Bone mineralization disorder in children with inflammatory bowel disease

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Abbreviations

aBMD - areal Bone Mineral Density (g/cm3)

ALP - Alkaline Phosphatase

ASCA - Anti-Saccharomyces cerevisiae antibodies

BMC - Bone Mineral Content

BMD - Bone Mineral Disease

BMAD - bone marrow apparent density

BMU - Bone Multicellular Unit

CBC - complete blood count

CD - Crohn's Disease

CRP - C-reactive Protein

DEXA/DXA - Dual-energy X-ray absorptiometry

ESR - Erythrocyte Sedimentation Rate

GH - Growth Hormone

IBD - Inflammatory Bowel Disease

IBDU - Inflammatory Bowel Disease Unclassified or Unclassified Colitis

IGF - Insulin Like Growth factor

IGFBP - Insulin Like Growth factor binding protein

IL-6 - Interleukin 6

ISCD - International Society for Clinical Densitometry

LFT- Liver Function Test

MAPK - p38 mitogen-activated protein kinase

NASPGHAN - North American Society for Pediatric Gastroenterology, Hepatology and Nutrition

pANCA - Perinuclear Anti-Neutrophil Cytoplasmic Antibodies

PCDAI - Pediatric Crohn's Disease Activity Index

PTH - Parathyroid Hormone

pQCT - Peripheral Quantitative Computed Tomography

PUCAI - Pediatric Ulcerative Colitis Activity Index

QCT - Quantitative Computed Tomography

QUS - Quantitative Ultrasound

RA - Rheumatoid Arthritis

RANK - Receptor Activator of Nuclear Factor-κB

RANKL - receptor activator of nuclear factor-κB ligand

SLE - Systemic Lupus Erythematosus

TNFα - Tumor Necrosis Factor alpha

UC - Ulcerative Colitis

vBMD - mean volumetric BMD (mg/cm3)

WHO - World Health Organization

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1. Abstract

Chronic inflammatory disorders such as Inflammatory Bowel Disease have a considerable effect on the metabolism of bone and are generally associated with Bone Mineral Disease (BMD) (1).

In children and adolescents, it is of particular importance because not only does it increase the risk of fracture but it has a deleterious effect on overall bone growth, development, and peak bone mass (2, 3-4). The mechanisms contributing to bone abnormalities are multifactorial however the most important is inflammatory cytokines found in high amounts in inflammatory diseases, the use of corticosteroids for treatment of IBD, lack of proper nutritional status and a delay in puberty in active disease. All mechanisms are correlated with one another, so there is difficulty in pinpointing what the real culprit behind the skeletal abnormalities is. Current diagnostic methods consist of several radiating and non-radiating and laboratory techniques, the most widely used and available of which is the DXA scan. Measurements from DXA scan are correlated to Z-scores that are standardized based on age and gender. With proper z-score measurment we can attempt to properly treat children and adolescents with pediatric-onset IBD before they reach their peak bone mass.

Nutritional interventions such as dietary Vitamin D and Calcium supplementation, even though are widely used, are not shown yet of substantial efficacy in patients with IBD. With understanding the mechanisms of BMD in Ulcerative Colitis and Crohn's Disease, it is crucial to focus on the development of targeted therapies that work to maximize growth yet limit disease activity in children with IBD.

Keywords: BMD, IBD, Crohns, Ulcerative Colitis, DXA, Vitamin D, Calcium, Z-score, peak bone mass

2. Sažetak

Kronični upalni poremećaji, kao što je upalna bolest crijeva, znatno utječu na metabolizam kostiju i općenito su povezani s poremećajem mineralizacije kostiju (1)

U djece i adolescenata to je od osobite važnosti jer ne samo da je povećan rizik od prijeloma kostiju, nego je dokazan je negativan učinak na ukupni rast kosti, razvoj i vršnu koštanu masu (2, 3-4). Mehanizmi koji pridonose abnormalnom razvoju kostiju su multifaktorni, međutim najvažniju ulogu imaju upalni citokini koji se nalaze u velikim količinama kod upalnih bolesti, zatim primjena kortikosteroida u liječenju , nedostatak odgovarajućih nutrijenata, i kašnjenje puberteta u aktivnoj bolesti . Navedeni mehanizmi su međusobno povezani jedni s drugima, stoga je teško odrediti koji je pravi uzrok za abnormalnosti u razvoju kostiju. Trenutne dijagnostičke metode uključuju nekoliko radijacijskih i ne-radijacijskih te laboratorijskih tehnika, od kojih je najčešće korištena i dostupna DXA denzitometrija. Mjerenja iz DXA skeniranja koreliraju se s Z-vrijednostima koji su standardizirani na temelju dobi i spola. S tim spoznajama možemo pokušati pravilno liječiti djecu i adolescente s ranim nastupom upalne bolesti crijeva, prije nego što dosegnu svoju vršnu masu kostiju.

Dodatak vitamina D i kalcija, u prehrani, iako se primjenjuju, nisu za sada pokazali značajni učinak u bolesnika s upalnim bolestima crijeva. Uz razumijevanje mehanizma mineralne bolesti kostiju kod ulceroznog kolitisa i Crohnove bolesti, ključno je usredotočiti se na razvoj ciljanih terapija koje potiču rast, ali istovremeno ograničavaju aktivnost bolesti kod djece s upalnim bolestima crijeva.

Ključne riječi: Poremećaj mineralizacije kostiju, Upalna bolest crijeva, Ulcerozni kolitisa, Crohnova bolest, DXA denzitometrija, vitamin D, Kalcija, Z-vrijednost, Vršna masa kostiju.

