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Section V: Bone Patho-Physiology

Lower Fibroblast Growth Factor 23 Levels in Young Adults With Crohn Disease as a Possible Secondary Compensatory Effect on the Disturbance of Bone and Mineral Metabolism

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Abstract

Fibroblast growth factor 23 (FGF-23) is a bone-derived circulating phosphaturic factor that decreases serum concentration of phosphate and vitamin D, suggested to actively participate in a complex renal-gastrointestinal-skeletal axis. Serum FGF-23 concentrations, as well as various other laboratory parameters involved in bone homeostasis, were measured and analyzed with regard to various diseases and patients' characteristics in 44 patients with Crohn disease (CD) and 20 healthy controls (HCs) included in this cross-sectional study. Serum FGF-23 levels were significantly lower in patients with CD (900.42 ± 815.85 pg/mL) compared with HC (1410.94 ± 1000.53 pg/mL), $p = 0.037$. Further analyses suggested FGF-23 as a factor independent from various parameters including age ($r = -0.218$), body mass index ($r = -0.115$), 25-hydroxy vitamin D ($r = 0.126$), parathyroid hormone ($r = 0.084$), and bone mineral density (BMD) of hip and lumbar ($r = 0.205$ and $r = 0.149$, respectively). This observation remained even after multivariate analyses, exhibiting that BMD was not affected by FGF-23, although parameters such as age ($p = 0.026$), cumulative prednisolone dose ($p < 0.0001$), and smoking status ($p = 0.024$) were strong determinants of BMD regarding hip. Lower FGF-23 levels in patients with bowel inflammation are accompanied but not directly correlated with lower vitamin D levels, showing no impact on BMD determination of young adults with CD. The downregulation of serum FGF-23 levels in CD appears as a secondary compensatory effect on the bone and mineral metabolism induced by chronic intestinal inflammation.

Key Words: Bone homeostasis; bone mineral density (BMD); Crohn disease (CD); fibroblast growth factor 23 (FGF-23); 25-hydroxy vitamin D (25OHD).

Introduction

Patients with inflammatory bowel disease (IBD) are at higher risk of developing osteopenia and osteoporosis than the general population *(1)*. Thus, a greater risk of fractures estimated up to 40% in IBD patients has been demonstrated *(2)*. The etiology of bone loss in IBD is multifactorial, including

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various risk factors such as increasing age, use of corticosteroids, malnutrition, vitamin D, calcium and vitamin K malabsorption and deficiency, immobilization, smoking, and the underlying inflammatory state *(3,4)*. The various risk factors acting through disequilibrium of bone and mineral metabolism in patients with IBD affect calcium/phosphate metabolism and its main regulatory pathways involving parathyroid hormone (PTH) and vitamin D *(1)*. Regarding calcium and vitamin D, numerous studies suggest that a deficit is present in IBD patients and recommend calcium and vitamin D supplementation for patients at risk *(1,4,5)*. However, phosphate regulation in bone homeostasis has not been fully elucidated. Phosphate regulation comprises interactions of a complex kidney-intestine-bone-parathyroid gland hormonal axis, which is still poorly understood *(6,7)*. A recently identified phosphatonin, known as fibroblast growth factor 23 (FGF-23), disclosed new pathways in the pathophysiology of mineral metabolism *(8)*.

FGF-23 is a novel phosphaturic hormone associated with diseases such as autosomal dominant hypophosphatemia, X-linked hypophosphatemic rickets, and acquired hypophosphatemic disorder tumor-induced osteomalacia *(9)*. FGF-23 is primarily produced by osteoblasts/osteocytes in bone, with low levels in other tissues, targeting the kidney to regulate phosphate homeostasis and vitamin D metabolism *(10)*. When phosphate is in excess, FGF-23 is secreted from bone and acts on the kidney to induce phosphaturia and suppress vitamin D synthesis, thereby inducing a negative phosphate balance to maintain phosphate homeostasis *(11)*. Its biological functions are exerted via binding to its principal receptor FGFR1, requiring Klotho protein—mostly expressed in the distal tubular epithelial cells—as a cofactor *(12)*.

