High platelet count is associated with low bone mineral density: The MrOS Sweden cohort

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Abstract

Summary In elderly ambulatory men, high platelet and high neutrophil counts are related to low bone mineral density (BMD), after adjustment for relevant covariates. Low hemoglobin (hgb) is even associated with low BMD, but this relationship seems to be dependent on estradiol and osteocalcin.

Purpose Blood and bone cells exist in close proximity to each other in the bone marrow. Accumulating evidence, from both preclinical and clinical studies, indicates that these cell types are interconnected. Our hypothesis was that BMD measurements are associated with blood count variables and bone remodeling markers.

Methods We analyzed blood count variables, bone remodeling markers, and BMD, in subjects from the MrOS cohort from Gothenburg, Sweden. Men with at least one blood count variable (hgb, white blood cell count, or platelet count) analyzed were included in the current analysis (n = 1005), median age 75.3 years (range 69–81 years).

Results Our results show that high platelet counts were related to low BMD at all sites (total hip BMD; \( r = -0.11, P = 0.003 \)). No statistically significant association was seen between platelet counts and bone remodeling markers. Neutrophil counts were negatively associated with total body BMD (\( r = -0.09, P = 0.006 \)) and total hip BMD (\( r = -0.08, P = 0.010 \)), and positively related to serum ALP (\( r = 0.15, P < 0.001 \)). Hgb was positively related to total hip BMD (\( r = 0.16, P < 0.001 \)), and negatively to...
serum osteocalcin ($r = -0.13$, $P < 0.001$). The association between platelet and neutrophil counts and total hip BMD was statistically significant after adjustments for other covariates, but the association between hgb and total hip BMD was dependent on estradiol and osteocalcin.

**Conclusions** Our observations support the hypothesis of an interplay between blood and bone components.

**Keywords** Aging · Bone mineral density · Hematopoiesis · Hemoglobin · Platelet count · White blood cell count

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**Abbreviations**

- **BMD** Bone mineral density
- **DXA** Dual-energy X-ray absorptiometry
- **hgb** Hemoglobin
- **PI1P** N-terminal propeptide of type I collagen
- **ALP** Alkaline phosphatase
- **BMI** Body mass index
- **EPO** Erythropoietin
- **iFGF23** Intact fibroblast growth factor 23
- **iPTH** Intact parathyroid hormone
- **CRP** C reactive protein
- **eGFR** Estimated glomerular filtration rate
- **G-CSF** Granulocyte colony-stimulating factor
- **SD** Standard deviation
- **IQR** Interquartile range
- **RANKL** Nuclear factor-kappa-B ligand

**Introduction**

Blood and bone cells are present in close proximity to each other in the bone marrow microenvironments. Accumulating evidence shows that these cell types interact in the hematopoietic stem cell niche. Bone-resorbing osteoclasts are multinucleated cells developed from hematopoietic stem cells, whereas bone-forming osteoblasts originate from mesenchymal stem cells [1]. Osteoblasts were the first bone cells identified as a part of the hematopoietic stem cell niche [2]. They have been implicated to play a role in regulating maturation of B-lymphocytes [3], as well as modulating erythropoiesis by producing erythropoietin (EPO) [4]. Osteoclasts have later been shown to be important for the establishment of hematopoietic stem cell niches [5]. Osteocytes are osteoblasts which have been incorporated in bone matrix and are the most abundant cells in the bone. Also, osteocytes have been shown to play a role in hematopoietic stem cell niches by regulation of both myelopoiesis [6] and lymphopoiesis [7]. Osteoporosis and osteoporotic fractures are frequently seen in a variety of hematopoietic diseases, such as thalassemia [8], myeloproliferative diseases [9], and lymphoma [10]. A recent population-based study showed that high platelet counts are associated with osteoporosis and osteopenia [11]. Others showed no consistent association between platelet count and bone mineral density (BMD) [12, 13]. A few studies have reported a negative association between low hemoglobin (hgb) or anemia and bone density [14, 15], or a high annual loss of BMD [12], although not supported by others [13]. Studies on the association between white blood cells and its subtypes and BMD have shown conflicting results [12, 13, 16].

The aim of our study was to assess the association between circulating blood cell counts and BMD in a well-described population-based cohort of ambulatory elderly men.