3. Introduction

Inflammatory Bowel Disease (IBD) is an unyielding, chronic inflammation of primarily the digestive tract with characteristic extraintestinal manifestations. IBD can be categorized into three subtypes, the most common being Crohn's Disease (CD) and Ulcerative Colitis. The third, least common form, localized primarily in the colon, when differentiation is not yet possible, is labeled as Unclassified Colitis (IBDU). IBD was described in early medical literature several centuries ago as an erratically occurring disease, but it was not until the 19th and early 20th century that its attention was gained in the medical community by US physician Crohn and British physician respectively. Similar to other diseases, UC and CD have a steady increase in their incidence since the early 20th century for UC and the mid and late 20th century for CD.

3.1 Epidemiology

The disease can occur from as early as childhood but is most commonly diagnosed between the ages of 15 to 30 years. Genetic and environmental factors are an explanation for the epidemiological differences of IBD in newly industrialized and westernized countries. There is also a difference of observations in studies performed in already westernized and newly industrialized countries due to increased diagnostic capabilities as shown in the Barnes and Kappelmann (7) study on the incidence of Pediatric onset IBD in the north of France. Such epidemiological differences can also be seen with two large-scale studies. One retrospective cohort study was done in the UK with a follow-up of 6 million person-years linking the use of antibiotics and pediatric-onset IBD. Another prospective cohort done on the Danish population also linking antibiotics to IBD but this time it was more specifically associated with CD (8,9). Although there are many associations of instigating factors that are linked to IBD including

smoking, hygiene hypothesis, microorganisms of the gut microbiome, appendectomy, medication, nutrition and stress, the exact mechanism behind these connections are still not well understood. More and more factors are being linked to IBD in the present and future studies and possibly one day will be more clearly understood (10).

3.2 Diagnosis and Features of Disease

There is variation in factors that distinguish the diagnosis of the different types of Inflammatory Bowel Disease. Initial evaluation of pediatric patients suspected of IBD consists of a series of diagnostic tests which include upper endoscopy, colonoscopy with ileoscopy (with biopsies), upper GI series with barium and small bowel follow-through or in older children MR enterography, Less commonly there is also serologic testing, capsule endoscopy, and abdominal CT. (1)

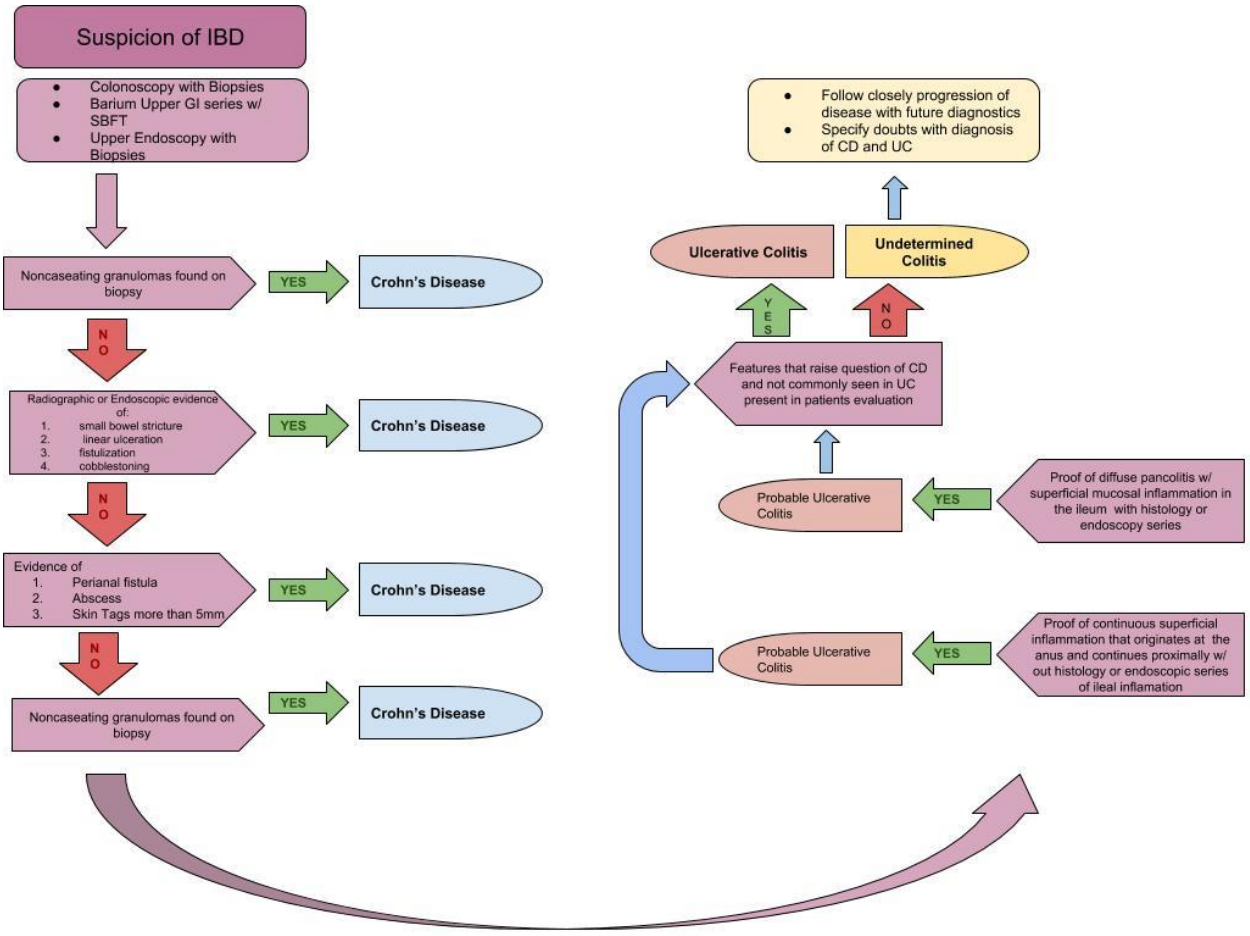
The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) has set up guidelines based on an algorithm that helps physicians in decreasing the variability in diagnoses between Crohn's disease, Ulcerative Colitis and minimizing needing to diagnose Indeterminate Colitis. This decrease in diagnosis variability is epidemiologically and medically crucial for future research of the disease, and for appropriate treatment in today's times. Based on NASPGHAN algorithm, UC and Unclassified Colitis (IBDU) are both diagnoses of exclusion from CD.

