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Original Article

Fibroblast Growth Factor-23, Sclerostin, and Bone Microarchitecture in Patients With Osteoporotic Fractures of the Proximal Femur: A Cross-sectional Study

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Abstract

This cross-sectional observational cohort study was designed to simultaneously investigate bone microarchitecture and serum markers of bone metabolism in elderly osteoporotic patients experiencing a trochanteric or femoral neck fracture. Special emphasis was put on renal function, sclerostin and fibroblast growth factor-23 (FGF-23). Eighty-two patients (median age: 84 years; 49 trochanteric fractures) scheduled for emergency surgery due to an osteoporotic fracture participated. Bone specimens for ex vivo microcomputed X-ray tomography were sampled during surgery. Blood samples for laboratory workup were collected before surgery (t_0) and 1 day afterward (t_1). Fifty-eight patients consented to dual-energy X-ray absorptiometry scanning of the lumbar spine and/or contralateral femoral neck after recovery during the in-patient stay. Samples were grouped according to the site of fracture. Regression coefficients were controlled for age and/or estimated glomerular filtration rate (eGFR), if appropriate. Patients experiencing a femoral neck fracture presented with better preserved renal function (eGFR) and lower C-terminal fragment of fibroblast growth factor-23 (cFGF-23) concentrations compared to those with trochanteric fractures. By contrast, serum sclerostin was similar at both time points and did not differ between groups. Age-adjusted correlation analysis revealed negative associations between eGFR and cFGF-23 determined at t_1 ($R = -0.34$; $p < 0.05$) as well as between eGFR and sclerostin levels at t_0 ($R = -0.45$; $p < 0.05$) in patients with trochanteric and femoral neck fractures, respectively. Our study provides evidence that not only an age-related decline of renal function but also the type of skeletal injury may contribute to the circulating concentrations of cFGF-23.

Key Words: μCT; DXA; osteoporosis; proximal femur fracture.

Introduction

Bone is a highly dynamic organ serving not only mechanical but also a variety of biochemical and endocrine functions *(1−3)*.

Biochemical markers reflecting skeletal activity either at the level of regulatory circuits or at the level of osteoclasts, osteoblasts, and osteocytes are continuously recognized as important clinical tools. Osteocytes turned out to be the key regulatory cells, controlling calcium and phosphate metabolism as well

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This work is original and has not been presented in whole or part previously.

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as bone remodeling via secretion of fibroblast growth factor-23 (FGF-23) and sclerostin (4). FGF-23, klotho, parathyroid hormone (PTH) and 1,25-dihydroxyvitamin D_3 (calcitriol) together with their related feedback loops form the regulatory system for mineral metabolism (bone-parathyroid-kidney axis) (5–7). Sclerostin, an osteocyte-derived protein inhibits canonical Wnt signaling and is a negative regulator of bone formation (8–10).

Bone metabolism and mineral density on the one hand and the regulatory endocrine network on the other hand are directly linked. Aberrations at either the level of bone mineral density (BMD) or hormonal control can be quantified with reasonable efforts and within routine clinical care. By contrast, bone quality is less stringently defined and thus much harder to assess in vivo. Currently, the association between the serum concentrations of compounds related to bone metabolism and physical characteristics of bone quality, for example, trabecular number, trabecular density, or porosity is still poorly defined. Furthermore, bone microarchitecture at the major trochanter and femoral neck is different. We hypothesized that osteoporotic fractures of the femur affect the circulating concentrations of FGF-23 and sclerostin and that these effects may differ in patients with trochanteric and femoral neck fractures, respectively. We addressed this issue within the setting of a cross-sectional observational study in osteoporotic patients suffering from either type of fracture. Emphasis was put on (1) assessment of bone microarchitecture by means of an ex vivo microcomputed X-ray tomography; (2) determination of the systemic concentrations of the C-terminal fragment of fibroblast growth factor-23 (cFGF-23) and sclerostin; and (3) assessment of areal BMD at the contralateral hip and/or lumbar spine.

