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Research Article

Serum Leptin, Ghrelin, and IGF-1 Levels and Their Association with Bone Mineral Density in Patients with Ulcerative Colitis

Abdulkerim Furkan Tamer[1], Ömer Yılmaz[2]

[1]Department of Internal Medicine and Nephrology, Adnan Menderes University Faculty of Medicine, Aydın, Türkiye
[2]Department of Internal Medicine and Gastroenterology, Atatürk University Faculty of Medicine, Erzurum, Türkiye

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ORCID IDs of the authors: A.F.T. 0000-0002-9820-5850, Ö.Y. 0000-0001-7471-4987.

ABSTRACT

Objective: This study aimed to investigate the relationship between serum leptin, ghrelin, and insulin-like growth factor-1 (IGF-1) levels and bone mineral density (BMD) in patients with ulcerative colitis (UC) to elucidate possible mechanisms underlying impaired bone mineralization in UC.

Methods: A total of 38 patients with UC and 38 age- and sex-matched healthy controls were included. Serum levels of leptin, ghrelin, IGF-1, and tumor necrosis factor-alpha (TNF-α) were measured during both the active and remission phases. Bone mineral densitometry was performed using dual-energy X-ray absorptiometry, and vertebral and femoral T- and Z-scores were recorded. The results were compared between disease phases and those of controls.

Results: Among UC patients, 27% had normal BMD, 50% were osteopenic, and 23% were osteoporotic. Mean T- and Z-scores were significantly lower in UC patients than in controls ($P < 0.05$). Serum leptin and IGF-1 levels during the active phase were significantly decreased, while ghrelin and TNF-α levels were significantly elevated, compared with controls ($P < 0.05$). In remission, ghrelin levels remained higher than in controls ($P < 0.05$), whereas leptin, IGF-1, and TNF-α levels were similar. A positive correlation was observed between IGF-1 and femoral neck T-scores in the active phase ($P < 0.05$).

Conclusion: BMD is significantly reduced in UC patients, particularly during active inflammation. Decreased secretion of leptin and IGF-1 and elevated ghrelin levels may contribute to bone loss, highlighting the interplay among inflammation, metabolism, and skeletal health in UC.

Keywords: Ulcerative colitis, leptin, ghrelin, IGF-1, bone mineral density, TNF-α

INTRODUCTION

Ulcerative colitis (UC), although primarily affecting the gastrointestinal tract, is also associated with extraintestinal manifestations and complications, such as decreased bone mineral density (BMD), which may result in osteopenia and osteoporosis. Over the past three decades, studies from different cohorts have reported a prevalence of osteopenia ranging from 22% to 77% and osteoporosis from 17% to 41% among UC patients.[1,2]

The major risk factors for reduced BMD in UC patients include low body weight and body mass index (BMI), chronic inflammation, prolonged corticosteroid therapy, immobilization, and malabsorption of vitamin D, calcium, and vitamin K.[3] Initially, the reduction in BMD was attributed primarily to corticosteroid use; however, the observation that corticosteroids are often used only for remission induction and not for maintenance therapy suggests that additional factors also contribute to decreased BMD.[4]

Corresponding author: Abdulkerim Furkan Tamer, **E-mail:** aftamer@gmail.com

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One possible mechanism involves alterations in the synthesis and secretion of adipokines, such as leptin and ghrelin, by adipose tissue. Anorexia, malnutrition, and cachexia associated with inflammatory bowel disease (IBD) can impair adipose tissue function, leading to alterations in leptin and ghrelin secretion. These disturbances may contribute to the higher prevalence of osteoporosis in UC patients.[3] White adipose tissue, which constitutes the majority of fat in the body, not only regulates energy homeostasis but also plays a critical role in immune and metabolic processes. Cytokines such as interleukin-6 and tumor necrosis factor-alpha (TNF-α), along with adipokines like leptin and ghrelin secreted from adipose tissue, have been shown to influence bone metabolism.[3]

Low circulating leptin levels or leptin resistance, commonly observed in obesity, has been associated with reduced BMD. Leptin replacement has been reported to significantly improve spinal BMD, and the presence of leptin receptors on osteoblasts and chondrocytes indicates direct effects on bone growth and metabolism.[5] Similarly, ghrelin, another adipokine secreted from white adipose tissue, has been implicated in growth hormone secretion, appetite stimulation, gastrointestinal motility, glucose tolerance, and energy homeostasis.[6] Beyond its metabolic effects, ghrelin has also been proposed to play a role in the link between bone mass and adipose tissue.[7]