Main features used in the diagnosis of CD is made by a thorough physical exam, Radiographic imaging, Colonoscopy, and Histology. On physical exam, perianal fistulas and abscesses can be found along with skin tags reaching a size of more than 5mm. On imaging one can see that there is definitive small bowel involvement. With colonoscopy, the classic linear

ulceration, cobblestone appearance, and ileocecal stenosis are found, as well as strictures and fistulas. Histologically CD consists of non-caseating granulomas in 25-61% of patients and with colectomy one can find transmural lymphoid aggregates (11).

Though the above criteria are diagnostic of CD, patients without these features should also be suspected of CD when having growth failure, an abdominal mass, discontinuous intestinal inflammation (as opposed to continuous lesions found in UC), or aphthous ulcers.

Figure 1 Differentiation between UC and CD and IBDU



NASPGHAN guidelines for differentiating diagnosis between UC, CD and IBDU, Modified (12).

When a patient has such suggestive features of CD but no diagnostic features, the diagnosis should primarily be put as IC and patients should be followed up until a more definitive diagnosis can be made. On the other side, we have UC which has its typical features of continuous diffuse inflammation that starts most commonly presents as pan colitis or left-sided colitis, or moves more proximally in the colon while sparing the rectum.

Serum antibodies can be tested for both Crohn's Disease and Ulcerative Colitis, ASCA, and P-ANCA respectively, but are not strongly associated and their Positive Predictive Values (PPV) are dependent on the level of symptoms. Patients who have an increased prior likelihood of having the disease will have less false positives than those lacking characteristic symptoms. There is also another serologic marker, anti-OmpC antibody, which is not specific to either CD or UC. However, it was found to be positive in some children with IBD which were not detected by other markers. The addition of this marker would increase sensitivity from 63% to 70%, as well as decrease the specificity from 97% to 94% (13). It is also necessary to look at inflammatory lab parameters such as Erythrocyte Sedimentation (ESR), C-reactive Protein (CRP), fibrinogen which would be elevated in active disease, and in CD levels of albumin and total albumin-globulin protein ratio which would be low.

3.3 Extraintestinal Manifestations

Although the gastrointestinal tract is the primary system affected by both CD and UC, multisystem involvement is possible as well. The prevalence of the presence of extraintestinal manifestations (EIM) of both conditions is not clearly outlined and is varying widely from author to author. Even so, there seems to be a combined finding that a higher number of pediatric patients versus adult patients develop more than just intestinal involvement. Extraintestinal

symptoms may appear before intestinal symptoms, synonymously with them or may develop later in the disease. For pediatric-onset IBD, the most striking feature would be growth retardation or cessation and lack of sexual development. Extraintestinal manifestations can commonly be seen in the oral cavity, liver, skin, joints and bones, blood, and eye. Such examples include arthritis,arthralgias, and spondyloarthropathies, erythema nodosum, aphthous stomatitis, episcleritis/uveitis and many less common ones. Other body systems can as well be affected but it is rare.

Inevitably with the chronicity of UC, CD, and IC in children, the toll it takes is on childhood development. The manifestation which will be the focus of this review will be bone mineralization disorder, of which the etiology is multifactorial yet still a direct consequence of all three forms of pediatric-onset IBD.

3.4 Treatment

Treatment of IBD is based on pharmacological, nutritional and/or surgical. Regarding pharmacological treatment, corticosteroids play still an important role in flare-ups and are important in inducing remission in a patient with active IBD. A good solution for avoiding steroid side effects is use of enteral nutrition. There is the same remission induction rate as with steroids alone and is mostly effective in mild or moderate nonfistulising Crohn's disease. For maintenance therapy, it is recommended to introduce immunomodulators such as azathioprine (AZA), a purine analog, for both CB and UC or methotrexate for CB, Biologic therapy, infliximab or adalimumab, the monoclonal antibodies that block TNFα, are recommended in severe cases. In pediatric patients, one of the main challenges is reducing the severity of

intestinal inflammation in order to optimize growth and pubertal development which will be further discussed later (14).

4.0 Pathophysiology of Bone Formation and Mineralization

The human skeleton, especially in the adolescent age, is a dynamic and influential organ that is continuously regenerating, growing and changing. Bone is important both structurally and metabolically. Metabolically, bones manage and store large amounts of calcium, carbonate, and phosphorus, and can control and buffer changes in hydrogen concentrations. Structurally, bone is crucial for mobility, respiration, and protection of internal organs and also the hematopoietic and immunologic cell's system (15).

