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Plasma periostin associates significantly with non-vertebral but not vertebral fractures in postmenopausal women: Clinical evidence for the different effects of periostin depending on the skeletal site

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ABSTRACT

Background: Periostin is preferentially expressed by the periosteum, which mainly covers the long bones. Therefore, the role of periostin in osteoporotic fracture (OF) may differ depending on bone type. We performed a case–control study to investigate whether periostin can serve as a predictor of OF risk, particularly after dividing OFs into non-vertebral and vertebral fractures.
Methods: Among 532 consecutive postmenopausal women not taking any drug or without any disease that could affect bone metabolism, 133 cases with OF (*i.e.*, non-vertebral and/or vertebral fractures) and 133 age- and body mass index-matched controls were enrolled. Non-vertebral (*i.e.*, forearm, humerus, hip, and pelvis; n = 81) and morphological vertebral (n = 62) fractures were identified by an interviewer-assisted questionnaire and lateral thoracolumbar radiographs, respectively. Bone mineral density (BMD) and plasma periostin levels were also measured.
Results: Plasma periostin was markedly higher in subjects with non-vertebral fracture than their controls even after adjustment for BMD and potential confounders ($P = 0.006$). Each standard deviation increment of plasma periostin was associated with a multivariable-adjusted odds ratio of 1.59 for non-vertebral fracture. The odds for non-vertebral fracture were 2.48-fold higher in subjects in the highest periostin tertile compared with those in the lowest periostin tertile (95% confidence interval = 1.10–5.61). However, associations between plasma periostin and vertebral fracture were not observed, regardless of the adjustment model used. Consistently, plasma periostin levels were inversely associated with proximal femur BMD ($P = 0.007$ to 0.030) but not lumbar spine BMD. In subgroup analyses, plasma periostin had no correlation with the levels of classical bone turnover markers.
Conclusions: Plasma periostin may be a potential biomarker of the risk of OF, especially in non-spinal skeletal sites, such as the limbs, rather than spine.

1. Introduction

Osteoporotic fracture (OF) is a leading cause of considerable morbidity and disability in older people and, as such, imposes a substantial economic burden on national health care systems [1–3]. OF is also likely to become a much more serious public health concern in the future because the number of aged people in modern societies is increasing. Bone mineral density (BMD) measured by dual-energy X-ray absorptiometry (DXA), which is often used to measure bone mass, is employed frequently for the diagnosis of osteoporosis, because bone mass accounts for approximately 70% of bone strength [4]. However, the

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ability of BMD measurements to predict OF is limited. Although the risk of OF increases as BMD values fall, about two-thirds of individuals who suffer a fracture do not have osteoporosis as defined on the basis of BMD values [5,6]. Given this low sensitivity of BMD testing, the World Health Organization formed a working group that identified clinical risk factors (CRFs) that could enhance fracture risk prediction with or without the use of BMD measurements. The CRFs identified were then used to build fracture risk assessment tool models [7,8]. However, the overall ability of this fracture risk assessment tool to predict OF is still less than perfect [9,10]. Therefore, additional biomarkers that predict the risk of OF independently of, or combined with, BMD and CRFs are needed.

When periostin was first isolated from the MC3T3-E1 osteoblastic cell line, it was initially termed osteoblast-specific factor 2 [11]. Thereafter, it was renamed to indicate that it is predominantly expressed in the periosteum [12,13]. As suggested by its name, many lines of evidence indicate that periostin plays a distinct role in bone metabolism. This 90-kDa secreted extracellular matrix protein binds integrins αvβ3 and αvβ5 and is thereby involved in the adhesion and mobility of osteoblasts [12,14]. When periostin activity in MC3T3-E1 cells is blocked, their expression of osteoblast-specific differentiation markers (including Runx2/Cbfa1) is severely reduced [15]. Furthermore, periostin-knockout mice exhibit periodontitis and osteoporosis with low BMD, altered microarchitecture, and decreased bone strength [16]. Interestingly, subsequent studies by the latter researchers indicated that periostin is an essential mediator of the response of bone to mechanical forces and parathyroid hormone [16–18]. Considered along with a secreted feature of periostin which can be easily measured in the blood, these findings suggest that periostin may be one of potential biomarkers for predicting osteoporosis-related phenotypes. However, despite its apparent role in bone metabolism, a review of the published literature only identified one study that examined the association between blood periostin levels and OF without replication in any other cohort [19]. In particular, although the effect of periostin could be different depending on the bone type due to its preferential expression in periosteum mainly covering long bones [12,13], there have been no clinical studies separately considering non-vertebral and vertebral fractures and showing significant association with BMD at various skeletal sites. In the present study, to clarify these unresolved points and to raise the possibility of using periostin as a predictor for OF risk, we performed a case–control study in postmenopausal Korean women.