Several studies have reported elevated ghrelin levels in patients with IBD compared with healthy controls, although findings remain inconsistent.[8,9] Furthermore, increased ghrelin concentrations have been positively correlated with reduced BMD in IBD patients.[7] In line with these findings, we aimed to investigate serum leptin and ghrelin levels in UC patients and their relationships with BMD. To further explore the impact of inflammation and catabolism, we included measurements of serum TNF-α and insulin-like growth factor-1 (IGF-1).

MATERIALS AND METHODS

Study Population

This study included 38 patients who were admitted to the Gastroenterology Clinic of Atatürk University Faculty of Medicine in 2009 and 2010 with complaints of bloody diarrhea, urgency, and abdominal pain, who were diagnosed with UC, and 38 healthy volunteers who served as the control group. The healthy controls were selected to match the UC patients as closely as possible in terms of age and sex. All participants were fully informed about the study, and written informed consent was obtained prior to enrollment.

Clinical Evaluation and Diagnosis

All patients were evaluated through a detailed medical history, physical examination, and laboratory assessments, including blood, urine, and stool analyses. Other gastrointestinal and systemic conditions with similar clinical manifestations were excluded during the differential diagnosis process. The diagnosis of UC was confirmed based on characteristic endoscopic findings and histopathological evaluation of colonic biopsy specimens.

Inclusion and Exclusion Criteria

Patients with renal failure, chronic liver disease, chronic heart disease, systemic infectious diseases, IBDs other than UC, systemic inflammatory or autoimmune disorders, hypertension, diabetes mellitus, or malignancy were excluded from the study.

Assessment of Disease Activity

The disease activity of UC patients was evaluated according to the Truelove-Witts criteria (Table 1).[10] Based on these criteria, patients were categorized as being in either the active phase or remission phase of the disease. Treatment regimens were adjusted for newly diagnosed or relapsed patients during the active phase. After achieving remission, patients were recalled for follow-up visits at intervals ranging from 3 months to 1 year.

Sample Collection and Biochemical Analysis

Before initiation of treatment, a 10 mL venous blood sample was collected from each patient in the morning after an overnight fast during the active phase, and a second 10 mL venous blood sample was collected after remission was achieved. Similarly, fasting venous blood samples were obtained from the control group. Serum leptin, ghrelin, and TNF-α levels were measured by enzyme-linked immunosorbent assay, and IGF-1 was measured by chemiluminescence.

BMD Measurement

BMD was evaluated during both the active and remission phases using dual-energy X-ray absorptiometry (DEXA). Measurements were obtained from the lumbar vertebrae (L1-L4) and femoral neck; BMD (g/cm^2) was calculated, and T and Z scores were derived. Osteopenia was defined as a T-score between -1.0 and -2.5, and osteoporosis as a T-score ≤ -2.5, according to World Health Organization criteria.[11]

Statistical Analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) for Windows, version 18.0 (IBM Corp., Armonk, NY, USA). Data were expressed as mean ± standard deviation.

MAIN POINTS

- In active ulcerative colitis, serum leptin and growth factor-1 (IGF-1) levels were significantly lower, whereas ghrelin and tumor necrosis factor-alpha (TNF-α) levels were elevated.
- Bone mineral density was reduced in Ulcerative colitis (UC) patients compared with controls, and this reduction persisted even during remission.
- A positive correlation was observed between IGF-1 levels and femoral neck T-scores in active UC patients.
- Corticosteroid exposure was associated with higher leptin levels, highlighting treatment-related metabolic effects.
- These findings support the interplay between inflammatory and metabolic pathways in UC pathophysiology.

Table 1. Truelove and Witts Criteria for Assessing Disease Activity in Ulcerative Colitis

Parameter	Mild Disease	Moderate Disease	Severe Disease
Stool frequency	≤ 4 stools/day	4-6 stools/day	≥ 6 bloody stools/day
Blood in stool	Present (occasional)	Frequent	Frequent/continuous
Temperature	Normal	< 37.8 °C	> 37.8 °C
Pulse	Normal	< 90/min	> 90/min
Hemoglobin	Normal	≥ 10.5 g/dL	< 10.5 g/dL
Erythrocyte Sedimentation Rate (ESR)	Normal	20-30 mm/h	> 30 mm/h
General condition	Well	Mild systemic disturbance	Severe systemic disturbance

· The Shapiro-Wilk test was used to assess the normality of data distribution.