During childhood growth and development, the skeleton goes through the process of modeling itself by depositing bone from one place to another until it reaches its maturity and ideal shape and size. Once the skeleton has reached its peak bone mass, modeling is replaced with the process of remodeling where there is a replacement of old bone with new, this process is done by specialized cells that make up the Bone Multicellular Unit (BMU). A BMU consists of osteoclasts, osteoblasts behind them, a blood supply, and connective tissue. In this order, there is first resorption of old bone by osteoclasts and the formation of new bone by osteoblasts (16). The result of a wholly remodeled cycle is the formation of an osteon. The function is not only for maintenance of the mechanical competence of bone but also to keep homeostasis for minerals in the body by mobilizing and storing calcium, magnesium and phosphorous. There is excellent coordination between the skeleton and intestines, the major contributor of ionic absorption, therefore, dysregulation of intestines can affect bones and bone development significantly. The

difference in the amount of bone removed and formed is called a bone balance, and this varies with gender, age and diseased versus healthy states (17-19).

Many regulators interact together for the processes of bone formation and mineralization, which are mainly divided into ones with systemic effects and ones which have both systemic and local or mainly/solely local effects on bone. The primary systemic regulators include parathyroid hormone (PTH), Vitamin D, Calcitonin, Estrogens, Androgens, Growth Hormone (GH)/ Insulin-like Growth Factor 1 (IGF-1), Thyroid Hormones, and Steroids. Other factors include cytokines, leukotrienes, nitric oxide (NO) prostaglandins and TNFα each promoting mainly resorption but may also be stimulative on the formation.

4.1 Parathyroid Hormone

PTH is the key regulator of calcium homeostasis. It maintains serum calcium concentrations in the blood not only by increasing the amount that is reabsorbed by the renal system and increasing calcitriol production by the kidneys. PTH has a stimulatory effect on bone formation when it is released or given intermittently. Consequently, it impedes on the production of collagen higher concentrations (20). Although PTH does stimulate bone formation, when it is given or secreted in a continuous flow it also has a bone resorptive effect in a process that is mediated by osteoclasts (21,22). PTH also increases the production of several local factors, including interleukin (IL)-6, IGF-1, and IGF-binding protein (IGFBP-5), and prostaglandins.

4.2 Vitamin D

The active Vitamin D metabolite 1,25(OH)2D mainly stimulates the gut to absorb calcium and phosphate, creating an optimal condition for mineralization. Therefore

insufficiencies lead to secondary hyperparathyroidism, and bone loss which later leads to osteomalacia and an increased risk of fractures. In the gastrointestinal tract, calcium is mostly absorbed in the duodenum and proximal jejunum. Depending on the segment and the concentration of calcium in the lumen, it is absorbed either through a weakly regulated paracellular route or by a highly regulated vitamin D3-sensitive transcellular pathway. Therefore if the concentration of calcium is low in the lumen, Vitamin D is needed to regulate and increase absorption of the calcium that is in the lumen to maintain sufficient levels (23).

As stated above continuously increased PTH (which is the case in hyperparathyroidism) is unfavorable due to its stimulatory effect on the bone turnover rate which is carried out by the BMU. An increased bone-turnover rate leaves more osteoid type bone or unmineralized bone which is undesirable, especially in a growing child (24). In contrast to Vit D, calcitonin inhibits osteoclast activity, reducing bone resorption. A body in homeostasis with the appropriate amount of actions of vitamin D and calcitonin results in a positive bone balance (25).

4.3 Estrogens and Androgens

In children that are going through puberty, sex hormones are critical in shaping the bone structure. (1) Increases of these hormones during puberty decrease resorption of bone and limit bone remodeling. Androgens act directly on receptors, found on the epiphyseal plates, to stimulate bone formation. Indirectly they stimulate muscle formation which gives bones incentive to grow and mineralize (26,27). Estrogens are responsible for the maturation and mineralization of bone. Indirectly, estrogens work on receptor activator of nuclear factor kappa-B ligands (RANKL), by inhibiting it, through the action of osteoprotegerin, a decoy receptor of the RANKL. RANKL is a cytokine that is secreted by osteoblasts and T cells which interacts

with the receptor activator of nuclear factor-κB (RANK), found on the membrane of osteoclasts, where it activates bone resorption (28). RANKL inhibition decreases differentiation and activation of osteoclasts. Therefore, deficiencies in estrogen and androgen cause bone loss due to an increased rate of bone remodeling and the imbalanced osteoclast and osteoblast proliferation ratio (29,30).

4.4 Growth Hormone and IGF-1

Growth hormone is a peptide hormone with essential effects on bone growth such as the proliferation of pre-chondrocytes, remodeling and formation of bone, and increasing net mineralization (31). Children that are deficient are faced with a failure to grow, short stature and delay of sexual maturity which all contribute to a lower peak bone mass and bone mineral disease. The relationship between IGF-1 and GH is abstruse, however, simply put, GH stimulates the gene transcription and secretion of IGF-1 by the liver and indirectly stimulates IGF-1 through the action of chondrocytes and osteoblasts. GH is a principal determinant of IGF-1 and IGF-1 is the mediator of most actions of GH (32).

