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Review Article

Bone and blood interactions in human health and disease

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ABSTRACT

Under physiologic conditions hematopoiesis takes place in the bone marrow, and the skeleton provides the structural and supportive network necessary for normal hematopoiesis. Chronic disorders affecting hematopoiesis such as sickle cell anemia and thalassemia demonstrate striking skeletal phenotypes including bone loss and increased fracture risk. There is mounting evidence that anemia in older populations may also be associated with bone fragility. Given the interconnectedness of bone and hematopoietic cells, it is important to review the potential clinical implications and opportunities for therapeutic intervention. There are recognized associations between blood-borne and solid tissue malignancy and skeletal health, but our review will focus on non-malignant disease.

Contents

1. Sites of hematopoiesis in health and disease

During embryonic development, hematopoietic cells migrate from the fetal liver to the bone marrow [1]. In adults, hematopoietic cells can be found in the vertebrae, pelvis, ribs, sternum, skull, proximal end of long bones and scapulae [2]. The bone marrow housed inside the skeleton is composed of cells with hematopoietic capacity (red marrow) and tissue rich in adipose cells (yellow or fatty marrow) which are readily distinguished by magnetic resonance imaging [3]. In childhood the skeleton is filled with mostly hematopoietic bone marrow, which is gradually converted with age to yellow marrow in a very specific pattern starting distally at the phalanges and moving centrally towards the axial skeleton. Within a particular long bone, fatty marrow moves from the distal epiphysis towards the proximal metaphysis [4]. The axial skeleton tends to convert at a slower rate. After skeletal maturity is reached the proportions of red to yellow marrow can vary according to skeletal site, and continue to change with age [5,6]. In older adults the bone marrow contains increasingly higher proportions of yellow marrow [7]. One necropsy study revealed that decreases in hematopoietic tissue volume were significantly correlated with decreases in trabecular bone volume and osteoid volume in the

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setting of aging, osteoporosis and aplastic anemia [8]. Increased bone marrow fat has been increasingly recognized in osteoporosis and is thought to be inversely related to bone density and integrity [9–11].

When there are increased demands for hematopoiesis, fatty marrow can undergo bone marrow reconversion to become hematopoietically active again. Strikingly, bone marrow reconversion occurs in exactly the reverse pattern of bone marrow conversion, i.e. proceeding distally from the axial skeleton [12]. Marrow reconversion has been described in smokers [13], individuals with sleep apnea [14], and after partial body radiation [15,16], and chronic conditions resulting in anemia can also lead to diffuse red marrow hyperplasia [17,18]. Thus, sites of hematopoiesis are not stable and unwavering but instead follow a choreographed pattern throughout normal skeletal development and aging but can also respond to disease. This is important to note when considering the potential impact of bone marrow activity and composition on skeletal structure, microarchitecture and function.

2. Bone phenotypes in primary hematopoietic disease

Thalassemia and sickle cell anemia are two disorders of hematopoiesis with prominent bone fragility phenotypes. Thalassemia is an autosomal recessive disorder caused by a mutation in the α or β globin gene that hampers the synthesis of the affected hemoglobin chains [19]. The resulting ineffective erythropoiesis leads to varying degrees of anemia and chronic bone marrow expansion [20,21]. Bone disease in thalassemia is multifactorial and can include direct bone effects such as marrow expansion into bone, endocrine factors such as hypogonadism and growth hormone deficiency, and treatment effects such as iron and deferoxamine toxicity [22,23]. Nevertheless, some interesting observations can be made which may be pertinent for people with other forms of anemia. Red blood cell transfusions can decrease erythroid marrow expansion in thalassemia [24]. One invasive study revealed that red blood cell transfusions in patients with thalassemia resulted in increased osteoblast numbers and bone formation as determined by double tetracycline labeling and histomorphometry [25]. This suggests that temporary relief of excessive erythropoiesis may have beneficial effects on bone formation. Similarly, one study of children with transfusion dependent and independent thalassemia found that erythropoietic activity, as measured by the soluble transferrin receptor, was negatively correlated with bone mineral density measured at the lumbar spine total hip and in the total body [26], consistent with the notion that excessive demands on erythropoiesis have a negative impact on bone. Patients with thalassemia have decreased bone mineral density (BMD). Estimated mean spine Z scores ranged from −1.64 to −2.37 by age 20 in one study, which also reported skeletal fractures in 36% of participants by a mean age of 23 [27]. The prevalence of fractures has been reported to be a high as 50% in some populations of patients with thalassemia, but this has improved with advances in red blood cell transfusion and concomitant iron chelation therapy [20].

