



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

H.L. Kristjansdottir¹ · D. Mellström^{2,3} · P. Johansson¹ · M. Karlsson⁴ · L. Vandenput^{2,5} · M. Lorentzon^{2,3,5} · H. Herlitz⁶ · C. Ohlsson^{2,7} · U.H. Lerner² · C. Lewerin¹

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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

✉ H.L. Kristjansdottir
hallgerdur.kristjansdottir@vgregion.se

D. Mellström
dan.mellstrom@gu.se

P. Johansson
peter.l.johansson@vgregion.se

M. Karlsson
magnus.karlsson@med.lu.se

L. Vandenput
liesbeth.vandenput@medic.gu.se

M. Lorentzon
mattias.lorentzon@medic.gu.se

H. Herlitz
hans.herlitz@vgregion.se

C. Ohlsson
claus.ohlsson@medic.gu.se

U.H. Lerner
ulf.lerner@gu.se

C. Lewerin
catharina.lewerin@vgregion.se

¹ Section of Hematology and Coagulation at the Sahlgrenska University Hospital and Department of Internal Medicine and Clinical Nutrition, Institute of Medicine, Sahlgrenska Academy at the University of Gothenburg, Bruna Stråket 5, 413 45 Gothenburg, Sweden

² Center for Bone and Arthritis Research (CBAR) at the Department of Internal Medicine and Clinical Nutrition, Institute of Medicine, Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden

³ Department of Geriatric Medicine, Internal Medicine, Institute of Medicine, Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden

⁴ Clinical and Molecular Osteoporosis Research Unit, Department of Clinical Sciences and Orthopedics, Skåne University Hospital (SUS), Lund University, Malmö, Sweden

⁵ Mary MacKillop Institute for Health Research, Australian Catholic University, Melbourne, Victoria, Australia

⁶ Department of Molecular and Clinical Medicine/Nephrology, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

⁷ Department of Drug Treatment, Sahlgrenska University Hospital, Region Västra Götaland, Gothenburg, Sweden

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

Abbreviations

BMD	Bone mineral density
DXA	Dual-energy X-ray absorptiometry
hgb	Hemoglobin
P1NP	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].

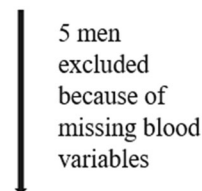
The aim of our study was to assess the association between circulating blood cell counts and BMD in a well-described population-based cohort of ambulatory elderly men.

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).

1010 men included in MrOS Gothenburg



1005 men available for data analysis

Fig. 1 Flow chart MrOS Gothenburg

Assessment of covariates

Body mass index (BMI) was calculated as weight in kilograms divided by height (in meters) squared (kg/m^2). Hand-grip strength was analyzed using a Jamar® dynamometer. Areal BMD (aBMD; g/cm^2), 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 $\mu\text{g}/\text{L}$ 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/m^2 (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 ($\times 10^9$ L)	6.1 (5.2–7.2)
Neutrophil count ($\times 10^9$ L)	3.5 (1.2)
Lymphocyte count ($\times 10^9$ L)	1.8 (1.4–2.2)
Platelet count ($\times 10^9$ L)	227 (197–266)
Total body BMD (g/cm^2)	1.09 (0.11)
Lumbar spine L1-L4 BMD (g/cm^2)	1.12 (0.20)
Total hip BMD (g/cm^2)	0.96 (0.14)
Osteocalcin ($\mu\text{g}/\text{L}$)	25.0 (20.0–31.0)
P1NP ($\mu\text{g}/\text{L}$)	36.7 (29.8–47.4)
ALP ($\mu\text{kat}/\text{L}$)	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 ($\mu\text{g}/\text{L}$)	154.6 (74.7)
Total estradiol (pmol/L)	77.0 (30.5)

Data shown are mean (SD) or median (IQR)

Table 2 Univariate correlations between hemoglobin, neutrophils, lymphocytes, platelets, and total hip BMD and selected variables in the study cohort MrOS Gothenburg (n = 1005)