4.5 Thyroid Hormone

Increased amounts of circulating thyroid hormone are associated with increased bone remodeling (resorption and formation) which leads to a lower BMD. Thyroid hormones may act on bone cells either indirectly by increasing secretion of growth hormone (GH) and insulin-like growth factor-1 (IGF-1), or directly by influencing target genes via specific nuclear receptors. It is thought that thyroid hormone may work indirectly on bone cells by activating secretion of growth hormone and insulin-like growth factor-1 or by directly influencing osteoblasts and

osteoclasts through the specialized receptor, thyroid receptor-alpha-1 (TR alpha-1) that is found in bone cells (33.). There is also significance in the increased levels of interleukin-6 (IL-6) found in patients with hyperthyroidism in which IL-6 acts excessively on osteoclast production by stimulating it, thus causing a lower BMD (34).

4.6 Corticosteroids

Steroids play a vital role in the resorption and formation of bone especially in children that are being treated with IBD flare-ups or treatment of initial flare-up with steroids. Corticosteroids cause bone loss by inhibiting formation, increasing resorption, decreasing the intestinal absorption of calcium, and increasing excretion of calcium through the kidney. This topic will be discussed in more detail later on with the pathogenesis of Glucocorticoid therapy.

4.7 Peak Bone Mass

Peak bone mass is defined as the amount of bone mass that is developed at the point in time in which skeletal maturity is reached. There is no definitive age in which normal peak bone mass is achieved, but it is mostly seen in late adolescence within the second decade of life (18). Throughout childhood, bone growth is linear and does not significantly differ between genders until the onset of puberty at which there is an acceleration in bone mass that accounts for more than 40% of the total adult bone mass and the differences of bone in boys and girls starts to differ.

Table 1. Summary of Actions of Hormones on Bone Resorption and Formation

Regulators	Resorption	Formation
PTH	↑a	↑ (↓)a
125(OH)2 Vit D	↑	↑ (↓)a
Calcitonin	↓	NA
Estrogen	↓	↓b
Androgen	NA	↑
GH/IGF-1	↑	↑
Thyroid Hormone	↑	↑
Steroids	↑c	↓

NA - unknown effects
a- PTH and VIt D decrease collagen synthesis in high doses.
b- Estrogen decreases bone formation but it is less than its effect on bone resorption, net effect results in increased bone mass
c- Indirect effect of steroids is inhibition of calcium absorption through the gut
Translated and modified (1).

There was a study done on 300 females ages 6 through 32 with measurement of BMD by Dual-energy X-ray absorptiometry (DXA) stating that the age of peak bone mass attainment at the hip is earlier than at the spine, and bone mineral density surface area at the spine may even continue to increase throughout the early 30s in females. At the spine, femoral neck, greater trochanter, and Ward triangle, the highest BMD level were observed at 23.0 ± 1.4, 18.5 ± 1.6, 14.2 ± 2.0, and 15.8 ± 2.1-years-old, respectively (19).

Therefore, it is crucial for the pre-pubertal to adolescent age group to have a reasonable bone balance. In pediatric-onset IBD there is the difficulty of maintaining adequate bone formation, resulting in growth failure as well as bone mineralization disease. It is important not to miss this time frame of bone modeling when diagnosing pediatric-onset IBD and intervene when needed.

5.0 Pathogenesis of BMD in children with IBD

In the population of pediatric patients suffering from IBD whether it be CD, UC, or IC, there are certain risk factors specific for this group that make them more susceptible in developing BMD. Malabsorption, Glucocorticoid Therapy, Chronic Inflammation due to the disease activity, and Hypogonadism all play a role in making children with IBD vulnerable to BMD. To properly assess disease activity in children and adolescents for both CD and UC there are Standardized Assessment Tools, Pediatric Crohn's Disease Activity Index (PCDAI) and Pediatric Ulcerative Colitis Activity Index (PUCAI), respectively, which are used, and based on a given numerical score are interpreted. Scores are evaluated by several factors such as abdominal pain, number of stools per day, blood in stool, weight, linear growth, lab studies etc. and then organized into three to four categories rating the severity of disease. Ranges are from inactive disease to mild, moderate and finally severe disease activity (35-39).

3.1 Malabsorption and Nutrient Deficiency

Malnutrition is the result of malabsorption, decreased dietary intake, sometimes maldigestion, and increased energy expenditure. Particularly apparent in CD, malabsorption of lactose and fat-soluble vitamins such as A, D, E and K are common (40). The cause is multifactorial, mostly being caused by, in some cases, shortening of the small bowel length, giving less surface area for nutrients to be absorbed and possibly bile acid deficiency from terminal ileum resection; and inflammation of the bowel, making the diffusion of nutrients through the bowel much harder. Bacterial overgrowth also plays a role in making nutrient absorption more difficult. Since the focus of this review is BMD, focus will be put on Vitamin D deficiency. As previously mentioned, a decrease in the active metabolite of vitamin D,

1,35(OH)2D leads to consequences like a decrease in calcium absorption from the intestines which in turn leads to bone loss and increase of bone-turnover due to activation of PTH. With an increase in bone turnover there is more remodeling of the surface of the bone and there is less mineralization due to the fact that the age of osteon is younger and mineral accumulation takes time after formation. With chronic malabsorption, leading to chronic vitamin D deficiency, the amount of unmineralized osteoid tissue can accumulate to more than 5% (14). It was shown in a study that deficiency in vitamin D is very common in IBD, about 65% of CD patients had low serum calcidiol (25-hydroxyvitamin D levels, most probably due to their increased risk of bowel segment removal surgeries and lactose intolerance which is more likely to keep them away from dairy products, an established source of calcium and Vitamin D (41,42).The cause of insufficient vitamin D is also multifactorial and can be attributed to genetic factors or lack of sun exposure.