Sickle cell disease is a monogenic disorder caused by a mutation in the β globin gene which leads to polymerization of β-globin chains, eventually resulting in sickling of the red blood cell with hemolysis and vaso-occlusion [28,29]. Studies in patients with sickle cell anemia have shown increased rates of bone related complications such as osteopenia, osteoporosis, fractures, avascular necrosis, vertebral bone deformities and bone and joint pain [30]. Over 70% of adults with sickle cell disease exhibit low BMD at a median age of 30 years old. The causes of bone abnormalities are attributed mainly to marrow expansion similar to patients with thalassemia with the addition of vaso-occlusion due to red cell sickling which can also cause acute bone syndromes [31].

Overall these studies reveal that bone formation and hematopoiesis are closely linked in primary hematopoietic disease. However, there are scarce clinical data regarding the role of bone health in hematopoiesis beyond these disease states.

3. Anemia and bone health

In older adults without primary hematopoietic disease, anemia is most commonly caused by a nutritional deficiency (over 50% are due to iron deficiency) and by the inflammation of chronic disease. Anemia is highly prevalent in all age groups and in most countries in the world. The estimated prevalence of anemia in adults residing in the United States (as defined by the WHO criteria of hemoglobin (Hgb) <13 g/dL for men and <12 g/dL in women) is 11.0% for men and 10.2% for women [32]. The estimated prevalence is as high as 23.9% in the elderly worldwide [33]. Anemia of chronic disease can result from disturbances of iron homeostasis, impaired proliferation of erythroid progenitor cells, and a blunted erythropoietin response to anemia, and can be difficult to correct [34]. There is a growing body of evidence outlining the relationship between anemia and bone health outside of primary hematopoietic disease states in humans.

4. Anemia and bone density measurements

Bone density is a commonly utilized measure to determine bone fragility and fracture risk [35–39]. The relationship between anemia and bone density has been evaluated by a few groups, although differences in study design and measurement of bone density limit the overarching conclusions. In the prospective observational study MrOS, community dwelling older men had serial bone density measurements by dual-energy X-ray absorptiometry (DXA) and one Hgb evaluation approximately 7 years after the baseline visit. We recently showed in an analytic sample of 2586 older men in MrOS that those with high annualized bone loss of over 0.5% per year at the femoral neck and total hip DXA sites (but not at the spine) had an increased risk of anemia (defined as Hgb <12 g/dL) of 79% and 110% respectively after multivariate adjustment [40]. Interestingly, a single bone density measurement at one time point was not associated with anemia. This shows that a relationship of impaired bone health and low Hgb can be appreciated even in relatively healthy individuals, but that a single DXA may not have the necessary resolution to detect this association. In the prospective population based observational InCHIANTI Study, a group of 530 women and 420 men underwent peripheral quantitative computed tomography (pQCT). Lower levels of Hgb and anemia by World Health Organization (WHO) criteria were found to be associated with lower bone density, which was more pronounced in cortical bone [41]. Women also had a small but significant association between anemia and measures of trabecular bone, suggesting that there may be sex differences in this relationship. The pQCT measurements used in this study were derived from 2.1 mm-thick transverse scans of the targeted bone areas, which are much higher resolution than conventional DXA and may have allowed them to detect smaller differences in bone density at a single time point. In a population based study in Tuscania, Italy, 358 men and women aged 75 and older were evaluated with ultrasound derived bone densitometry. A cross sectional evaluation of this cohort revealed that measurements of bone stiffness and derived T-scores by ultrasound were positively associated with Hgb levels [42]. In this study participants with anemia by WHO criteria had significantly lower T scores. In a retrospective study of 358 postmenopausal Turkish women undergoing osteoporosis screening, anemia was associated with greater than twofold increased odds of having low bone mass, defined as a DXA BMD derived T score < −1, at the spine but not the femoral neck after adjustment for multiple confounders [43]. A summary of findings with bone density parameters can be found in Table 1.

More recently a study of the Taiwan national healthcare database used claims data and a case control design to evaluate the association between diagnosis of iron deficiency anemia and osteoporosis. Using a large sample of over 200,000 individuals they found that those with iron deficiency anemia of an average duration of 6.86 years had an 81% increased risk for osteoporosis after adjusting for other covariates [44]. In this study, patients who were treated with intravenous iron

Table 1
Associations of bone mineral density and hemoglobin.