	Hemoglobin		Neutrophils		Lymphocytes*		Platelets		Total hip BMD	
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
Age	− 0.12	< 0.001	− 0.01	0.689	0.06	0.055	− 0.06	0.078	− 0.06	0.039
BMI	0.19	< 0.001	0.02	0.462	− 0.09	0.007	0.02	0.46	0.45	< 0.001
Total body BMD	0.06	0.056	− 0.09	0.006	− 0.04	0.171	− 0.08	0.012	0.73	< 0.001
Total hip BMD [^]	0.16	< 0.001	− 0.08	0.010	− 0.05	0.150	− 0.11	0.003	NA	NA
LS L1–4 BMD [^]	0.06	0.069	− 0.03	0.292	− 0.00	0.904	− 0.06	0.041	0.66	< 0.001
Hemoglobin	NA	NA	0.08	0.018	0.13	< 0.001	− 0.01	0.686	0.16	< 0.001
Neutrophils	0.08	0.018	NA	NA	0.06	0.048	0.32	< 0.001	− 0.08	0.010
Lymphocytes*	0.13	< 0.001	0.06	0.048	NA	NA	0.11	< 0.001	0.02	0.441
Platelets	− 0.01	0.686	0.32	< 0.001	0.11	< 0.001	NA	NA	− 0.11	0.003
Hand-grip strength	0.15	< 0.001	− 0.07	0.02	0.01	0.857	0.00	0.898	0.16	< 0.001
Walking speed test	0.06	0.080	− 0.17	< 0.001	0.00	0.161	0.01	0.629	0.00	0.904
Current smoker	0.02	0.483	0.23	< 0.001	0.02	0.563	0.02	0.606	− 0.11	< 0.001
Osteocalcin*	− 0.13	< 0.001	− 0.01	0.751	− 0.11	< 0.001	0.06	0.068	− 0.31	< 0.001
ALP*	− 0.01	0.743	0.15	< 0.001	− 0.02	0.521	0.05	0.087	− 0.10	0.003
P1NP*	− 0.06	0.075	− 0.02	0.528	− 0.08	0.009	0.00	0.918	− 0.18	< 0.001
eGFR	0.13	< 0.001	− 0.17	< 0.001	0.03	0.275	− 0.02	0.589	− 0.01	0.810
25(OH)D**	− 0.02	0.468	− 0.01	0.801	0.02	0.628	0.02	0.625	0.04	0.219
Estradiol	0.26	< 0.001	− 0.00	0.983	0.017	0.601	− 0.03	0.401	0.14	< 0.001
CRP*	− 0.11	< 0.001	0.318	< 0.001	− 0.06	0.032	0.15	< 0.001	0.02	0.616
Phosphate	− 0.12	< 0.001	0.08	0.010	0.08	0.016	0.07	0.022	− 0.05	0.100
PTH*	− 0.04	0.235	− 0.02	0.573	− 0.05	0.096	− 0.07	0.020	− 0.08	0.008
Serotonin	− 0.00	0.911	0.10	0.001	0.12	< 0.001	0.27	< 0.001	− 0.08	0.010
EPO*	− 0.32	< 0.001	− 0.10	0.001	− 0.17	0.003	− 0.18	< 0.001	0.11	< 0.001
Iron deficiency	− 0.18	< 0.001	0.19	< 0.001	− 0.02	0.494	0.14	< 0.001	0.01	0.734
iFGF23*	− 0.09	0.004	0.07	0.020	− 0.06	0.063	− 0.08	0.018	0.09	0.007
Prevalent cancer	− 0.12	< 0.001	0.01	0.750	0.04	0.227	0.02	0.481	− 0.01	0.799
Physical activity	− 0.02	0.585	− 0.14	< 0.001	0.04	0.190	− 0.00	0.881	0.01	0.667
Comorbidity index	− 0.03	0.416	0.19	< 0.001	0.05	0.100	− 0.05	0.094	0.12	< 0.001

Comorbidity index: diabetes mellitus, stroke, myocardial infarction, hypertension, chronic bronchitis. *LS* lumbar spine

*Log variable; **Seasonal 25(OH)D; [^]Standardized

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

Table 3 Multivariate linear regression model for total hip BMD in the study cohort MrOS Gothenburg ($n = 995$)