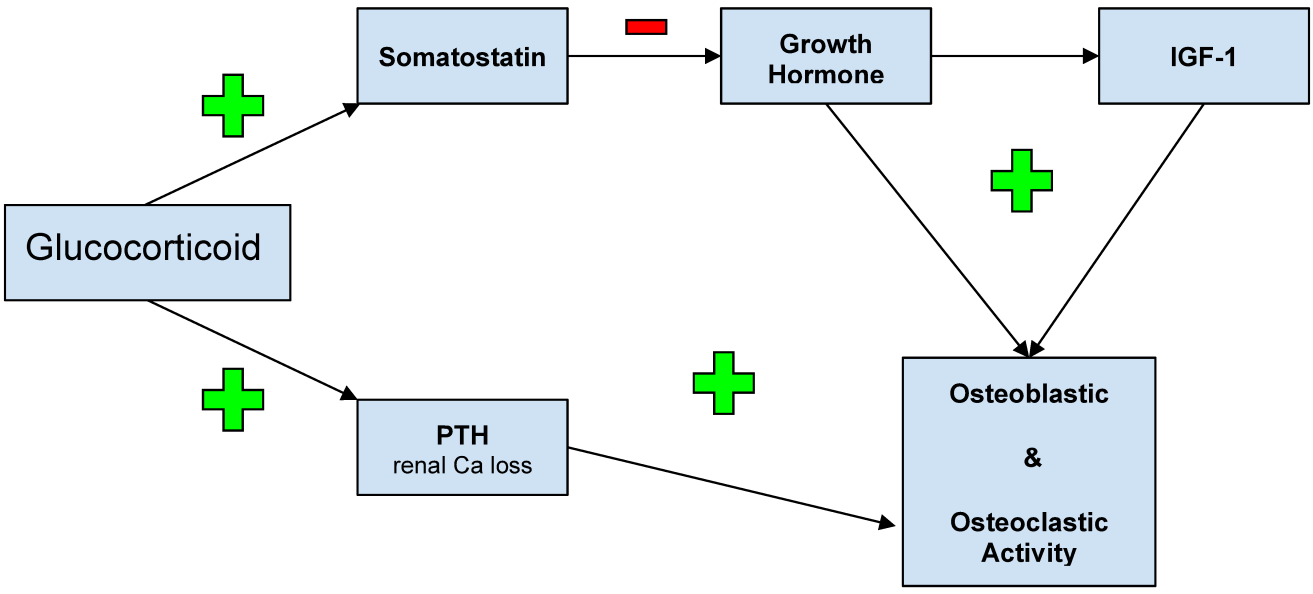
5.2 Glucocorticoid Therapy

Corticosteroids regulate a diverse array of physiological processes and are used in the treatment of several inflammatory diseases. It is more prevalent in patients with IBD that are treated with corticosteroids to have bone loss (43). They have a well known detrimental effect on bone and growth. It was first described by Cushing in 1931 and later in 1992 was demonstrated in rabbits the direct inhibitory effect dexamethasone had on the growth plate when it was given directly into the epiphyseal plate (44,45). In treatment with steroids, the time at which the risk of bone loss is most prominent is in the first few months of use. Continued use showed that there was a steady decrease in overall bone mass (46.). It was shown that particularly with high dose steroids, there was not only a decrease in the production of osteoblasts but also an increase in the apoptosis of osteoblasts and osteocytes (47). Osteoclast proliferation is stimulated by steroids

through suppression of osteoprotegerin (OPG) and by increasing production of RANK. Higher doses or levels of steroids also stimulate the synthesis of RANKL by the preosteoblasts which gives even more strength and support to osteoclast differentiation and increases the net bone resorption (48). A study that was performed on the risk of fracture in patients with IBD and it stated that the risk increased together with duration of glucocorticoid use, however Paganelli argued that, at least in pediatric-onset IBD, corticosteroids appeared to play a lesser role in the pathogenesis of low BMD (49). This statement was concluded after a study done on the correlation of bone marrow apparent density (BMAD) and inflammatory cytokines. There was found to be an inverse correlation between BMAD and IL-6 and no correlation between other cytokines and corticosteroids (49).

As previously mentioned, other effects of steroids that indirectly affect bone are shown in Figure 2 below. Steroids are an essential option to have in the treatment of active IBD. There are ongoing research and attempts in finding the optimal dosage in which there are minimal side effects and maximal anti-inflammatory effects of this hormone (50).

Figure 2: Indirect effects of corticosteroids on bone activity



5.3 Inflammatory Cytokines

The effects of glucocorticoid use versus the effects of inflammatory activity due to chronic disease are hard to differentiate (51). It is, however, apparent that the mechanism of BMD in IBD is similar to other chronic systemic inflammatory diseases such as Rheumatoid Arthritis (RA) or Systemic Lupus Erythematosus (SLE) (52). BMD is found in patients without any other factor to be accountable and this is exemplified by observations such as mild cortical bone loss found in children who are newly diagnosed and on histomorphometric analysis of subjects with clinically dormant IBD (more precisely CD) were also found to have low BMD and a decrease in mineral apposition rate (53-56). Although the mechanism of low BMD is not well understood, there is a possibility that the chronic inflammation leads to excessive production of cytokines, such as RANK (through dual action by osteoprotegerin) and IL-6, IL-1β, TNFα (Tumor Necrosis Factor alpha). Osteoprotegerin, the decoy receptor of RANKL, is secreted by osteoblasts along with RANKL and it was shown to be elevated in the plasma in patients with CD and UC, compared to controls, unlike RANKL which was not very different from control subjects (57). An increase of these cytokines causes resorption of bone without any compensatory increase in the formation of new bone (51, 58, 59). IL-6, IL-1β, TNFα are shown to be elevated in chronic inflammatory states like IBD and are involved in osteoclast-mediated bone resorption through the action of the p38 mitogen-activated protein kinase (MAPK) pathway (60). High concentration of IL-1β are found in both CD and UC, and it is a key mediator of bone resorption through the action of RANKL, which promotes the production of osteoclasts. IL-6 is also significantly increased in monocytes in patients with IBD, and there is a significant reduction in osteoclast formation and bone erosion with blockade of IL-6 (61). Evidence supporting the action of cytokines can be seen through pharmacological studies done which worked on the blockade of said cytokines such as IL-6 and