Bone density measure	Hemoglobin level	Findings	Study design	Reference
Men				
BMD (g/cm^2) by DXA	Hgb < 12 g/dL	No association	Prospective Observational	Valderrábano et al. [38]
>0.5% BMD decrease/year	Hgb < 12 g/dL	Increased risk of low Hgb with >0.5%/year hip BMD decrease	Prospective Observational	Valderrábano et al. [38]
Cortical bone density (mg/cm^3) by qCT	Continuous Hgb levels	Positive association	Cross-sectional	Cesari et al. [39]
Trabecular bone density (mg/cm^3) by qCT	Continuous Hgb levels	No association	Cross-sectional	Cesari et al. [39]
Women				
Trabecular bone density (mg/cm^3) by qCT	Continuous Hgb levels	Positive association	Cross-sectional	Cesari et al. [39]
Cortical bone density (mg/cm^3) by qCT	Continuous Hgb levels	Positive association	Cross-sectional	Cesari et al. [39]
Spine T score < −1 by DXA	Hgb <12 g/dL	Increased odds of low spine T-score	Retrospective	Kormaz et al. [41]
Not stratified by sex				
Ultrasound derived bone Stiffness index	Continuous Hgb levels	Positive association	Cross-sectional	Laudisio et al. [40]

Hgb: Hemoglobin, DXA: Dual energy x-ray absorptiometry, qCT: Peripheral quantitative computed tomography, BMD: bone mineral density.

replacement were at higher risk for osteoporosis than those treated with oral iron therapy or transfusion therapy as compared to those without anemia with a 121%, 80% and 47% increased risk for developing or being diagnosed with osteoporosis respectively. The authors theorized that therapy chosen may be a marker of disease severity, which could account for the differences in the magnitude of osteoporosis risk increase, but it is interesting that those with transfusion therapy had a lower risk for osteoporosis than those with oral iron replacement.

5. Anemia and fractures

Anemia has also been identified in large population-based studies as a risk factor for skeletal fracture. In a nested case-control study of the UK general practice research database where 231,778 adult patients with fracture were compared with age and sex matched controls, anemia was observed to be a significant risk factor for fractures after evaluation of a broad group of diseases and drug exposures [45]. A retrospective cohort study of the same database found that pernicious anemia specifically was also associated with a 74% increased risk of hip fracture as compared to age and sex matched controls [46]. Similarly, a large population based cohort study of the residents of the Swedish county of Upsala evaluated hip fracture risk across 117,494 participants aged over 50 across a broad range of diagnoses (based on ICD-10 codes) and found that diseases of blood/blood-forming organs (which encapsulates many different types of anemia) inferred an estimated threefold increased risk for hip fracture [47].

A few studies have directly evaluated the impact of anemia on skeletal fractures in groups of older men and women using more uniform methodology. We recently showed that anemia was associated with a 60–68% increased risk of non-spine fracture in an analytical cohort of 3632 older men across 7.2 years of follow up [48]. Importantly the fracture risk was independent of cross sectional BMD at the total hip and BMD loss at the total hip prior to the start of fracture follow up. Anemia was not significantly associated with spine fracture in men. An evaluation of the Women's Health Initiative (WHI), the largest study of postmenopausal women in the US, observed 160,080 multi-ethnic women and found that anemia was associated with a 38% increased risk of hip fracture and a 30% increased risk of spine fracture after adjustment for multiple covariates including number of falls, hormone use, and osteoporosis diagnosis [49]. A population based study in Tromsø, Norway prospectively followed non-vertebral fractures in 2511 men and 2775 women over 8 years and found that the relative risk of non-vertebral fracture was increased by 115% in men with anemia compared with those with a Hgb above 15.2 g/dL after adjustment for covariates which included forearm BMD by DXA, grip strength by dynamometry and measures of inflammation. Women with anemia in this study did not have significantly increased risk of fracture after adjustment for covariates [50]. Looker used data from the Third National Health and Nutrition Examination Survey (NHANES III) linked with corresponding Medicare claims data to examine the association of low and high hemoglobin levels with hip fracture in a representative US population. Specific attention was given to the etiology of anemia in this study [51]. In this population of 2122 adults aged 65 or older at baseline the groups of people with the lowest and highest sex-specific Hgb, by decile, had increased risk of hip fractures by 124% and 137% respectively when compared to middle 5–6 deciles. The author evaluated the individual contributions of some variables and found that adjustment for femoral neck BMD and iron deficiency status but not chronic inflammation decreased the estimated fracture risk for those with the lowest Hgb, indicating that those two factors may play a modulating role. The highest decile of hemoglobin adjustment for femoral neck BMD increased the magnitude of the association in those with the highest Hgb levels, indicating that hematopoiesis and bone density may interact differently across the Hgb spectrum. Fig. 1 summarizes fracture risk estimates across these studies.

