

## BONE MINERAL DENSITY IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE IN MOSUL CITY – IRAQ

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### ABSTRACT

**Background and Objective:** Osteopenia and osteoporosis are common metabolic disorders in advanced ages, particularly in menopausal women and those with other secondary causes, including inflammatory bowel disease (IBD). Bone mineral density (BMD) reduction, leading to osteopenia and osteoporosis, is higher in patients with (IBD) than in the general population. The primary goal of this study is to determine the frequency of osteoporosis or osteopenia in patients with IBD in a sample of the Iraqi population in Mosul City. **Patients and Methods:** A cross-sectional, observational study was conducted on fifty adult patients with established diagnosis of IBD who had been referred to Ibn -Sena Teaching Hospital for tertiary care from September 1, 2020 – March 1, 2021. The patient's ages ranged (18-50), with an average age (31.3±10.0) at time of the diagnosis. Data was collected from the patients through interviews according to a specialized questionnaire. Based on Dual energy x-ray absorptiometry (DEXA), the bone mineral density (BMD) and the T-score were calculated. **Results:** A total of nine patients had osteoporosis (T score: ≤ -2.5), six had Crohn's disease, and three had ulcerative colitis. A total of thirty-two (64%) patients had osteopenia (T-score: -1 to -2.5), eleven patients with CD, and twenty-one patients with UC. The remaining nine patients with IBD had a normal BMD (T-score: >-1), six patients had CD, and three had UC. **Conclusion:** Low BMD is one of the crucial complications of IBD, and its frequency is comparable in both UC and CD.

**KEYWORDS:** Inflammatory bowel disease, Osteoporosis, Osteopenia.

### INTRODUCTION

Inflammatory bowel disease (IBD) includes ulcerative colitis (UC), Crohn's disease (CD) and sometimes a third group named indeterminate colitis (IC) that shares features common for both diseases and contributes to (5-10%) of IBD.<sup>[1]</sup> It is a chronic disorder characterized by recurrent inflammation of the bowel with remission and relapsing course.<sup>[1]</sup> UC and CD are considered together because of multiple similarities, including gastrointestinal inflammation, waxing and waning severity and symptoms, and unknown etiology. However, the major disparities between these two diseases are that the CD can affect any part of the gastrointestinal tract from the mouth to the anus with skip lesions. The lesions in CD are trans mural (total thickness of the bowel) with granuloma formation in up to 50%; in contrast, the UC is limited to colonic mucosa, and rectal sparing is an unexpected finding.<sup>[2]</sup> Extra-

intestinal involvement, including osteopenia and or osteoporosis, is frequent in IBD.<sup>[3]</sup> IBD is worldwide in distribution. Genetic and environmental factors influence susceptibility to inflammatory bowel disease.<sup>[4,5]</sup> The IBD develops in genetically susceptible persons in response to environmental triggers.<sup>[6]</sup> Ultimately, the inflammatory process releases inflammatory moderators such as IL23, IL12, and TNF, leading to tissue damage.<sup>[7]</sup> Moreover, the prevalence of these two diseases is influenced strongly by racial and ethnic backgrounds. In the USA, IBD was more common in non-Hispanic whites compared to non-Hispanic blacks. In the Jewish population, the risk of occurrence of IBD is higher than elsewhere. There are limited epidemiologic data from developing countries; however, the prevalence of IBD are higher in Northern and Western Europe and North America than in Asia and the Middle East (e. g. UC incidence is 19.2 per 100,000 in North America, 24.3 per

100,000 in Europe, and 6.3 per 100,000 in Asia and the Middle East.<sup>[8]</sup> Osteoporosis is a major health problem, affecting about 200 million worldwide, particularly in the elderly population. It is a systemic skeletal disorder that develops slowly and is usually asymptomatic unless bone fractures or postural changes occur. Therefore, it is essential to diagnose the disease early for timely prevention and treatment of osteoporotic fractures and their consequences. The disease is characterized by low bone density and gradual microarchitecture deterioration, eventually decreasing bone strength and a high incidence of fracture risk.<sup>[9]</sup> The technique for assessing of bone mineral density is dual-energy X-ray absorptiometry (DEXA). It is a practical, painless, and relatively safe technique except for little radiation exposure. The measurement is usually from the hips, and sometimes the spine and other sites. DEXA measures both T score and Z scores. The T-score compares the patient's bone mineral density with a healthy 30-year-old of the same sex. The Z-score compares the patient's bone mineral density (BMD) with that of an average person of the same age and sex.<sup>[10-12]</sup> According to WHO criteria for osteopenia and osteoporosis, osteopenia is defined when a T-score is between (-1 to 2.5), and osteoporosis is defined when a T-score  $\leq -2.5$ .<sup>[13]</sup> The patients with IBD carry a higher risk for bone mineral loss than the general population. The incidence of osteoporosis and osteopenia in a patient with IBD ranges from 17-41%; also, the prevalence of fracture in a patient with IBD is 40% higher than in other populations.<sup>[14-16]</sup> The pathogenesis of the occurrence of osteopenia and osteoporosis in patients with IBD is multifactorial. It includes the following risk factors: older age, low body mass index, malabsorption, vitamin D and calcium deficiency, bowel resection, corticosteroid treatment, smoking, reduced physical activity, genetic factors and inflammatory cytokines.<sup>[17]</sup>