TNFα. Tocilizumab, a humanized antibody that blocks IL-6, has shown promise in inflammatory arthritis patients in reducing systemic bone resorption (62). Miheller et al. also demonstrated that in patients treated with infliximab (an inhibitor of TNFα) there was a decrease in the osteoprotegerin levels, improvement in BMD status and a higher BMAD (63). Based on the role RANKL has on bone resorption, there is a chance that a monoclonal antibody, denosumab, can one day be an effective therapy in the prevention and treatment of BMD in children with IBD (64).

5.4 Hypogonadism and Decrease in Sex hormones

Hypogonadism and pubertal delay are common in the pediatric population that has active IBD. A consequence of this is a decrease in linear growth, lack of lean muscle accumulation and delay of bone age which can affect peak bone mass during adolescence. Malnutrition, inflammatory processes and use of corticosteroids in the treatment of IBD all contribute to the hypogonadism in children (65). Inflammatory cytokines directly inhibit gonadal sex hormone production and the deficiency in body mass (which can be assessed by leptin levels which are equivalent to body fat) found in many IBD patients is preventing the onset of puberty by disrupting pituitary-gonadal function and activation of the gonadotropin-releasing hormone (66).

6.0 Diagnosis and Assessment of BMD

The World Health Organization (WHO) classification of BMD should not be used when assessing children and adolescents according to the International Society for Clinical Densitometry (ISCD) (67). In the pediatric group, Z-scores (instead of T-scores) are used to interpret DXA scans. This is due to the fact that it is not pertinent to compare an adolescent or child who has not reached peak bone mass with an adult who already has. Densitometric criteria alone are not enough for diagnosis of osteoporosis. There must be an apparent history of fracture

and low Bone Mineral Content (BMC). A clinically significant fracture history must contain at least one of three incidences: fracture of a long bone of the lower extremity, vertebral compression fracture, and/or two or more fractures of a long bone in the upper extremity. BMD or low BMC is defined as a Z-score (that is adjusted for body size, age, and gender) less than or equal to -2.0 and the term osteopenia should not be used in the pediatric population (68). Precise BMD measurement is difficult in the pediatric population due to confounders one of which is the lack of a standardized reference database for Z-scores (69). DXA scan is the most widely used tool in measuring BMC. There are however other methods such as Peripheral Quantitative Computed Tomography (pQCT), Quantitative ultrasound (QUS) and Biochemical markers to screen for BMD.

6.1 DXA scan and Z-score

Beginning in the 1980s, DXA scan has become the most accessible, non-invasive clinical procedure for investigating BMD. In adult medicine, for people suffering from osteopenia and osteoporosis, DXA scan is the gold standard for diagnosis (70). The growing concern for bone health in children has made its use increase rapidly as well in the pediatric population, and has become a widely available bone densitometry technique for bone status measurements in children (71). DXA scan BMC measurements of the lumbar spine (as oppose to hip) is the most widely used technique in assessment of BMD in the pediatric population.

DXA is a two-dimensional technique that uses x-ray transmission through the body at both high and low energy levels (72). The reason for both energy levels is because they are each attenuated differently, and thus information about soft tissue and bone is achievable along with the ability to distinguish between the two. DXA scan pixels measure the areal BMD (aBMD) which is expressed in g/cm3. The BMC is calculated by multiplying the Bone area (BA) by the

measure aBMD. The absolute value is then expressed as either a T-score or Z-score, in this case, for children, it is Z-score (73). A Z-score is a comparison of bone density to the average for one's gender and age, whereas a T-score reports the difference in bone mass of an average 30-year-old male. When BMC Z-scores are between -1.0 and -1.9 they are suggested to be classified as an "at risk for low bone mineral density or bone mineral content for chronologic age" group. When BMC Z-scores are less than or equal to -2.0, "low bone mineral density or bone mineral content for chronologic age" is suggested (74). Diagnosis of osteoporosis is made with a Z-score of -2.0 and a history of fracture that falls under the three previously mentioned categories.

Advantages of using DXA are rapid scan times, the availability of reference data in the pediatric population and cost is inexpensive. DXA scan can be used to measure the whole body or particular regions of interest, especially lumbar spine, and it is currently the only technique used in the measurement of hip region BMD in children (75).