**Methods**

**Study population**

The MrOS (osteoporotic fractures in men) study is an international, multicenter, prospective observational study with the primary objective of evaluating risk factors for osteoporosis and fracture in elderly men. The general study design has previously been described [17]. In brief, men were recruited from Sweden ($n = 3014$, including a Gothenburg cohort $n = 1010$), the USA, and Hong Kong. Participants in MrOS Sweden were men in the age 69–81 years that were randomly identified from national population registries and invited to participate by letter. At the time of inclusion (Gothenburg: April 2002–December 2004), subjects had left blood samples, performed dual-energy X-ray absorptiometry (DXA), and answered standardized questionnaires. Men participating in the Gothenburg part of the Swedish study who had available measurements of at least one blood cell count (hgb, white blood cells, or platelets) were investigated in the present study ($n = 1005$; see Fig. 1). The MrOS study was approved by the ethics committee at the University of Gothenburg, Sweden (M 014-01).

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![Fig. 1 Flow chart MrOS Gothenburg](image-url)
**Assessment of covariates**

Body mass index (BMI) was calculated as weight in kilograms divided by height (in meters) squared (kg/m²). Hand-grip strength was analyzed using a Jamar® dynamometer. Areal BMD (aBMD; g/cm²), later referred to as BMD, was assessed using DXA with the Hologic QDR 4500/A-Delphi (Hologic, Waltham, MA). DXA of the lumbar spine was taken in the anteroposterior (AP) projection. Values for lumbar spine BMD and total hip BMD were standardized; the method used to calculate standardized BMD values has previously been described [17]. The coefficients of variation (CVs) for the BMD measurements were 0.5–3%. Information regarding falls during the 12 months preceding baseline visit, smoking, and physical activity was gathered through a standardized questionnaire. Information about medical history and medications was also obtained. Diabetes mellitus was defined as previously diagnosed diabetes, fasting plasma glucose concentration > 7.0 mM, or the use of insulin or other hypoglycemic medication. A comorbidity index was constructed that included the following concomitant disorders at baseline: diabetes, hypertension, chronic bronchitis, stroke, and myocardial infarction.

**Blood sampling and analytical methods**

Blood samples were collected at the baseline visit and were obtained at 8:00 a.m. after an overnight fast and abstinence from smoking. Blood counts were analyzed immediately in an automated cell counter (Cell-Dyn 4000; Abbott Diagnostics, Abbott Park, IL, USA), at Sahlgrenska University Hospital, Gothenburg, Sweden. Serum and plasma samples were frozen within 1 h, and stored at −80 °C until required for analysis. Methods regarding concentrations of EPO, iFGF23, serotonin, osteocalcin, N-terminal propeptide of type I collagen (P1NP), iron, ferritin, total iron-binding capacity (TIBC), 25(OH)D, ALP, C-reactive protein (CRP), intact parathyroid hormone (iPTH), estradiol, estimated glomerular filtration rate (eGFR), and calculation using a cystatin C-based formula have previously been described [18–25]. Iron deficiency was defined as ferritin < 20 µg/L or transferrin saturation < 15%. As 25(OH)D varies according to season, a z-score was calculated and an expected value of 25(OH)D was attained for each participant according to season [26] and was used in statistical analysis of 25(OH)D values.

**Statistical analyses**

All parametric values are presented as mean with standard deviation (SD) and values that were not normally distributed are presented as median with interquartile range (IQR). Skewed continuous variables were analyzed in the log scale (lymphocytes, EPO, iFGF-23, ALP, osteocalcin, iPTH, CRP, and P1NP). The Pearson correlation test was used for the assessment of univariate correlations. Multivariate linear regression analysis was performed testing the association of total hip BMD and blood count variables after adjustment for variables identified in the univariate correlation (Table 2). Covariate was considered as a confounding factor if it was associated with both any of the blood variables (hgb, neutrophil, or platelet counts) and total hip BMD. Separately we added other possible confounding factors, identified from previous studies. The software used was SAS for Windows, version 9.3 (SAS Institute, Inc. Cary, NC, USA), Stata version 15.1 (StataCorp LLC, College Station, TX, 77845, USA) and a database and statistics program package developed at the Department of Community Medicine and Public Health, Gothenburg University.