Low hemoglobin has been consistently associated with non-spine and hip fractures in older men and inconsistently associated with other types of fractures in men and women. It is unclear why the risk of fractures for women would differ from men but it may be that the increase in fracture risk with low Hgb is of smaller magnitude in women and so was only detected in the study with the largest sample size (WHI). It may also be that the effects of anemia on bone health in women are overshadowed by the hormonal changes of menopause, which do not occur in men. It appears that the increased fracture risk in anemia is independent of BMD, which makes a Hgb measurement an attractive candidate as a clinical adjunct for fracture risk stratification and management in men.

6. Possible mechanisms of bone fragility in anemia

There are several mechanisms by which clinically detectable anemia could be a signal for bone fragility. We have learned from animal models that bone cells interact with hematopoietic cells [52]. We have shown that osteoblasts and their precursors appear to have a supportive or regulatory role in myelopoiesis [53], and in B-lymphocyte differentiation [54,55]. Others have shown that osteoblasts can directly modulate erythropoiesis [56,57] and that ablation of osteoblasts can result in deficits of hematopoiesis [58]. So, it is possible that clinically observable anemia or decreasing trend in Hgb might result from an impairment of bone cells in providing a supportive microenvironment needed to maintain erythropoiesis. In post-menopausal women we have shown that teriparatide increases circulating hematopoietic stem cells in peripheral blood [59], highlighting that bone targeted therapies may impact hematopoiesis.

Some authors have suggested that anemia or iron deficiency can place increased pressure on hematopoietic activity, with a net increase in cells of hematopoietic lineage (including osteoclasts) and marrow expansion with a decrease in bone volume [60] similar to the prominent

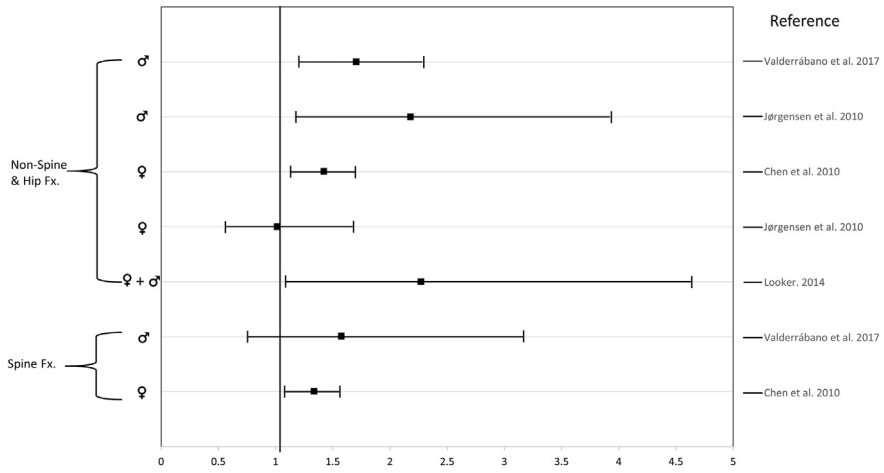

Fig. 1. Risk estimates for non-spine, hip and spine fracture by low hemoglobin level in selected studies. Fx: Fracture, ♂: men, ♀: women.

hematopoietic marrow expansion in individuals with thalassemia [20]. A recent meta-analysis concluded that bone density changes are negatively correlated with bone marrow cellularity in a variety of hematopoietic diseases [61]. As discussed earlier blood transfusion increased osteoblasts in thalassemia [25] and transfusion in patients with iron deficiency anemia was associated with a lower risk of osteoporosis than those treated with oral or intravenous iron [44]. It may be that anemia of any etiology and the resulting increased erythropoiesis may contribute to lower bone density and increased skeletal fragility.

One potential mechanism might be mediated by increased levels of erythropoietin, which stimulates bone marrow erythropoiesis. Pre-clinical studies in mice have demonstrated that high doses of erythropoietin can induce bone loss [62,63]. Hypoxia is a potent stimulator of erythropoietin production; individuals with anemia have decreased oxygen carrying capacity [64,65] and hypoxia has previously been implicated in loss of bone mineral density [66]. Osteoporosis is highly prevalent in patients with chronic obstructive pulmonary disease who have chronic hypoxia [67–69], although this is likely confounded by other factors such as increased glucocorticoid use.