The primary aim of this study is to determine the frequency of low BMD in patients with IBD.

## PATIENTS AND METHODS

**The study design and setting:** The current study is a cross-sectional, observational study conducted on fifty adult patients with an established diagnosis of IBD. The patients referred to receive hospital tertiary care at the gastroenterology consulting outpatient clinic, medical wards, endoscopy unit, and the biologic-drugs providing clinics at Ibn-Sena Teaching Hospital. The ages ranged (from 18 to 50), with an average age ( $31.3 \pm 10.0$ ) at the time of the diagnosis. According to current international guidelines, the diagnosis of IBD is based on clinical, endoscopic, and histological criteria.

**The patient's consent and ethical issues:** before data collection, we obtained verbal consent from the participants, explained the purpose of the study, ensured the data's privacy, and obtained the original approval from the hospital authorities.

**Inclusion criterion:** A newly or previously diagnosed adults ( $>18$  years) with UC or CD.

**Exclusion criteria:** Female at menopause. Patients with indeterminate colitis (IC). Patients with co-morbidities other than osteopenia/osteoporosis.

**Data collection:** Data was collected through face-to-face interviews with each patient using a specialized questionnaire. The principle items in the questionnaire include preliminary data and data about general socio-geographic, biochemical and hematological indices, especially those related to IBD complications and bone mineral indices, and the regional disease extension according to the most recent endoscopic findings. The disease extension was applicable only for UC as data and endoscopic reports were very clear, while the case didn't fit CD. For description purpose, the local (regional) disease extension of the UC is divided into two major categories.

1. Non-extensive colitis includes one or more grades: Rectum or (G1); the inflammation is limited to rectal mucosa. Recto-sigmoid (G2) and (G3) when the inflammation extended proximally to left-sided colon up to splenic flexure.

2. Extensive colitis (G4) is when the disease extends beyond splenic flexure, and may involve the entire colon. We also collected information from other sources, such as the current and the previous summary discharge cards, labelled diagnosis cards, endoscopy reports, and the current and prior investigations performed on the patient. Moreover, we did clinical examinations for all. The investigators and patients took strict precautions against COVID-19 spreading during the interviews and clinical examination.

**Bone mineral density measurement and t score calculation:** Dual x-ray absorptiometry (DEXA) (MODEL: OSTEOSYS H3MC-500A) affiliated with Ibn Sena Teaching Hospital was used to measure BMD, and the test was free of charge. DEXA is currently the method of choice for measuring BMD. The measurements were from the femoral head and lumbar spine and T-score is calculated. DEXA results are expressed as osteopenia when T-score (-1 to -2.5) and osteoporosis when T-score ( $\leq -2.5$ ).

**Statistical analysis:** The Minitab version 18 software statistical program is applied to analyze and calculate the data. We used "Descriptive Statistics" to describe the different characteristics of the sample: the mean and standard deviation (SD) for the quantitative variables, the Chi square test, and the independent t-test of two means.

## RESULTS

The personal characteristics and the main parameters of the studied sample (50 patients) with a diagnosis of IBD during six months are clarified in Table (1).

**Table (1): Personal characteristics and the main parameters of patients with IBD, Mosul 2021.**

Parameters		Mean $\pm$ SD	Range
Age (years)		31.3 $\pm$ 10.0	19 – 49
Duration of IBD (months)		47.3 $\pm$ 31.8	3 – 180
BMI (kg/m <sup>2</sup> )		22.1 $\pm$ 4.1	15.5 – 36.0
Sex		No.	%
	Male	28	56.0
	Female	22	44.0
Smoking	Current smokers	6	12.0
	EX-smokers	5	10.0
	Non-smokers	39	78.0
Family history of IBD		2	4.0

Table (2) DEXA test shows the frequency of osteoporosis and osteopenia in fifty (50) patients with IBD. Nine (9) patients (18%) were osteoporotic and included six (6) patients with CD and three (3) with ulcerative colitis. A total of thirty-two (32) patients had

osteopenia; eleven (11) patients were located in a group of CD and twenty-one (21) of them were located in a group of UC. Nine (9) patients with IBD had normal T scores, Six (6) with CD and 3 with UC.