Based on the fact that IBD and particularly Crohn disease (CD) may involve defects of the hormonal axis implicated in mineral metabolism such as intestinal malabsorption, osteoporosis, and even renal function deterioration *(13,14)*, we hypothesized that FGF-23 concentrations may be altered in CD to maintain bone and mineral homeostasis. The aim of this study was to assess the possible role of FGF-23 with regard to bowel inflammation and various parameters implicated in bone homeostasis of patients with CD.

Patients and Methods

Patients and Controls

Forty-four patients with CD and 20 HC aged less than 50 years were included in this single center cross-sectional study. All patients had a definitive diagnosis of CD, confirmed by clinical, endoscopic, radiologic, and histologic workup, and based on standard criteria *(15)*, and the Montreal classification was used for disease phenotyping *(16)*. Disease activity in patients with CD was determined by the Crohn Disease Activity Index *(17)*. A score greater than 150 was compatible with active CD, whereas further assessment of clinical activity divided patients with CD in the following subgroups: inactive (remission), $\leq$150; mild activity, 151−220; moderate activity, 221−450; and high activity, $>$450 points. Evaluation of disease activity was performed at the time of serum collection. Patients with cancer or other malignancies, hepatic disease, renal failure, cardiovascular disease, parathyroid or thyroid disease, and postmenopausal females were excluded from the study. Cumulative dose of corticosteroids (prednisolone and budesonide) was cautiously assessed and included in all analyses.

Ethical Considerations

An informed consent was obtained from all patients, and the study was approved by the local Ethics Review Board of the University Hospital of Larissa.

Bone Mineral Density Measurements

All subjects underwent measurement of lumbar spine (anterior-posterior projection at L1−L4) and hip (total proximal femur) bone mineral density (BMD) using dual-energy X-ray absorptiometry (DXA) (Hologic QDR Discovery (UMCG), Waltman, MA). BMD value is expressed in grams per square centimeter. In accordance with BMD reporting recommendations from the International Society of Clinical Densitometry, abnormal BMD was defined as a Z-score <-2.0 because participants were aged less than 50 years *(18)*. Z-scores were calculated using the NHANES reference database. Patients were categorized by the lowest Z-score of the lumbar spine or hip. All results were reviewed by a single study investigator (VMK) with extensive experience in clinical and research DXA. Daily quality control of the DXA device gave a long-term precision error of $<$0.5%, and the in vivo coefficient of variation (CV) was 1.0−1.7% for the measurement sites. Weight and height were measured at the time of BMD assessment using scales that were calibrated annually.

Laboratory Tests

Peripheral blood samples were collected from all patients and healthy controls (HCs) at the time of inclusion in the study. Samples were centrifuged for 15 min at 3000 $\times$ *g*, followed by serum storage at −80°C until assayed. To adequately assess renal function, estimated glomerular filtration rate (eGFR) was calculated using the Cockroft-Gault formula, whereas serum creatinine, calcium, phosphate, and magnesium were routinely quantified using photometry with AU2700 Analyzer (Olympus Diagnostics, Hamburg, Germany). Vitamin D and PTH levels were determined by an automated electrochemiluminescent immunoassay using Roche Modular E170 Analyzer (Roche Diagnostics, Mannheim, Germany). Serum C-reactive protein (CRP) measurement was performed by immunonephelometry with the Behring Nephelometer Analyzer II (BNII), using the N High Sensitivity kit (Dade Behring Gmbh, Marburg, Germany).

Serum FGF-23 levels were measured by commercially available sandwich enzyme-linked immunosorbent assay (Uscn Life Science, Wuhan, China) according to the manufacturer's instructions. FGF-23 concentrations were determined in duplicate. According to manufacturers, the lower