From a bioengineering perspective it has been suggested that fluid shear could provide a significant stimulant for osteoprogenitor recruitment in the bone marrow [70] and bone marrow viscosity is thought to be important in the modulation of shear stresses on bone surfaces [71]. As reviewed above, anemia is associated with red marrow hyperplasia which would result in changes in bone marrow composition [17,18]. This could change its overall viscosity and the transmitted fluid shear forces to cells residing in the bone marrow. It is unclear what the net effects of bone marrow composition changes would be, but it is possible that anemia could be affecting bone strength by changing the mechanical and loading properties of bone marrow.

From a practical standpoint anemia has been associated with several clinical parameters, including frailty [72,73], decreased physical functioning [74], and increased number of injurious falls [75], which could all lead to increased fracture risk. Other clinical factors such as decreased testosterone levels, impaired renal function and chronic inflammation have been linked with both anemia and low bone mineral density or fractures [34,76–82] and could be possible sources of confounding.

7. White blood cells and bone density

Bone cells may have reciprocal interactions with other hematopoietic cell types beyond erythrocytes. We have shown that older men with high annualized bone loss also have increased risk of having high neutrophils and separately low lymphocytes [40], which match predictions based on animal models of altered bone metabolism [53–56]. Low lymphocytes, high neutrophils and anemia appeared to affect different groups of men with high bone loss, with little overlap. This indicates that there may be various mechanisms leading to hematopoietic dysfunction and that distinct bone cell types might support hematopoiesis differently. In a separate pilot study in postmenopausal women, those with osteoporosis (T-score < -2.5) had decreased numbers of B lymphocytes when compared to women with normal BMD [83]. Women with osteoporosis were also found to have altered secretion of inflammatory cytokines by B and T lymphocytes, raising the possibility that osteoporosis may contribute to immune impairment of aging.

8. Conclusions

Hematopoiesis in humans is a dynamic phenomenon which has extensive interactions with the skeletal system. Blood disorders such as thalassemia and sickle cell disease give us extreme examples of how bone health can be negatively impacted by a hematologic disorder. Given the high prevalence of anemia and the frequent availability of complete blood counts in medical records it is intriguing to consider its potential clinical utility. The available human studies evaluating bone health in individuals with anemia appear to show an association with low bone density with a possible propensity for cortical sites, however differences in study methodology, populations evaluated and differences in BMD measurements preclude generalized conclusions. More work is needed to elucidate the relationship between Hgb levels and bone density, and to evaluate the utility of Hgb measurement as a signal for osteoporosis screening. Low hemoglobin has been consistently associated with increased hip and non-spine fractures in men and may have some fracture risk increase in women. More studies in prospective cohorts are necessary to identify if the association remains consistent across different populations, and to test if a hemoglobin measurement can improve fracture risk stratification.

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References

[1] K.S. Fernandez, P.A. de Alarcon, Development of the hematopoietic system and disorders of hematopoiesis that present during infancy and early childhood, Pediatr. Clin. N. Am. 60 (6) (2013) 1273–1289.
[2] B.F. Rodak, G.A. Fritsma, E.M. Keohane, Hematology: Clinical Principles and Applications, 4th Edition Elsevier Saunders, St. Louis, MO, 2012.
[3] A. Cohen, W. Shen, D. Dempster, et al., Marrow adiposity assessed on transiliac crest biopsy samples correlates with noninvasive measurement of marrow adiposity by proton magnetic resonance spectroscopy (1H-MRS) at the spine but not the femur, Osteoporos. Int. 26 (10) (2015) 2471–2478.