**Results**

**Study population**

Basic characteristics of the whole group are presented in Table 1. The present cohort consisted of 1005 men with a median age of 75.3 years (IQR 72.9–78.6, range 69–81 years) and a mean BMI of 26.2 kg/m² (SD 3.5). A total of 777 had all blood cell count variables (hgb, neutrophil, lymphocyte, and platelet count) within the reference range and four individuals had all blood cell count variables outside the reference range.

| Table 1 Selected demographic and laboratory data for the study cohort MrOS Gothenburg (n = 1005) |
|---------------------------------------------------------------|
| Hemoglobin (g/L) | 147 (12) |
| Total white blood cell count (× 10⁹ L) | 6.1 (5.2–7.2) |
| Neutrophil count (× 10⁹ L) | 3.5 (1.2) |
| Lymphocyte count (× 10⁹ L) | 1.8 (1.4–2.2) |
| Platelet count (× 10⁹ L) | 227 (197–266) |
| Total body BMD (g/cm²) | 1.09 (0.11) |
| Lumbar spine L1-L4 BMD (g/cm²) | 1.12 (0.20) |
| Total hip BMD (g/cm²) | 0.96 (0.14) |
| Osteocalcin (µg/L) | 25.0 (20.0–31.0) |
| P1NP (µg/L) | 36.7 (29.8–47.4) |
| ALP (µkat/L) | 0.86 (0.71–1.03) |
| eGFR (ml/min) | 71.2 (19.2) |
| iFGF23 (pg/mL) | 42.5 (33.2–54.1) |
| Phosphate (nmol/L) | 1.06 (0.16) |
| iPTH (pmol/L) | 5.4 (4.2–7.9) |
| CRP (mg/L) | 2.0 (1.6–3.0) |
| EPO (IU/L) | 10.0 (7.8–13.1) |
| Serotonin (µg/L) | 154.6 (74.7) |
| Total estradiol (pmol/L) | 77.0 (30.5) |

Data shown are mean (SD) or median (IQR)
Univariate analysis of blood cell counts

Table 2 presents a univariate correlation between blood cell counts (hgb, neutrophil, lymphocyte, and platelet counts), total hip BMD, and other variables. In univariate analysis, hgb was positively correlated to total hip BMD ($r = 0.16, P < 0.001$), and negatively associated to serum osteocalcin ($r = -0.13, P < 0.001$). No statistically significant association was seen with the other bone remodeling markers P1NP and ALP. Neutrophil counts were negatively correlated to total body BMD ($r = -0.09, P = 0.006$) and total hip BMD ($r = -0.08, P = 0.010$) and positively to serum ALP ($r = 0.15, P < 0.001$), but not to serum osteocalcin and P1NP. Lymphocyte counts were not associated with BMD at any sites, whereas they were negatively correlated to osteocalcin ($r = -0.11, P < 0.001$) and P1NP ($r = -0.08, P = 0.009$). Platelet count was negatively correlated to BMD at all sites, with the strongest association seen with total hip BMD ($r = -0.11, P = 0.003$). No statistically significant association was seen between platelet count and bone remodeling markers.

Multivariate analysis of blood cell counts and total hip BMD

Multiple linear regression models were constructed to see if hgb, neutrophil, and platelet counts were associated with total hip BMD (see Table 3). The results show that hgb was associated with total hip BMD after adjustments for age and BMI, but when adding estradiol or osteocalcin, the association was not statistically significant. Platelet and neutrophil counts...
were independently associated with total hip BMD ($\beta = -0.013$ per SD platelets, $P = 0.010$ and $\beta = -0.013$ per SD neutrophils, $P = 0.008$), in multivariate analysis.

**Discussion**

We evaluated the relationship between BMD and the number of blood cell counts (hgb, neutrophil, lymphocyte, and platelet counts) in a cohort of ambulatory elderly men from the MrOS Sweden cohort. We found that platelet counts were negatively associated with BMD at all sites, and neutrophil counts were negatively associated with total body BMD and total hip BMD. Hgb was positively correlated to total hip BMD after adjustment for age and BMI, but the association was not statistically significant after adjustment for estradiol and osteocalcin. Our results support the hypothesis that blood and bone cells are interconnected.