Material and Methods

Patients being at least 65 years old, with a low-energy-trauma fracture (i.e., osteoporotic fracture) of the proximal femur and undergoing surgery at our institution were eligible for this cross-sectional observational cohort study. Patients with a pathologic fracture due to a malignant disease with end-stage renal disease, as well as those receiving antiestrogenic or antiandrogenic therapy during the last 12 months were excluded. Eighty-two patients (21 male) of 104 patients fulfilled the inclusion or exclusion criteria and consented to participate between April 2010 and June 2011. Exclusion of patients was due to (1) age <65 years ($n = 11$); (2) malignant disease ($n = 4$); (3) end-stage renal disease requiring dialysis therapy ($n = 5$); (4) endocrinologic therapy as stated above ($n = 1$); and (5) unwillingness ($n = 1$). Patients were grouped according to the type of fracture, that is, trochanteric or femoral neck fracture. The study received ethics committee's approval from the institutional review board and was performed in accordance with the Declaration of Helsinki. Subjects and/or their legal guardian gave assent and written informed consent before participation to provide bone specimens and/or blood samples for subsequent investigations.

Procedures

All patients were scheduled for emergency surgery. In case of trochanteric femur fracture, we performed closed reduction and osteosynthesis with a proximal femoral intramedullary nail (Targon PFT; Aesculap, Tuttlingen, Germany) using the standardized operative approach according to the instructions of the manufacturer. Medial femoral neck fractures were treated with either double cup hemiprothesis (Mathys, Bettlach, Switzerland) or total hip arthroplasty (Aesculap). Bone specimens removed during surgery, that is, a cylinder from the mediotrochanteric region or a chip from the distal femoral neck (Fig. 1), were immediately transferred to 70% ethanol and stored at 4°C until further processing. During the in-patient stay, dual-energy X-ray absorptiometry (DXA; Lunar Prodigy; GE Healthcare, United Kingdom) with constant direct voltage (100 kV), and a K-edge filter was performed according to current guidelines to assess areal BMD (11). Target regions for DXA measurements were the lumbar spine (LS; L1–L4) and the contralateral femoral neck (FN) for patients without orthopedic implants at this particular location. Analysis of DXA measurements was performed according to international guidelines (12). The intrameasurement and intermeasurement coefficients of variation based on regular calibration tests were $<0.5\%$. Results are expressed as sex-specific standard deviations of peak bone mass (i.e., T-score$_{LS}$, T-score$_{FN}$) based on data provided together with the instrument. Dehydration and body composition were determined by multifrequency impedance analysis before surgery (BCM Body Composition Monitor; Fresenius Medical Care, Bad Homburg, Germany). Blood samples for laboratory investigations were drawn at the day of fracture before surgery and anesthesia (i.e., 6–8 h after the last meal) (t_0) and on the morning of the first postoperative day (t_1) before breakfast. Routine laboratory workup included alkaline phosphatase, intact PTH (iPTH), 25-hydroxyvitamin D_3 (25-OHD; vitamin D), sex hormones, insulin-like growth factor 1 (IGF-1), IGF-binding protein 3 (IGFBP-3), cystatin C, creatinine, calcium, and phosphate measurements (11). All measurements were done with established automated laboratory procedures, which in turn provided a precision of at least 10%. In particular, instruments from Beckman Coulter, Krefeld, Germany (UniCel DxC Clinical Systems for alkaline phosphatase, creatinine, calcium and phosphate; Immage for cystatin C) and Roche, Basel, Switzerland (Elecsys for iPTH, 25-OHD, sex hormones [total testosterone and 17β-estradiol, respectively], IGF-1, and IGFBP-3) were used. The estimated glomerular filtration rate (eGFR) was calculated according to the Modification of Diet in Renal Disease Study group formula (13). The plasma concentration of cFGF-23 and the serum concentration of sclerostin were determined in samples taken at both time points using manual enzyme-linked immunosorbent assay kits (cFGF-23: Immutopics, San Clemente, CA; sclerostin: Tecco Medical, Sissach, Switzerland) essentially as described (14). The interassay and intra-assay coefficients of variation for cFGF-23 and sclerostin were 5.1% and 5.0%, respectively,