	Covariates adjusted for	β coefficient	Standard error	P value
Hemoglobin	Age, BMI	0.010 per SD	0.004	0.015
	Age, BMI, estradiol	0.006 per SD	0.004	0.190
	Age, BMI, osteocalcin	0.007 per SD	0.004	0.081
	Age, BMI, CRP, eGFR	0.010 per SD	0.004	0.012
	Age, BMI, estradiol, osteocalcin, hand-grip strength, EPO, iFGF23	0.007 per SD	0.004	0.103
Neutrophils	Hand-grip strength, current smoking, ALP, serotonin, iFGF23, comorbidity index	-0.013 per SD	0.004	0.008
	Hand-grip strength, current smoking, ALP, serotonin, iFGF23, comorbidity index, CRP, iron deficiency	-0.015 per SD	0.005	0.003
Platelets	Serotonin, iPTH, iFGF23, EPO	-0.013 per SD	0.005	0.010
	Serotonin, iPTH, iFGF23, EPO, CRP, iron deficiency, age, BMI	-0.011 per SD	0.005	0.015

Dependent variable: Total hip BMD

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

granulocyte colony-stimulating factor (G-CSF) in vitro [6]. 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 not 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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References

1. Taichman RS (2005) Blood and bone: two tissues whose fates are intertwined to create the hematopoietic stem-cell niche. *Blood*. 105(7):2631–2639
2. Calvi LM, Adams GB, Weibrecht KW, Weber JM, Olson DP, Knight MC, Martin RP, Schipani E, Divieti P, Bringhurst FR, Milner LA, Kronenberg HM, Scadden DT (2003) Osteoblastic cells regulate the haematopoietic stem cell niche. *Nature*. 425(6960):841–846
3. Wu JY, Purton LE, Rodda SJ, Chen M, Weinstein LS, McMahon AP et al (2008) Osteoblastic regulation of B lymphopoiesis is mediated by Gs{alpha}-dependent signaling pathways. *Proc Natl Acad Sci U S A* 105(44):16976–16981
4. Rankin Erinn B, Wu C, Khatri R, Wilson Tremika LS, Andersen R, Araldi E et al (2012) The HIF signaling pathway in osteoblasts directly modulates erythropoiesis through the production of EPO. *Cell*. 149(1):63–74
5. Mansour A, Abou-Ezzi G, Sitnicka E, W. Jacobsen SE, Wakkach A, Blin-Wakkach C. Osteoclasts promote the formation of hematopoietic stem cell niches in the bone marrow. *J Exp Med* 2012;209(3):537–549
6. Fulzele K, Krause DS, Panaroni C, Saini V, Barry KJ, Liu X, Lotun S, Baron R, Bonewald L, Feng JQ, Chen M, Weinstein LS, Wu JY, Kronenberg HM, Scadden DT, Divieti Pajevic P (2013) Myelopoiesis is regulated by osteocytes through Galpha-dependent signaling. *Blood*. 121(6):930–939
7. Sato M, Asada N, Kawano Y, Wakahashi K, Minagawa K, Kawano H, Sada A, Ikeda K, Matsui T, Katayama Y (2013) Osteocytes regulate primary lymphoid organs and fat metabolism. *Cell Metab* 18(5):749–758
8. Vogiatzi MG, Macklin EA, Fung EB, Cheung AM, Vichinsky E, Olivieri N, Kirby M, Kwiatkowski JL, Cunningham M, Holm IA,