· Comparisons between two independent groups were made using the independent samples t-test or the Mann-Whitney U test, as appropriate.

· Categorical variables were compared using the chi-square test.

· Correlations between continuous variables were examined using Pearson's or Spearman's correlation coefficients, depending on their distribution. A *P* value of <0.05 was considered statistically significant.

Ethical Approval

The study protocol was approved by the Ethics Committee of Atatürk University Faculty of Medicine (Department of Internal Medicine, session no: 01, January 13, 2009), the Atatürk University Faculty of Medicine Ethics Committee (session no: 4, May 15, 2009; decision no: 122), and the Internal Medicine Division Council (session no: 4, June 17, 2009; decision no: 48).

RESULTS

Among the 38 patients in the active phase, 10 (27%) had normal BMD, 9 (23%) had osteoporosis, and 19 (50%) had osteopenia. The mean T- and Z-scores of BMD, measured during both the active and remission phases, were significantly lower compared with those of the control group ($P < 0.05$, Tables 2 and 3).

No statistically significant differences were observed in the mean T and Z scores of BMD at the lumbar spine (L1-L4), femoral neck, and total hip between patients in the active and remission phases ($P > 0.05$, Table 4).

Serum leptin and IGF-1 levels were significantly lower in patients with active UC than in the control group ($P < 0.05$). In contrast, serum levels of ghrelin and TNF-α were significantly higher in the active phase than in controls ($P < 0.05$, Table 5).

In the remission phase, serum leptin, IGF-1, and TNF-α levels did not differ significantly from those of the control group ($P > 0.05$, Table 5). However, ghrelin concentrations remained significantly elevated compared with controls ($P < 0.05$; Table 6). This persistent increase in ghrelin, even during clinical remission, may reflect ongoing subclinical inflammation or a compensatory metabolic response to chronic disease burden.

Table 2. Comparison of Mean T and Z Scores of BMD Between Active UC Patients and Controls

Parameter	Active (Mean ± SD)	Control (Mean ± SD)	*P*
L1-L4 T	-1.49 ± 1.26	-0.73 ± 0.94	***P < 0.05***
L1-L4 Z	-1.07 ± 1.11	0.07 ± 1.00	***P < 0.05***
F. Neck T	-0.88 ± 1.03	-0.23 ± 0.72	***P < 0.05***
F. Neck Z	0.02 ± 1.12	0.96 ± 1.04	***P < 0.05***
Total Hip T	-0.78 ± 1.02	-0.04 ± 0.62	***P < 0.05***
Total Hip Z	-0.30 ± 0.99	0.76 ± 0.77	***P < 0.05***

F.: Femur.

Table 3. Comparison of Mean T and Z Scores of BMD Between UC Patients in Remission and Controls

Parameter	Remission (Mean ± SD)	Control (Mean ± SD)	*P*
L1-L4 T	-1.55 ± 1.14	-0.73 ± 0.94	***P < 0.05***
L1-L4 Z	-1.13 ± 1.01	0.07 ± 1.00	***P < 0.05***
F. Neck T+	-0.73 ± 1.15	-0.23 ± 0.72	***P < 0.05***
F. Neck Z	0.11 ± 1.01	0.96 ± 1.04	***P < 0.05***
Total Hip T	-0.69 ± 1.02	-0.04 ± 0.62	***P < 0.05***
Total Hip Z	-0.25 ± 0.92	0.76 ± 0.77	***P < 0.05***

F.: Femur.

Table 4. Comparison of Mean T and Z Scores of BMD Between Active and Remission UC Patients

Parameter	Active (Mean ± SD)	Remission (Mean ± SD)	*P*
L1-L4 T	-1.49 ± 1.26	-1.55 ± 1.14	*P* > 0.05
L1-L4 Z	-1.07 ± 1.11	-1.13 ± 1.01	*P* > 0.05
F. Neck T	-0.88 ± 1.03	-0.73 ± 1.15	*P* > 0.05
F. Neck Z	0.02 ± 1.12	0.11 ± 1.01	*P* > 0.05
Total Hip T	-0.78 ± 1.02	-0.69 ± 1.02	*P* > 0.05
Total Hip Z	-0.30 ± 0.99	-0.25 ± 0.92	*P* > 0.05

F.: Femur; BMD, bone mineral density; UC, ulcerative colitis.