**Table (2): The frequency of osteoporosis and osteopenia in IBD patients, [n= 50].**

Dexa result [T-score]	UC No. (%)	CD No. (%)	Total No. (%)	P-value
Osteoporosis ( $\leq -2.5$ )	3 (11.1)	6 (26.1)	9 (18.0)	0.089*
Osteopenia ( $-2.4 - -1.0$ )	21 (77.8)	11 (47.8)	32 (64.0)	
Normal BMD ( $> -1.0$ )	3 (11.1)	6 (26.1)	9 (18.0)	
Total	27 (100.0)	23 (100.0)	50 (100.0)	---
Mean $\pm$ SD	- 1.4 $\pm$ 0.90	- 1.6 $\pm$ 1.17	- 1.5 $\pm$ 1.03	0.459**

\* Chi-square test was used. \*\* Independent T-test of two means was used.

The distribution of osteopenia and osteoporosis according to the extent of UC is shown in table (3).

**Table (3): The relationship between extension of UC and BMD, [n = 27].**

Dexa result [T-score]	Extension of Ulcerative colitis				Total No. (%)
	1 No. (%)	2 No. (%)	3 No. (%)	4 No. (%)	
Osteoporosis ( $\leq -2.5$ )	0(0.0)	1(20.0)	0(0.0)	2(14.3)	3(11.1)
Osteopenia ( $-2.4 - -1.0$ )	2(100.0)	4(80.0)	5(83.3)	10(71.4)	21(77.8)
Normal BMD ( $> -1.0$ )	0(0.0)	0(0.0)	1(16.7)	2(14.3)	3(11.1)
Total	2(100.0)	5(100.0)	6(100.0)	14(100.0)	27(100.0)

\* Invalid Chi-square test because small expected frequencies of cells.

The result of the principle bone minerals status (calcium and phosphate) and ALP in the serum of patients with

IBD in this study with the mean, standard deviation, and ranges is shown in Table (4).

**Table (4): The mean bone minerals indices in IBD patients, [n = 50].**

Bone minerals indices	Mean	SD	Range
S. Calcium (mmol/l)	2.0	0.18	1.6 – 2.4
S. Phosphate (mmol/l)	1.1	0.27	0.5 – 1.9
S. Alkaline phosphatase (IU/l)	180.4	89.8	70.0 – 584.0

The effect of the duration of IBD on bone mineral density (BMD) indices (calcium, phosphate and alkaline phosphatase) is observed in this study as there was a decline in the mean value of serum calcium and a reversible increase in the mean level of phosphate in patients with disease duration  $> 36$  months in comparison to patients with disease duration  $< 36$  months, but these were non-significant statistically (p-

value  $> 0.05$ ). However, significant changes (p-value  $< 0.05$ ) were observed in serum alkaline phosphatase and T-score values from (161.4 to 211) and from -1.2 to -1.9, respectively, table (5).

**Table (5): The effect of duration of IBD on BMD indices.**

BMD indices	Duration of IBD (months)		P-value*
	≤ 36 [n = 31]	> 36 [n = 19]	
S. Calcium (mmol/l)	2.0 ± 0.19	1.99 ± 0.16	0.761
S. Phosphate (mmol/l)	1.0 ± 0.25	1.13 ± 0.28	0.158
S. Alkaline phosphatase (IU/l)	161.4 ± 64.3	211.0 ± 42.0	0.033
T – score	- 1.2 ± 0.58	- 1.9 ± 0.84	0.041
* Independent T-test of two means was used			