[4] T. Laor, D. Jaramillo, MR imaging insights into skeletal maturation: what is normal? Radiology 250 (1) (2009) 28–38.
[5] C. Ricci, M. Cova, Y.S. Kang, et al., Normal age-related patterns of cellular and fatty bone marrow distribution in the axial skeleton: MR imaging study, Radiology 177 (1) (1990) 83–88.
[6] M. Cristy, Active bone marrow distribution as a function of age in humans, Phys. Med. Biol. 26 (3) (1981) 389.
[7] C.J. Rosen, C. Ackert-Bicknell, J.P. Rodriguez, A.M. Pino, Marrow fat and the bone microenvironment: developmental, functional, and pathological implications, Crit. Rev. Eukaryot. Gene Expr. 19 (2) (2009) 109–124.
[8] R. Burkhardt, G. Kettner, W. Bohm, et al., Changes in trabecular bone, hematopoiesis and bone marrow vessels in aplastic anemia, primary osteoporosis, and old age: a comparative histomorphometric study, Bone 8 (3) (1987) 157–164.
[9] P.K. Fazeli, M.C. Horowitz, O.A. MacDougald, et al., Marrow fat and bone—new perspectives, J. Clin. Endocrinol. Metab. 98 (3) (2013) 935–945.
[10] J. Paccou, P. Hardouin, A. Cotten, G. Penel, B. Cortet, The role of bone marrow fat in skeletal health: usefulness and perspectives for clinicians, J. Clin. Endocrinol. Metab. 100 (10) (2015) 3613–3621.
[11] M.J. Devlin, C.J. Rosen, The bone–fat interface: basic and clinical implications of marrow adiposity, Lancet Diabetes Endocrinol. 3 (2) (2015) 141–147.
[12] R.M. Steiner, D.G. Mitchell, V.M. Rao, M.E. Schweitzer, Magnetic resonance imaging of diffuse bone marrow disease, Radiol. Clin. N. Am. 31 (2) (1993) 383–409.
[13] T.B. Poulton, W.D. Murphy, J.L. Duerk, C.C. Chapek, D.H. Feiglin, Bone marrow reconversion in adults who are smokers: MR imaging findings, AJR Am. J. Roentgenol. 161 (6) (1993) 1217–1221.
[14] T. Cosentini, R. Le Donne, D. Mancini, A.R. Aleandri, N. Colavita, Magnetic resonance imaging evaluation of bone marrow changes in obstructive sleep apnoea syndrome in adults, Radiol. Med. 111 (4) (2006) 572–584.
[15] P. Rubin, N.A. Elbadawi, R.A. Thomson, R.A. Cooper, Bone marrow regeneration from cortex following segmental fractionated irradiation, Int. J. Radiat. Oncol. Biol. Phys. 2 (1) (1977) 27–38.
[16] P. Rubin, S. Landman, E. Mayer, B. Keller, S. Ciccio, Bone marrow regeneration and extension after extended field irradiation in Hodgkin's disease, Cancer 32 (3) (1973) 699–711.
[17] S. Hwang, D.M. Panicek, Magnetic resonance imaging of bone marrow in oncology, part 1, Skelet. Radiol. 36 (10) (2007) 913–920.
[18] S. Hwang, D.M. Panicek, Magnetic resonance imaging of bone marrow in oncology, part 2, Skelet. Radiol. 36 (11) (2007) 1017–1027.
[19] H.L. Muncie Jr, J. Campbell, Alpha and beta thalassemia, Am. Fam. Physician 80 (4) (2009) 339–344.
[20] P. Wong, P.J. Fuller, M.T. Gillespie, F. Milat, Bone disease in thalassemia: a molecular and clinical overview, Endocr. Rev. 37 (4) (2016) 320–346.
[21] F. Centis, L. Tabellini, G. Lucarelli, et al., The importance of erythroid expansion in determining the extent of apoptosis in erythroid precursors in patients with β-thalassemia major, Blood 96 (10) (2000) 3624–3629.
[22] M. Angastiniotis, A. Eleftheriou, Thalassaemic bone disease. An overview, Pediatr. Endocrinol. Rev. 6 (Suppl. 1) (2008) 73–80.
[23] M. Toumba, N. Skordis, Osteoporosis syndrome in thalassaemia major: an overview, J. Osteoporos. 2010 (2010).
[24] M. Cazzola, P.D. Stefano, L. Ponchio, et al., Relationship between transfusion regimen and suppression of erythropoiesis in β-thalassaemia major, Br. J. Haematol. 89 (3) (1995) 473–478.
[25] P. Pootrakul, S. Hungsprenges, S. Fucharoen, et al., Relation between erythropoiesis and bone metabolism in thalassemia, N. Engl. J. Med. 304 (24) (1981) 1470–1473.