Table 5. Comparison of Serum Leptin, Ghrelin, IGF-1, and TNF-α Between Active UC Patients and Controls

Parameter	Active (Mean ± SD)	Control (Mean ± SD)	*P*
Leptin	5.10 ± 6.67 ng/dL	14.30 ± 1.80 ng/dL	***P < 0.05***
Ghrelin	91.23 ± 62.00 pg/mL	13.40 ± 1.78 pg/mL	***P < 0.05***
IGF-1	103.66 ± 46.38 ng/mL	189.0 ± 12.0 ng/mL	***P < 0.05***
TNF-α	10.93 ± 12.36 pg/mL	2.41 ± 0.18 pg/mL	***P < 0.05***

IGF-1, insulin-like growth factor-1; TNF-α, tumor necrosis factor-alpha.

Table 6. Comparison of Serum Leptin, Ghrelin, IGF-1, and TNF-α Between UC Patients in Remission and Controls

Parameter	Remission (Mean ± SD)	Control (Mean ± SD)	*P*
Leptin	15.67 ± 16.62 ng/dl	14.30 ± 1.80 ng/dl	***P > 0.05***
Ghrelin	65.24 ± 46.89 pg/ml	13.40 ± 1.78 pg/ml	***P < 0.05***
IGF-1	170.08 ± 68.43 ng/ml	189.0 ± 12.0 ng/ml	***P > 0.05***
TNF-α	4.19 ± 7.35 pg/ml	2.41 ± 0.18 pg/ml	***P > 0.05***

IGF-1, insulin-like growth factor-1; TNF-α, tumor necrosis factor-alpha; UC, ulcerative colitis.

Table 7. Comparison of Serum Leptin, Ghrelin, IGF-1, and TNF-α Between Active and Remission UC Patients

Parameter	Active (Mean ± SD)	Remission (Mean ± SD)	*P*
Leptin	5.10 ± 6.67 ng/dL	15.67 ± 16.62 ng/dL	***P < 0.05***
Ghrelin	91.23 ± 62.00 pg/mL	65.24 ± 46.89 pg/mL	***P > 0.05***
IGF-1	103.66 ± 46.38 ng/mL	170.08 ± 68.43 ng/mL	***P < 0.05***
TNF-α	10.93 ± 12.36 pg/mL	4.19 ± 7.35 pg/mL	***P < 0.05***

IGF-1, insulin-like growth factor-1; TNF-α, tumor necrosis factor-alpha; SD, standard deviation; UC, ulcerative colitis.

Serum leptin and IGF-1 levels were significantly lower in patients during the active phase compared with those in remission ($P < 0.05$). Although serum ghrelin concentrations were higher in active UC patients than in remission, this difference did not reach statistical significance ($P>0.05$). By contrast, serum TNF-α levels were significantly elevated in the active phase compared with levels during remission ($P < 0.05$, Table 7).

Serum leptin levels were significantly higher in UC patients who received for induction of remission compared with those who did not ($P < 0.05$). No statistically significant differences were observed between steroid-treated and untreated patients in serum concentrations of ghrelin, IGF-1, or TNF-α ($P > 0.05$, Table 8).

No correlations (positive or negative) were observed between serum leptin or ghrelin levels and either serum TNF-α or BMD in patients in both the active and remission phases. However, in patients with active UC, a statistically significant positive correlation was detected between femoral neck T-scores and serum IGF-1 levels (Tables 9 and 10).

DISCUSSION

The most important findings of this study are that, in patients with UC, serum leptin and IGF-1 levels were reduced, ghrelin levels were increased in patients with UC, and BMD was positively associated with IGF-1 but not with leptin or ghrelin.