## DISCUSSION

IBD incidence and prevalence are high in Northern Europe and North America. In addition to genetic factors, environmental changes, specifically industrialization and improved socioeconomic status, appear to play a role in the pathogenesis of these diseases in such countries.<sup>[18, 19]</sup> IBD continues to rise in low-incidence areas such as southern Europe, Asia, and many developing worlds.<sup>[19]</sup> IBD is commonly encountered during our daily practice in medical wards, outpatient clinics, and endoscopic units in Mosul hospitals. Unlike in Western countries, unfortunately, population-based epidemiological studies dealing with this problem are lacking in most developing countries, including Iraq.<sup>[19]</sup> Generally speaking, ulcerative colitis is recorded more frequently than Crohn's disease in our country. The results of this study indicate that IBD is predominantly a disease of younger ages (the mean age of patients in this study was 31.3 years); this is in contrast to the bimodal (young and old ages) distribution of IBD in Western countries; this can be explained in terms of varying exposure to two separate environmental risk factors that affected consecutive age groups differently over the 20th century.<sup>[20]</sup> The prevalence of osteopenia and osteoporosis in patients with inflammatory bowel disease varies significantly depending on the study populations, location, and design but ranges from 22%- 77% and 17%- 41%, respectively.<sup>[16, 21, 22]</sup> The frequency of osteopenia and osteoporosis in our study was 64% and 18%, respectively, without a statistically significant difference between UC and CD. Thus, despite our small sample, the results were similar to those of the above studies. The duration of IBD has an impact on predicting osteopenia/osteoporosis. The incidence of malnutrition, including vitamin D and calcium malnutrition and malabsorption, bowel resection, prolonged drug therapy, and the inflammatory process itself, are increased during IBD; however, this complication could appear early in the course of the disease.<sup>[17, 23]</sup> The current study found a significant correlation between IBD duration and the decline in T score. A T-score: (-1.2 ± 0.58) in patients with illness less than 36 months versus (-1.9 ± 0.84) in those with a period of disease more than 36 months. Body mass index (BMI) is a good indicator of nutrition status so patients underweight with low BMI (BMI ≤ 18.5) could reflect inadequate nutritional intake. In contrast, a high or normal BMI may indicate a good nutritional status.<sup>[24]</sup> In addition, a high BMI may protect against osteopenia/osteoporosis<sup>[25]</sup>, in our study, the mean BMI was within the normal range (22.1 ± 4.1.)

A review article published in 2020<sup>[26]</sup> showed higher rates of CD in females in Europe and the USA and males in Asia. The gender factor for IBD in our result shows more males than females (28 VS.22); this difference probably loses value because of the limited study sample. The gender factor in osteopenia/osteoporosis in patients below fifty years is not discussed here because it is out of the study's scope. Smoking, particularly in women, is considered a risk factor for CD; it is also a risk factor for low bone mineral density. Smoking may play a protective role against ulcerative colitis.<sup>[27, 28]</sup> In our study, the number of non-smokers and ex-smokers was much higher than that of smokers (44 Vs. 6). Up to 90% (24 out of 27) of patients in our series were non-smokers. The above result might influence the total number of patients with UC in the current study. Because the number of total smokers was only six for both UC and CD, we are reluctant to consider it because it is unlikely to affect the results. IBD may run in the family due to genetic sharing<sup>[4, 29]</sup>; however, because the number of patients with a positive family history of IBD is low (only two patients), in addition to the small sample size, we can't compare our results with that of other studies. Tests for bone mineral indices (serum calcium, phosphate, and alkaline phosphatase) were performed too, and one observation is that the positive relationship between the mean level of bone alkaline phosphatase (ALP) (NR: 40–125 U/L) and disease duration (see table 4). Although bone alkaline phosphatase is expected to be normal in osteoporosis, it may be increased following episodes of micro or overt fractures in such patients in the absence of other causes like hepato-biliary disease which may be associated with IBD, and it may be considered a predictor of osteoporosis in elderly females.<sup>[30]</sup> Additionally, other complications of IBD may lead to an increased level of ALP. The serum calcium level is generally within the accepted average in osteopenia/osteoporosis. Therefore, a calcium level decline is likely based on other complications associated with IBD. Anyhow, there was no significant change in the mean serum calcium levels (NR: 2.1–2.6 mmol/L) and phosphate, even in those with a longer duration of the illness. Concerning the relationship between local disease extension in UC and bone mineral density, we observed that the number of osteoporotic and osteopenia patients is much higher in extensive ulcerative colitis than in non-extensive colitis, because the extensive UC exposes the patient to increased morbidity, adverse effects of prolonged drug use, particularly for steroid which was taking by almost all patients during the disease, malabsorption, malnutrition, etc.<sup>[17]</sup> The impact



of the medications used through the course of IBD, particularly regarding steroids and their causal link with a low BMD, is a complex issue and needs a separate study.<sup>[31]</sup>

## CONCLUSION

IBD is associated with a low BMD. A significant number of patients in this study are complicated with the development of low BMD, and its frequency is comparable in both UC and CD.

**Recommendations:** Regular DEXA is indicated for IBD patients, particularly in the advanced stage of the disease, and meticulous care of nutritional status is advised. Again, studies on a larger scale are needed.

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