2. Materials and methods

2.1. Study subjects and protocol, including fracture assessment

All consecutive Korean postmenopausal women who attended the osteoporosis clinic of Asan Medical Center (Seoul, Korea) between January 2011 and June 2012 were included in this case–control study. All of these women visited the osteoporosis clinic because they were concerned about having osteoporosis or they had been referred because they had been diagnosed with osteoporosis during a routine examination. Menopause was defined as the absence of menstruation for at least 1 year and was confirmed by measuring serum follicle-stimulating hormone levels. Women who exhibited premature menopause (<40 years of age) and those who had taken drugs that could affect bone metabolism (*e.g.*, bisphosphonate, systemic glucocorticoid, or hormone-replacement therapy) for more than 6 months or within the previous 12 months were excluded. Subjects with diseases that could affect bone metabolism (*e.g.*, diabetes, neoplastic diseases, hyperparathyroidism, rheumatoid arthritis, asthma/chronic obstructive pulmonary disease, and major cardiovascular diseases) were also excluded, along with subjects who exhibited osteophyte formation that exceeded grade four of the Nathan classification [20] and/or severe facet joint osteoarthritis in the lumbar spine, as determined by conventional spine radiographs. Other exclusion criteria were the presence of fever (oral temperature ≥ 38.0 °C), abnormal findings on complete blood counts regarding leukocytes (<4.0 or >10.0 × 10^9/L) or platelets (<150 or >350 × 10^9/L), and abnormal liver, kidney, or thyroid function. All of these criteria were imposed so that subjects with a systemic illness would be excluded.

The prevalence of morphological vertebral fracture in all study subjects was determined by obtaining lateral thoracolumbar (T4–L4) radiographs, which were analyzed at Asan Medical Center according to the recommendations of the Working Group on Vertebral Fractures [21] by expert radiologists in a blind manner. A vertebral fracture was quantitatively defined as >20% reduction in any measured vertebral height (*i.e.*, anterior, middle, or posterior) [22]. Non-vertebral fractures, namely, those at the forearm, humerus, hip, and pelvis, were assessed by applying an interviewer-assisted questionnaire. Fractures that were considered to be non-osteoporotic (*i.e.*, fractures due to major trauma such as motor vehicle accidents or falls from higher than standing height, and all fractures of the fingers, face, skull, and toes) were excluded. The remaining fractures, all of which were at osteoporosis-related sites and had clearly been caused by low trauma after the age of 50 years or after menopause, were regarded as OFs in our present study.

The following patient information was obtained *via* a self-administered questionnaire: smoking habits (current smoker), alcohol intake (≥3 units/day), regular outdoor exercise (≥30 min/day), history of medication use, previous medical or surgical procedures, and reproductive status (including menstruation). An interviewer-assisted questionnaire was used to assess whether each subject had a parental history of OF. After adopting the above exclusion criteria, 532 women were deemed eligible for participation. Among these women, we identified 133 cases with some type of OF (*i.e.*, non-vertebral and/or vertebral fractures). To perform the case–control analysis, controls were randomly selected from the remaining 399 subjects and matched 1:1 to cases according to both age (within 2.5 years) and body mass index (BMI; within 1.0 kg/m^2). This study was approved by the Institutional Review Board of Asan Medical Center. All enrolled subjects provided written informed consent.

2.2. BMD measurement

Areal BMD (g/cm^2) was measured at the lumbar spine (L1–L4) and proximal femur (femur neck, total femur, trochanter, and shaft) by DXA using Lunar equipment (running software version 9.30.044; Prodigy, Madison, WI). The precision values of the equipment, in terms of the coefficients of variations (CVs), were 0.67% and 1.25% for the lumbar spine and femur neck, respectively, which were determined by measuring 17 volunteers who were not enrolled in this study. Each volunteer underwent five scans on the same day and were required to get on and off the table between examinations.

2.3. Biochemical measurements

Serum calcium concentrations were measured using the cresolphthalein complexone method on a Toshiba 200FR Auto-analyzer (Toshiba Medical Systems Co., Ltd., Tokyo, Japan). The intra- and inter-assay CVs were 1.24% and 2.06%, respectively, and the reference interval was 2.07–2.50 mmol/L. Serum phosphorus concentrations were measured using the phosphomolybdate ultraviolet method (Toshiba 200FR instrument). The intra- and inter-assay CVs were 1.28% and 2.54%, respectively, and the reference interval was 0.81–1.45 mmol/L. The glomerular filtration rate (GFR; milliliters per minute per 1.73 m^2), an indicator of renal function, was calculated using the Cockcroft–Gault formula [23]. To measure biochemical bone turnover markers (BTMs), fasting blood samples were obtained in the morning. Serum bone-specific alkaline phosphatase (BSALP) levels were determined using the MetraTM BAP immunoassay kit (Quidel Corp., San Diego, CA), with inter- and intra-assay CVs of 4.4% and 3.6%, respectively. The reference interval for postmenopausal women was 14.2–42.7 U/L. The serum C-terminal telopeptide of type I collagen