While numerous factors play a role in this inflammatory process, recent evidence has suggested that adipokines secreted from mesenteric adipose tissue—now increasingly recognized as a novel immune cell compartment—may also contribute to the pathogenesis of UC. These adipokines have been reported to exert both pro-inflammatory and anti-inflammatory effects. Studies have demonstrated conflicting findings regarding serum leptin levels and the presence of IBD, with some reporting negative associations and others reporting statistically significant positive associations. More recent research has highlighted the potential influence of ethnic and racial variation on circulating leptin levels; however, the underlying mechanisms remain to be fully elucidated. Leptin concentrations are generally lower among non-White patients, suggesting that ethnic variation may indeed play an important role in the correlation between leptinemia and IBD.[12]

Under normal conditions, leptin secreted by adipose tissue is thought to enhance anti-inflammatory macrophage populations and thereby exert an inflammation-reducing effect.[13]

Karmiris et al.[8] reported that serum leptin levels measured during the active phase of UC were significantly lower compared with healthy controls, suggesting that reduced circulating leptin may be associated with intestinal inflammation. Similarly, Franchimont et al. demonstrated that in patients with IBD, serum leptin concentrations increased following treatment with infliximab, an anti-TNF-α agent, accompanied by a reduction in intestinal inflammation.[14]

Table 8. Comparison of Serum Leptin, Ghrelin, IGF-1, and TNF-α According to Steroid use in UC Patients

Parameter	Steroid (+) (Mean ± SD)	Steroid (-) (Mean ± SD)	*P*
Leptin	30.33 ± 18.67 ng/dL	10.05 ± 11.99 ng/dL	***P < 0.05***
Ghrelin	85.53 ± 70.00 pg/mL	57.98 ± 34.24 pg/mL	*P* > 0.05
IGF-1	159.90 ± 55.10 ng/mL	173.71 ± 73.16 ng/mL	*P* > 0.05
TNF-α	2.16 ± 2.25 pg/mL	4.91 ± 8.23 pg/mL	*P* > 0.05
Femur Neck T	-0.75 ± 1.03	-0.83 ± 1.15	*P* > 0.05

IGF-1, insulin-like growth factor-1; TNF-α, tumor necrosis factor-alpha.

Table 9. Correlation Analysis of Serum Leptin, Ghrelin, and IGF-1 with TNF-α and BMD T-Scores in Active UC Patients

Parameter	TNF-α	L1-L4 T	Femur Neck T	Total Hip T
Leptin	0.241 (P > 0.05)	0.164 (P > 0.05)	0.185 (P > 0.05)	0.271 (P > 0.05)
Ghrelin	-0.006 (P > 0.05)	0.017 (P > 0.05)	-0.015 (P > 0.05)	-0.029 (P > 0.05)
IGF-1	-0.167 (P > 0.05)	0.166 (P > 0.05)	0.373 (P < 0.05)	0.316 (P > 0.05)

IGF-1, insulin-like growth factor-1.

Table 10. Correlation Analysis of Serum Leptin, Ghrelin, and IGF-1 with TNF-α and BMD T-scores in Remission UC Patients

Parameter	TNF-α	L1-L4 T	Femur Neck T	Total Hip T
Leptin	0.096 (*P* > 0.05)	0.008 (*P* > 0.05)	-0.090 (*P* > 0.05)	-0.024 (*P* > 0.05)
Ghrelin	-0.188 (*P* > 0.05)	-0.118 (*P* > 0.05)	-0.180 (*P* > 0.05)	-0.195 (*P* > 0.05)
IGF-1	-0.100 (*P* > 0.05)	0.192 (*P* > 0.05)	0.187 (*P* > 0.05)	0.064 (*P* > 0.05)

BMD, bone mineral density; DEXA, dual-energy X-ray absorptiometry; TNF-α, tumor necrosis factor-alpha; IGF-1, insulin-like growth factor-1.

Reduced leptin concentrations appear to contribute to impaired anti-inflammatory regulation in UC. During the active phase, serum leptin levels are significantly lower than those observed in both the remission and control groups (Tables 5 and 7). Notably, leptin concentrations remain decreased even during remission compared with healthy controls, suggesting the persistence of subclinical inflammation (Table 6). Given leptin's anorexigenic properties, the marked reduction in its levels during active disease may represent a compensatory mechanism aimed at mitigating malnutrition, which either precedes or arises as a consequence of intestinal inflammation. In light of leptin's established anti-inflammatory functions, persistently reduced concentrations—both during active disease and relative to controls—support the hypothesis that insufficient leptin-mediated immunoregulatory activity may contribute to the perpetuation of intestinal inflammation in UC.