[26] P. Mahachoklertwattana, P. Pootrakul, A. Chuansumrit, et al., Association between bone mineral density and erythropoiesis in Thai children and adolescents with thalassemia syndromes, J. Bone Miner. Metab. 24 (2) (2006) 146–152.
[27] M.G. Vogiatzi, E.A. Macklin, E.B. Fung, et al., Bone disease in thalassemia: a frequent and still unresolved problem, J. Bone Miner. Res. 24 (3) (2009) 543–557.
[28] H.F. Bunn, Pathogenesis and treatment of sickle cell disease, N. Engl. J. Med. 337 (11) (1997) 762–769.
[29] D.C. Rees, T.N. Williams, M.T. Gladwin, Sickle-cell disease, Lancet 376 (9757) (2010) 2018–2031.
[30] I. Osunkwo, An update on the recent literature on sickle cell bone disease, Curr. Opin. Endocrinol. Diabetes Obes. 20 (6) (2013) 539–546.
[31] A. Almeida, I. Roberts, Bone involvement in sickle cell disease, Br. J. Haematol. 129 (4) (2005) 482–490.
[32] J.M. Guralnik, R.S. Eisenstaedt, L. Ferrucci, H.G. Klein, R.C. Woodman, Prevalence of anemia in persons 65 years and older in the United States: evidence for a high rate of unexplained anemia, Blood 104 (8) (2004) 2263–2268.
[33] E. McLean, M. Cogswell, I. Egli, D. Wojdyla, B. de Benoist, Worldwide prevalence of anaemia, WHO vitamin and mineral nutrition information system, 1993–2005, Public Health Nutr. 12 (4) (2009) 444–454.
[34] G. Weiss, L.T. Goodnough, Anemia of chronic disease, N. Engl. J. Med. 352 (10) (2005) 1011–1023.
[35] O. Johnell, J.A. Kanis, A. Oden, et al., Predictive value of BMD for hip and other fractures, J. Bone Miner. Res. 20 (7) (2005) 1185–1194.
[36] J. Compston, A. Cooper, C. Cooper, et al., Guidelines for the diagnosis and management of osteoporosis in postmenopausal women and men from the age of 50 years in the UK, Maturitas 62 (2) (2009) 105–108.
[37] J.A. Kanis, Diagnosis of osteoporosis and assessment of fracture risk, Lancet 359 (9321) (2002) 1929–1936.
[38] E.S. Siris, Y.T. Chen, T.A. Abbott, et al., Bone mineral density thresholds for pharmacological intervention to prevent fractures, Arch. Intern. Med. 164 (10) (2004) 1108–1112.
[39] J.A. Kanis, E. McCloskey, H. Johansson, A. Oden, W.D. Leslie, FRAX® with and without bone mineral density, Calcif. Tissue Int. 90 (1) (2012) 1–13.
[40] R.J. Valderrábano, L.Y. Lui, J. Lee, et al., Bone density loss is associated with blood cell counts, J. Bone Miner. Res. 32 (2) (2017) 212–220.
[41] M. Cesari, M. Pahor, F. Lauretani, et al., Bone density and hemoglobin levels in older persons: results from the InCHIANTI study, Osteoporos. Int. 16 (6) (2005) 691–699.
[42] A. Laudisio, E. Marzetti, F. Pagano, R. Bernabei, G. Zuccalà, Haemoglobin levels are associated with bone mineral density in the elderly: a population-based study, Clin. Rheumatol. 28 (2) (2009) 145–151.
[43] U. Korkmaz, N. Korkmaz, S. Yazici, et al., Anemia as a risk factor for low bone mineral density in postmenopausal Turkish women, Eur. J. Inter. Med. 23 (2) (2012) 154–158.
[44] M.-L. Pan, L.-R. Chen, H.-M. Tsao, K.-H. Chen, Iron deficiency anemia as a risk factor for osteoporosis in Taiwan: a nationwide population-based study, Nutrients 9 (6) (2017) 616.
[45] T. Van Staa, H. Leufkens, C. Cooper, Utility of medical and drug history in fracture risk prediction among men and women, Bone 31 (4) (2002) 508–514.
[46] N.A. Merriman, M.E. Putt, D.C. Metz, Y.X. Yang, Hip fracture risk in patients with a diagnosis of pernicious anemia, Gastroenterology 138 (4) (2010) 1330–1337.
[47] B. Leavy, K. Michaëlsson, A.C. Åberg, H. Melhus, L. Byberg, The impact of disease and drugs on hip fracture risk, Calcif. Tissue Int. 100 (1) (2017) 1–12.