To the best of our knowledge, only one previous study has shown a negative association between platelet count and BMD. A recent publication in two Korean cohorts, with over 8000 adults of both genders, showed that the BMD of femur, femur neck, and lumbar spine was negatively associated with platelet count [11]. Two other studies, the Cardiovascular Health Study including nearly 6000 adults of both sexes and the MrOS USA cohort, including almost 2600 men, found no consistent association between BMD and platelet count [12, 13]. Contradictory results have even been seen when analyzing mean platelet volume or platelet distribution volume, with some showing a negative association with BMD [27], and others showing a positive association [28]. Serotonin is stored in platelets [29]; thus, as suspected, platelet counts are positively correlated to serotonin values. The role of serotonin in bone metabolism is complicated, but studies have indicated that high serum serotonin is associated with decreased bone mass [30]. Platelet counts are well known to be correlated to inflammation, and previous studies have shown an association between inflammation and osteoporosis [31]. In our cohort, no association between BMD measurements and CRP values were seen. The apparent association of high platelet count and lower BMD values might partly be explained by higher serotonin and inflammation, but not solely, as the association was independent of those variables, thus indicating that other hormones or cytokines are involved. In vitro data suggests that activated platelets can induce osteoclastogenesis via prostaglandin and nuclear factor-kappa-B ligand (RANKL)-dependent mechanism [32], or by providing a source of TGF-beta and activating osteoclastogenetic signaling pathways [33]. Other studies have shown that megakaryocytes enhance osteoblast proliferation and inhibit osteoclast formation [34]. The current study is consistent with some previous studies on BMD and neutrophils [12, 16], although not supported by others [13]. Our finding of neutrophils being positively correlated to iFGF23 further supports previous studies implying a relationship between inflammation and FGF23 [35]. We did not find an association between lymphocytes and BMD, in contrast to others who have reported that low lymphocyte counts are associated with decreased BMD [12].

The association between total hip BMD and hgb was not statistically significant after adjustment for estradiol or osteocalcin. Previous studies have shown that estradiol is positively associated with BMD [17] and hgb [36]. In two Italian studies showing a positive association between hgb and bone mass, no adjustments were made for estradiol [14, 15], which might explain the difference between our findings. In addition, they measured bone mass with a pQCT and ultrasound derived, respectively. Thus, hgb may affect bone mass in a way not captured by DXA. The association between hgb and osteocalcin has previously been reported by our group [37]. Adjusting for CRP did not change our results substantially. The possible mechanism of interaction between hematopoietic cells and bone cells, in preclinical settings, was recently reviewed [38]. Put concisely, osteocytes have been shown to regulate myelopoiesis, by secreting factors such as
Studies in mice have shown that severe lymphopenia is associated with ablation of osteocytes [7]. The relationship does not seem to be restricted to the myeloid or lymphoid cell lines. In mice, osteoblasts have been seen to play a role in both lymphopoiesis [3, 39] and erythropoiesis [4, 40]. This is further supported by mouse models where osteoblast deficiency is induced, which results in only decreased bone mass but also loss of lymphoid and erythroid progenitors [41].

The association between blood and bone cells can even be observed in numerous diseases in humans. Osteopetrosis is a disease caused by dysfunctional or arrested osteoclast formation leading to increased bone mass. This is associated with anemia and sometimes pancytopenia. The only cure is with an allogeneic stem cell transplantation [42]. A recent meta-analysis performed by Steer et al. reported that hematopoietic disorders, due to increased marrow cell proliferation, are associated with significant deterioration of bone health, independently of the affected cell line [43]. The association between blood and bone health is even seen in non-proliferative hematopoietic diseases, such as Diamond-Blackfan anemia, which is categorized by anemia, osteopenia, and various bone anomalies [42].

A noticeable study strength is the relatively large cohort, a standardized blood sampling, in the morning around 8 a.m. and after fasting. DXA measurement was performed on the same day as the blood sampling. We have data on comorbidities and many variables known to influence BMD, thus making it possible to adjust for possible confounders. Nevertheless, we cannot rule out residual confounding. We also acknowledge several limitations in our study. It is a cross-sectional study, with only single measurements of whole blood, serum and plasma variables, and BMD. We only have BMD measured by DXA available and we were therefore not able to distinguish between cortical and trabecular bone. An important limitation is that the cohort only included elderly men and the results might not apply to men in other ages, or in women.

Further testing to evaluate if extreme high or low values of blood counts are associated with BMD would be of interest. The vast majority, or 777 of the subjects, had all hematological variables within the reference range, thus making such an analysis impossible due to the small sample size. Consequently, a trephine biopsy might be more representative of hematopoietic health, but was not performed in the MrOS cohort.

**Conclusions**

In conclusion, we demonstrate that BMD and blood cell counts are associated in this cohort of elderly men. The association is most consistent between BMD and platelet counts. The association between hgb and BMD is dependent in estradiol and osteocalcin. This might support the hypothesis of the interconnection between blood and bone cells.

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**Compliance with ethical standards**

**Conflicts of interest** Mattias Lorentzon has received lecture or consulting fees from Amgen, Lilly, Meda, UCB Pharma, Renapharma, Radius Health and Consilient Health, all outside the submitted work.

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