In UC patients receiving steroids, serum leptin levels measured during remission were significantly higher than in those not receiving steroids. This finding suggests that steroid therapy enhances anti-inflammatory activity, leading to higher leptin concentrations in these patients than in non-users. In other words, serum leptin levels increased in parallel with a reduction in inflammation (Table 8).

Leptin is also believed to have important effects on bone metabolism, promoting bone mineralization and enhancing osteoblastic activity. Consistent with this, our study demonstrated reduced leptin levels in patients with UC. However, correlation analysis did not reveal any statistically significant positive or negative association between leptin concentrations and BMD measurements (Tables 9-10).[15]

In a study by Karmiris et al.[8] that included 100 patients (46 with UC and 54 with Crohn's disease) and 60 healthy controls, serum ghrelin levels were higher in IBD patients than in healthy controls. Moreover, when IBD patients were compared with controls, elevated ghrelin levels were correlated with reduced leptin concentrations. The authors concluded that ghrelin levels positively correlate with the severity of inflammation in IBD and that impaired secretion of adipose tissue-derived proteins may play a role in IBD pathogenesis. Consistent with these findings, our study also demonstrated higher serum ghrelin levels and lower leptin levels in patients with active UC compared with healthy controls.[8]

Ates et al.[16] reported that serum ghrelin levels measured during the active phase were significantly higher than those measured during remission. The same study demonstrated negative correlations between serum ghrelin levels and both serum IGF-1 concentrations and BMI. Consequently, the authors concluded that elevated ghrelin levels correlate positively with disease severity and may serve as a useful marker in assessing both disease activity and nutritional status in UC. In our study, however, no statistically significant difference was observed between ghrelin levels in the active and remission phases. Nevertheless, the borderline trend toward higher ghrelin levels during active disease suggests results consistent with those of Ates et al.[16]

In a study conducted by Konturek et al.[17], colonic mucosal biopsy specimens from 15 UC patients were compared with those from 15 healthy controls, revealing increased mucosal mRNA expression of ghrelin in the UC group. The authors suggested that this elevated colonic mucosal expression of ghrelin may represent a protective response triggered by the heightened mucosal inflammation.[17]

In our study, serum ghrelin levels in active UC patients were marginally higher than in patients in remission, although the difference was not statistically significant. The absence of a significant difference may be explained by the multitude of factors influencing ghrelin secretion, and by its active involvement in numerous metabolic and inflammatory processes. However, ghrelin levels in active UC patients were significantly higher than those in healthy controls. This finding suggests that increased ghrelin secretion occurs during inflammatory processes and that this increase—ghrelin being known for its pro-inflammatory effects— may itself contribute to intestinal inflammation. During remission, serum ghrelin levels in UC patients remained significantly higher than in healthy controls, indicating that, despite clinical remission, the effects of chronic inflammation persist in UC patients for an extended period.

Although Peracchi et al.[18] reported a positive correlation between ghrelin and TNF-α levels, no such association was observed in our study. In both the active and remission phases, ghrelin levels showed no correlation with TNF-α concentrations or BMD. Furthermore, there was no significant difference in ghrelin levels between patients who received steroids for remission induction and those who did not. Taken together, our findings suggest that the dysregulated secretion of ghrelin—known to possess pro-inflammatory properties—may contribute to intestinal inflammation. Alternatively, the increased ghrelin secretion may represent a compensatory protective response of the organism to inflammation. Elevated ghrelin levels could also be interpreted as a response to malnutrition developing during intestinal inflammation, serving to preserve energy stores and counteract cachexia by promoting fat accumulation and appetite stimulation.[18]

In IBD, dysfunction of the growth hormone/IGF-1 axis has been demonstrated. IGF-1, synthesized in the liver, exerts anabolic effects in multiple tissues and plays a crucial role in the regulation of growth and metabolism. During inflammatory processes, hepatic synthesis of IGF-1 is reduced, resulting in decreased serum IGF-1 levels. Growth retardation has frequently been reported in children with UC and Crohn's disease. IGF-1 also plays an important role in bone metabolism and calcium balance, and has been shown to correlate positively with bone mineralization.[19]

In a cohort study including 1,004 individuals, Pöykkö et al.[20] reported a negative correlation between serum ghrelin levels and IGF-1 concentrations. They suggested that this relationship may play an important role in regulating energy metabolism, although further studies are needed to clarify the underlying mechanisms. In our study, while serum ghrelin levels were higher in patients compared with the control group, serum IGF-1 levels were lower than those of healthy controls.[20]

