CONTATO:
RENDA MENSAL:		ESCOLARIDADE:		ENTREVISTADOR:

1 – Possui comorbidades? ( ) Não ( ) Sim Qual(is)? _____

2 – Faz uso regular de algum tratamento medicamentoso? ( ) Sim ( ) Não CC (cm):_____

Se sim, qual (is)? _____

3 – Algum tipo de ressecção intestinal? ( ) Não ( ) Sim Se sim, qual? _____

4 – Você pratica atividade físico regular? ( ) Sim ( ) Não. Se sim, qual(is)? _____Há quanto tempo:_____

5 – Tabagismo? ( ) Sim ( ) Não ( ) Ex-tabagista. Se sim, qual frequência:_____Há quanto tempo:_____

6 – Você faz uso de suplemento alimentar? ( ) Sim ( ) Não

Se sim, qual: ( ) Completo ( ) Proteína ( ) Cálcio ( ) Plurivitamínico ( ) Plurimineral

( ) Outro: _____ Posologia: _____

8.4 ANEXO D - RESUMOS PUBLICADOS EM ANAIS DE CONGRESSOS, CAPÍTULO DE LIVRO.

XII Semana Brasileira do Aparelho Digestivo	Goiânia	2013
Lima CA, Almeida NP, Lopes M, Coqueiro F, Rocha R, Lyra AC, Santana GO. **Densidade mineral óssea X Gravidade de doença em pacientes com Doença Inflamatória Intestinal**		

VIII Workshop de Doenças Inflamatórias Intestinais	Campinas	2014
Lima CA, Santana GO. **Psoríase pustulosa induzida por anti-TNF associada à uveíte grave em paciente com doença de Crohn refratária: qual a melhor opção terapêutica?**		

VIII Workshop de Doenças Inflamatórias Intestinais	Campinas	2014
Lima CA, Lopes M, Coqueiro F, Rocha R, Lyra AC, Santana GO. **Densidade mineral óssea X Gravidade de doença em pacientes com Doença Inflamatória Intestinal**		

Capítulo de livro

SANTANA, G O; **LIMA, CA**. **Manifestações cutâneas nas Doenças Inflamatórias Intestinais.** In: Dídia Bismara Cury; Alan Colm Moss. (Org.). Doenças Inflamatórias Intestinais: retocolite ulcerativa e doença de Crohn. 2ª edição. Rio de Janeiro: Rubio, 2015.