- Lane J, Schneider R, Fleisher M, Grady RW, Peterson CC, Giardina PJ, for the Thalassemia Clinical Research Network (2009) Bone disease in thalassemia: a frequent and still unresolved problem. *J Bone Miner Res* 24(3):543–557
9. Farmer S, Horvath-Puho E, Vestergaard H, Hermann AP, Frederiksen H (2013) Chronic myeloproliferative neoplasms and risk of osteoporotic fractures; a nationwide population-based cohort study. *Br J Haematol* 163(5):603–610
 10. Johansson P, Lind Kristjansdottir H, Johansson H, Jakir A, Mellstrom D, Lewerin C (2020) Increased risk of hip fracture in patients with lymphoma, a Swedish population study of 37,236 lymphoma patients. *Calcif Tissue Int* 106:591–598
 11. Kim J, Kim HS, Lee HS, Kwon YJ (2020) The relationship between platelet count and bone mineral density: results from two independent population-based studies. *Arch Osteoporos* 15(1):43
 12. Valderrabano RJ, Lui LY, Lee J, Cummings SR, Orwoll ES, Hoffman AR et al (2017) Bone density loss is associated with blood cell counts. *J Bone Miner Res* 32(2):212–220
 13. Valderrabano RJ, Buzkova P, Chang PY, Zakai NA, Fink HA, Robbins JA et al (2019) Association of bone mineral density with hemoglobin and change in hemoglobin among older men and women: the Cardiovascular Health Study. *Bone*. 120:321–326
 14. Cesari M, Pahor M, Lauretani F, Penninx BW, Bartali B, Russo R et al (2005) Bone density and hemoglobin levels in older persons: results from the InCHIANTI study. *Osteoporos Int* 16(6):691–699
 15. Laudisio A, Marzetti E, Pagano F, Bernabei R, Zuccala G (2009) Haemoglobin levels are associated with bone mineral density in the elderly: a population-based study. *Clin Rheumatol* 28(2):145–151
 16. Ozturk ZA, Yesil Y, Kuyumcu ME, Bilici M, Ozturk N, Yesil NK et al (2013) Inverse relationship between neutrophil lymphocyte ratio (NLR) and bone mineral density (BMD) in elderly people. *Arch Gerontol Geriatr* 57(1):81–85
 17. Mellstrom D, Johnell O, Ljunggren O, Eriksson AL, Lorentzon M, Mallmin H et al (2006) Free testosterone is an independent predictor of BMD and prevalent fractures in elderly men: MrOS Sweden. *J Bone Miner Res* 21(4):529–535
 18. Eriksson AL, Movérare-Skrtic S, Ljunggren Ö, Karlsson M, Mellström D, Ohlsson C (2014) High-sensitivity CRP is an independent risk factor for all fractures and vertebral fractures in elderly men: the MrOS Sweden study. *J Bone Miner Res* 29(2):418–423
 19. Johansson H, Oden A, Lerner UH, Jutberger H, Lorentzon M, Barrett-Connor E et al (2012) High serum adiponectin predicts incident fractures in elderly men: osteoporotic fractures in men (MrOS) Sweden. *J Bone Miner Res* 27(6):1390–1396
 20. Kindblom JM, Ohlsson C, Ljunggren O, Karlsson MK, Tivesten A, Smith U, Mellström D (2009) Plasma osteocalcin is inversely related to fat mass and plasma glucose in elderly Swedish men. *J Bone Miner Res* 24(5):785–791
 21. Lewerin C, Ljunggren O, Nilsson-Ehle H, Karlsson MK, Herlitz H, Lorentzon M, Ohlsson C, Mellström D (2017) Low serum iron is associated with high serum intact FGF23 in elderly men: the Swedish MrOS study. *Bone*. 98:1–8
 22. Lewerin C, Ljungman S, Nilsson-Ehle H (2007) Glomerular filtration rate as measured by serum cystatin C is an important determinant of plasma homocysteine and serum methylmalonic acid in the elderly. *J Intern Med* 261(1):65–73
 23. Kristjansdottir HL, Lewerin C, Lerner UH, Herlitz H, Johansson P, Johansson H, Karlsson M, Lorentzon M, Ohlsson C, Ljunggren Ö, Mellström D (2020) High plasma erythropoietin predicts incident fractures in elderly men with normal renal function: the MrOS Sweden Cohort. *J Bone Miner Res* 35:298–305. <https://doi.org/10.1002/jbmr.3900>