In an experimental study by Haris et al.[21] using colitis-induced mice, BMD and serum TNF-α and IGF-1 levels were evaluated during both the active and remission phases of IBD. They observed that elevated TNF-α and reduced IGF-1 levels during active disease paralleled the reduction in BMD. With disease remission, TNF-α levels decreased, IGF-1 levels increased, and BMD improved. Similarly, our study found a positive correlation between IGF-1 concentrations and BMD in active UC patients. However, no significant correlation was detected between IGF-1 and TNF-α levels during activity. Consistent with the findings of Haris et al.[21], we also observed that IGF-1 levels were lower during the active phase compared with remission. Furthermore, IGF-1 values increased once patients achieved remission. Given its well-known anabolic effects in multiple tissues, as well as its role in enhancing bone mineralization and osteoblastic activity, the observed reduction in IGF-1 levels and the associated correlation with decreased BMD in our study are consistent with previous reports. The observation that IGF-1 concentrations in patients with active UC were lower than in patients in remission and in healthy controls suggests that the IGF-1 axis is disrupted in UC. This impairment may result from altered secretion of adipokines (e.g., leptin and ghrelin) by adipose tissue, as well as from other inflammatory processes upregulated in UC. Ultimately, this disturbance of the IGF-1 axis and reduced serum IGF-1 levels may help explain the increased catabolic state observed in these patients.[21]

TNF-α plays a key role in the pathogenesis of UC, as it does in many other inflammatory diseases, and is an important therapeutic target in UC. Inhibition of TNF-α with monoclonal antibodies such as infliximab and adalimumab has emerged as an effective therapeutic strategy for the management of the most treatment-resistant cases of chronic UC.[22]

Komatsu et al.[23] reported that serum TNF-α levels in UC patients were up to 380 times higher than those in healthy individuals. In their study, TNF-α concentrations were significantly higher during the active phase compared with remission, highlighting the central role of TNF-α in the pathophysiology of IBD and underscoring its value as an important biomarker for assessing disease activity.[23]

In our study, serum TNF-α levels were significantly higher in patients during the active phase compared with both the remission and healthy-control groups, confirming the well-established pro-inflammatory role of TNF-α. No statistically significant difference was observed between patients in remission and controls. The decline in TNF-α levels with remission supports the rationale for the successful outcomes achieved with TNF-α inhibitors, which are increasingly being adopted as a cornerstone in the treatment of UC. The changes observed in our study, together with the recent widespread use of TNF-α inhibitors, further emphasize the role of TNF-α as one of the principal cytokines driving intestinal inflammation in UC.

IBD is recognized as a significant risk factor for reduced BMD, leading to osteopenia and osteoporosis. Previous reports have demonstrated a prevalence of osteopenia and osteoporosis among IBD patients ranging from 7% to 56%. In a cohort study by Koutroubakis et al.[7], BMD was evaluated in 118 patients with UC Crohn's disease, revealing that 40 patients (33.9%) had normal BMD, 55 patients (46.6%) were osteopenic, and 23 patients (19.5%) were osteoporotic. Importantly, this study reported that higher circulating ghrelin levels and longer disease duration were significantly associated with lower BMD and increased osteoporosis frequency, whereas no correlation was observed between leptin levels and BMD.[7]

Consistent with these findings, our analysis of 38 patients demonstrated that 10 (27%) had normal BMD, 19 (50%) were osteopenic, and 9 (23%) were osteoporotic. In contrast to the ghrelin association reported in the previous study, we did not identify any significant correlation between BMD and levels of either ghrelin or leptin.