6.2 QCT and vBMD

Quantitative Computed Tomography(QCT) consists of axial QCT (spine) and peripheral QCT (pQCT; radius, tibia, femur). These methods became regularly used during the 1980's before the DXA scan was popularized. QCT results are presented as the mean volumetric BMD (vBMD) and expressed as mg/cm3. When measuring the trabecular vBMD, which is one of the advantages QCT has over DXA scan, the result is an amalgamation of the bone and the marrow per voxel which may confound the measurements in adults. However, in children, bone marrow fat is limited. Therefore, vBMD results are more precise. The limitations of axial QCT such as a several-fold increase in the dose of ionizing radiation, lack of accessibility to equipment and analysis software, and the need for skilled technical staff has prevented it from developing

further. pQCT, since it is only applicable to the peripheral skeletal bones, vBMD measurements are attained at a lower rate of radiation exposure and cost, even so, QCT has been put to limited use in the pediatric population (76).

Table 2.What is Measured per Technique in Relation to the Bones' Biological Composition

Method	BMD compartment		BMD Total
	Cortical	Trabecular	
DXA	YES	NO	YES
QCT	YES	YES	YES

QUS is not included because it does not measure bone mineral density
DXA, dual-energy x-ray absorptiometry; QCT, quantitative computer tomography
modified according to (75)

6.3 Quantitative Ultrasound

Quantitative ultrasound (QUS) was developed in 1984 to assess the status of the calcaneal bone in adults (77). Since QUS is cheap, low cost and does not involve ionizing radiation, it is an advantage especially for use in children however clinical utility of US has not been yet adequately assessed, and its ability to predict fracture in children is not yet known (78). A study from 2012 reported a linear relationship between serum 25(OH)Vit D levels and QUS to support the use of QUS in measuring BMD as an indicator for Vitamin D status of bones in young children (79).

6.4 Laboratory Evaluation

There are several markers connected to bone formation and resorption that can be identified in daily practice. Markers for osteoblast activity, such as osteocalcin and bone alkaline phosphatase (ALP), osteoclast activity such as tartrate-resistant acid phosphatase, and other breakdown products can be used. There have been investigations into these markers in screening for BMD in IBD but have been of limited use in the clinical setting (80-82). Bone sensitive ALP in high concentrations has been considered a reliable biomarker to predict bone mineral status and as an indicator to continue with radiological diagnostics (83). In patients already found to have low BMC, laboratory diagnostic tests can help distinguish possible other causes of bone loss such as hyperparathyroidism, Vitamin D deficiency , renal disease or liver disease. As a general rule, necessary tests that should be ordered are a Biochemistry profile (Ca2+, phosphorus, albumin and total proteins, creatinine, liver function tests (LFTs), and electrolytes), 25(OH) Vit D levels, complete blood count (CBC) and Testosterone for males.

7.0 Treatment and Follow up of BMD in children with IBD

According to the NASPGHAN, there are current recommendations regarding the monitoring and stabilizing bone health in adolescents and children suffering from UC, CD or IC. Clinicians should obtain consistent follow-up measurements of BMD every one to two years in patients with pediatric-onset IBD who have a total body (minus head and spine) Z-score of less than -1.0 (76). There is not much data on the prevention and treatment of low BMC in patients with IBD especially data that is specifically for the pediatric population. Based on the 2017 American College of Rheumatology guidelines for steroid induced prevention of osteoporosis, nutritional interventions such as dietary Vitamin D and Calcium supplementation are widely

used in patients treated with steroids and patients that are seen to have low z-scores, even though there is not much evidence proving its efficacy (84). The overview of maintenance of bone health includes changes in lifestyle habits (exercise); correction of gonadal steroid hormone and vitamin D deficiencies, minimizing the use of glucocorticoid (i.e., changing the dose, type, and duration) and pharmacologic therapy if all else fails (85-89). When it comes to pharmacologic therapy, there is a minimal connection that the use of biologics has favorable outcomes concerning bone health and there are no current recommendations for these solely to control low BMC in children. Oral bisphosphonates have been found to be effective in improving bone mineralization status of children with significant morbidity from their compromised bone health (90). Again, there is little evidence and research that accurately examines specifically the treatment of BMD in pediatric-onset IBD.

8. Discussion

1964 was when the first connection between IBD and BMD was proposed, by Edwards and Truelove, after which came several studies concluding that low BMC is a common problem in children and adolescents suffering from IBD (2, 3-4).

It is of great importance to understand the mechanism of BMD specifically for children in IBD to shorten the time till diagnosis, to maximize efficacy of the treatment and to overall improve the treatment options in children. Unfortunately there are not many choices for pediatric patients in this disease, therefore there is not much individualization in treatment of it. Understanding the reason behind the low BMC, whether it be inflammation based or from treatment of flare-ups with steroids, we can develop and learn to use more efficient drugs that are targeting key regulators in bone mineralization. Denosumab, a highly specific inhibitor of

RANKL, has shown efficacy in the pediatric population to increase bone mineral density with minimal side effects, one of which is reduced calcium with increased parathyroid hormone (91). However this drug is used very rarely and not at all in most countries for the treatment in IBD. The mainstay of therapy for BMD in children is still Vitamin D and Calcium and will continue to be until there is enough studies done on a more targeted approach to this condition. Beginning there's studies on the targeting of main culprits, such as with denosumab on RANKL, is a step in the right direction for a more individualized approach in treatment of Bone Mineral Disease in children with Inflammatory Bowel Disease.

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10. Biography

Lea Bach-Bachich is a soon to be graduate of the 6-year medical program at the University of Zagreb School of Medicine in Croatia. She was born and raised in Westchester County, New York. From a young age Lea always had an interest in science and in the last few years of her high school began taking advanced science courses to help her build a good foundation of the natural sciences before pursuing her medical school career. Now after passing 6 years worth of pre-clinical and clinical courses she is ready to continue her educational journey in medicine as a practicing physician.