 24. Kristjansdottir HL, Lewerin C, Lerner UH, Waern E, Johansson H, Sundh D, Karlsson M, Cummings SR, Zetterberg H, Lorentzon M, Ohlsson C, Mellström D (2018) High serum serotonin predicts increased risk for hip fracture and nonvertebral osteoporotic fractures: the MrOS Sweden study. *J Bone Miner Res* 33(9):1560–1567
 25. Mellstrom D, Vandenput L, Mallmin H, Holmberg AH, Lorentzon M, Oden A et al (2008) Older men with low serum estradiol and high serum SHBG have an increased risk of fractures. *J Bone Miner Res* 23(10):1552–1560
 26. Haghsheno M-A, Mellström D, Behre C-J, Damber J-E, Johansson H, Karlsson M, Lorentzon M, Pecker R, Barret-Connor E, Waern E, Sundh V, Ohlsson C, Hammarsten J (2013) Low 25-OH vitamin D is associated with benign prostatic hyperplasia. *J Urol* 190(2):608–614
 27. Li XS, Zhang JR, Meng SY, Li Y, Wang RT (2012) Mean platelet volume is negatively associated with bone mineral density in postmenopausal women. *J Bone Miner Metab* 30(6):660–665
 28. Akbal A, Gokmen F, Gencer M, Inceer BS, Komurcu E (2014) Mean platelet volume and platelet distribution width can be related to bone mineralization. *Osteoporos Int* 25(9):2291–2295
 29. Bader M (2020) Inhibition of serotonin synthesis: a novel therapeutic paradigm. *Pharmacol Ther* 205:107423
 30. Modder UI, Achenbach SJ, Amin S, Riggs BL, Melton LJ 3rd, Khosla S (2010) Relation of serum serotonin levels to bone density and structural parameters in women. *J Bone Miner Res* 25(2):415–422
 31. Adamopoulos IE (2018) Inflammation in bone physiology and pathology. *Curr Opin Rheumatol* 30(1):59–64
 32. Maitz P, Kandler B, Fischer MB, Watzek G, Gruber R (2006) Activated platelets retain their potential to induce osteoclast-like cell formation in murine bone marrow cultures. *Platelets*. 17(7):477–483
 33. Weicht B, Maitz P, Kandler B, Fischer MB, Watzek G, Gruber R (2007) Activated platelets positively regulate RANKL-mediated osteoclast differentiation. *J Cell Biochem* 102(5):1300–1307
 34. Ciovacco WA, Cheng YH, Horowitz MC, Kacena MA (2010) Immature and mature megakaryocytes enhance osteoblast proliferation and inhibit osteoclast formation. *J Cell Biochem* 109(4):774–781
 35. David V, Francis C, Babitt JL (2017) Ironing out the cross talk between FGF23 and inflammation. *Am J Physiol-Ren Physiol* 312(1):F1–F8
 36. Lewerin C, Nilsson-Ehle H, Jacobsson S, Johansson H, Sundh V, Karlsson MK, Lorentzon M, Barrett-Connor E, Vandenput L, Ohlsson C, Mellström D (2014) Serum estradiol associates with blood hemoglobin in elderly men: the MrOS Sweden study. *J Clin Endocrinol Metab* 99(7):2549–2556
 37. Lewerin C, Johansson H, Karlsson MK, Lorentzon M, Lerner UH, Kindblom JM, Ohlsson C, Smith U, Mellström D (2016) High plasma osteocalcin is associated with low blood hemoglobin in elderly men: the MrOS Sweden study. *J Intern Med* 280(4):398–406
 38. Valderrabano RJ, Wu JY (2019) Bone and blood interactions in human health and disease. *Bone*. 119:65–70
 39. Panaroni C, Fulzele K, Saini V, Chubb R, Pajevic PD, Wu JY (2015) PTH signaling in osteoprogenitors is essential for B-lymphocyte differentiation and mobilization. *J Bone Miner Res* 30(12):2273–2286
 40. Wu C, Giaccia AJ, Rankin EB (2014) Osteoblasts: a novel source of erythropoietin. *Curr Osteoporos Rep* 12(4):428–432
 41. Visnjic D, Kalajzic Z, Rowe DW, Katavic V, Lorenzo J, Aguila HL (2004) Hematopoiesis is severely altered in mice with an induced osteoblast deficiency. *Blood*. 103(9):3258–3264
 42. Teti A, Teitelbaum SL (2019) Congenital disorders of bone and blood. *Bone*. 119:71–81
 43. Steer K, Stavnychuk M, Morris M, Komarova SV (2017) Bone health in patients with hematopoietic disorders of bone marrow origin: systematic review and meta-analysis. *J Bone Miner Res* 32(4):731–742