In a cohort study conducted by Ottaviani et al.[24] involving 336 patients with IBD, osteopenia was identified in 115 patients (34%), while osteoporosis was detected in 40 patients (12%). The study found that older age and female sex were significantly associated with lower BMD. Following clinical evaluation, Vitamin D replacement therapy was initiated for 153 patients (45%), and 24 (7%) began treatment specifically for osteoporosis. The findings emphasize the critical importance of a systematic and multidisciplinary assessment regarding bone fragility in this patient population.[24]

Intestinal inflammation accelerates bone loss by increasing osteoclastic activity and decreasing osteoblastic activity through the release of pro-inflammatory cytokines, such as interleukin-6, interleukin-1, and TNF-α.[25] Studies have shown that even in newly diagnosed and untreated patients with IBD, initial BMD values are already low.[26] Furthermore, the long-term use of glucocorticoids, which are frequently employed in IBD treatment, leads to an additional decline in BMD by inhibiting osteoblasts. In addition, the intake and absorption of essential nutrients for bone health, such as Vitamin D and calcium, are lower in IBD patients compared to healthy individuals, further impacting BMD negatively.[25]

In our study, no statistically significant differences were observed between BMD T- and Z-scores of patients during active and remission phases. This finding may be attributed to factors such as the relatively short interval between active and remission periods (ranging from 3 months to 1 year) and the limited sample size. However, BMD T- and Z-scores in patients in the active phase were significantly lower than those in the healthy control group. This suggests that intestinal inflammation in UC and the associated increase in cytokine release may initiate the osteoporotic process in affected patients.

Furthermore, BMD T- and Z-scores measured during the remission phase were significantly lower than those in healthy controls. These findings indicate that the osteoporotic process initiated during the active phase does not regress immediately upon achieving remission. T his highlights the need for a more proactive and potentially aggressive approach to the prevention and treatment of osteoporosis in patients with UC.

Lee SJ et al.[27] demonstrated that approximately one-third of patients with IBD diagnosed before the age of 50 had low BMD at the time of diagnosis. In that study, the similar prevalence of low BMD in the UC and Crohn's disease subgroups suggested that bone loss may begin early in the disease course, independent of disease duration and treatment. These findings indicate that assessment of BMD at diagnosis in young patients with IBD may be clinically meaningful for early risk stratification and the implementation of preventive strategies.[27]

In our study, BMD T- and Z-scores measured during the remission phase were found to be significantly lower in patients who had received corticosteroids for remission induction compared with those who had not. This finding indicates that the pre-existing risk of osteoporosis among patients with UC is further exacerbated by steroid therapy. Therefore, in the management of UC, all potential risk factors for the development of osteopenia or osteoporosis—ranging from lifestyle-related factors to the therapeutic regimens administered—must be carefully considered.

The pathophysiology and etiology of UC remain incompletely understood. It has become increasingly evident that dysregulated secretion of adipose tissue–derived cytokines may play a critical role in the pathogenesis of UC and in the development of its clinical manifestations and complications. Altered levels of cytokines such as leptin, ghrelin, and TNF-α, together with disturbances in the IGF-1 axis, appear to contribute to the osteopenic and osteoporotic processes observed in UC patients. Given the increased prevalence of osteopenia and osteoporosis in this population, particularly among those receiving corticosteroid therapy, the implementation of appropriate preventive strategies and, when necessary, prophylactic treatments should be considered as part of comprehensive patient management.

Study Limitations

This study has certain limitations. The sample size was relatively small and was derived from a single center, which may limit the generalizability of the findings. In addition, the cross-sectional design precludes causal inference between hormonal changes and BMD. Future multicenter longitudinal studies with larger cohorts are needed to validate and expand upon these results.

CONCLUSION

In conclusion, the pathophysiology and etiology of UC have not yet been fully elucidated. It has become increasingly evident that dysregulated secretion of adipose tissue–derived cytokines may play a critical role in the pathogenesis of UC as well as in the development of its clinical manifestations and complications. Altered levels of cytokines such as leptin, ghrelin, and TNF-α, together with disturbances in the IGF-1 axis, appear to contribute to the osteopenic and osteoporotic processes observed in UC patients. Given the increased prevalence of osteopenia and osteoporosis in this population, particularly among those receiving corticosteroid therapy, the implementation of appropriate preventive strategies and, when necessary, prophylactic treatments should be considered as part of comprehensive patient management.

Ethics

Ethics Committee Approval: The study protocol was approved by the Ethics Committee of Atatürk University Faculty of Medicine (decision no: 122, date: 15.05.2009).

Informed Consent: All participants were fully informed about the study, and written informed consent was obtained prior to enrollment.

Footnotes

Author Contributions

Concept Design – Ö.Y.; Data Collection or Processing – A.F.T.; Analysis or Interpretation – A.F.T.; Literature Review – A.F.T.; Writing, Reviewing and Editing – A.F.T.

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