[48] Rodrigo J. Valderrábano, Jennifer Lee, Li-Yung Lui, Andrew R. Hoffman, Steven R. Cummings, Eric S. Orwoll, Joy Y. Wu, Older men with anemia have increased fracture risk independent of bone mineral density, J. Clin. Endocrinol. Metab. 102 (7) (2017) 2199–2206.
[49] Z. Chen, C.A. Thomson, M. Aickin, et al., The relationship between incidence of fractures and anemia in older multiethnic women, J. Am. Geriatr. Soc. 58 (12) (2010) 2337–2344.
[50] L. Jorgensen, T. Skjelbakken, M.L. Lochen, et al., Anemia and the risk of non-vertebral fractures: the Tromso study, Osteoporos. Int. 21 (10) (2010) 1761–1768.
[51] A. Looker, Hemoglobin and hip fracture risk in older non-Hispanic white adults, Osteoporos. Int. 25 (10) (2014) 2389–2398.
[52] C. Panaroni, Y.S. Tzeng, H. Saeed, J.Y. Wu, Mesenchymal progenitors and the osteoblast lineage in bone marrow hematopoietic niches, Curr. Osteoporos. Rep. 12 (1) (2014) 22–32.
[53] K. Fulzele, D.S. Krause, C. Panaroni, et al., Myelopoiesis is regulated by osteocytes through Gsalpha-dependent signaling, Blood 121 (6) (2013) 930–939.
[54] J.Y. Wu, L.E. Purton, S.J. Rodda, et al., Osteoblastic regulation of B lymphopoiesis is mediated by Gs{alpha}-dependent signaling pathways, Proc. Natl. Acad. Sci. U. S. A. 105 (44) (2008) 16976–16981.
[55] C. Panaroni, K. Fulzele, V. Saini, R. Chubb, P.D. Pajevic, J.Y. Wu, PTH signaling in osteoprogenitors is essential for B-lymphocyte differentiation and mobilization, J. Bone Miner. Res. 30 (12) (2015) 2273–2286.
[56] E.B. Rankin, C. Wu, R. Khatri, et al., The HIF signaling pathway in osteoblasts directly modulates erythropoiesis through the production of EPO, Cell 149 (1) (2012) 63–74.
[57] C. Wu, A.J. Giaccia, E.B. Rankin, Osteoblasts: a novel source of erythropoietin, Curr. Osteoporos. Rep. 12 (4) (2014) 428–432.
[58] D. Visnjic, Z. Kalajzic, D.W. Rowe, V. Katavic, J. Lorenzo, H.L. Aguila, Hematopoiesis is severely altered in mice with an induced osteoblast deficiency, Blood 103 (9) (2004) 3258–3264.
[59] E.W. Yu, R. Kumbhani, E. Siwila-Sackman, et al., Teriparatide (PTH 1-34) treatment increases peripheral hematopoietic stem cells in postmenopausal women, J. Bone Miner. Res. 29 (6) (2014) 1380–1386.
[60] O. Gurevitch, S. Khitrin, A. Valitov, S. Slavin, Osteoporosis of hematologic etiology, Exp. Hematol. 35 (1) (2007) 128–136.
[61] Kieran Steer, Mariya Stavnichuk, Martin Morris, Svetlana V. Komarova, Bone health in patients with hematopoietic disorders of bone marrow origin: systematic review and meta-analysis, J. Bone Miner. Res. 32 (4) (2017) 731–742.
[62] S. Singbrant, M.R. Russell, T. Jovic, et al., Erythropoietin couples erythropoiesis, B-lymphopoiesis, and bone homeostasis within the bone marrow microenvironment, Blood 117 (21) (2011) 5631–5642.
[63] S. Hiram-Bab, T. Liron, N. Deshet-Unger, et al., Erythropoietin directly stimulates osteoclast precursors and induces bone loss, FASEB J. 29 (5) (2015) 1890–1900.
[64] S.M. Cain, Oxygen delivery and uptake in dogs during anemic and hypoxic hypoxia, J. Appl. Physiol. 42 (2) (1977) 228–234.
[65] H.G. Klein, D.R. Spahn, J.L. Carson, Red blood cell transfusion in clinical practice, Lancet 370 (9585) (2007) 415–426.
[66] H. Fujimoto, K. Fujimoto, A. Ueda, M. Ohata, Hypoxemia is a risk factor for bone mass loss, J. Bone Miner. Metab. 17 (3) (1999) 211–216.
[67] G.T. Ferguson, P.M. Calverley, J.A. Anderson, et al., Prevalence and progression of osteoporosis in patients with COPD: results from the towards a revolution in COPD health study, CHEST J. 136 (6) (2009) 1456–1465.
[68] D.R. Silva, A.C. Coelho, A. Dumke, et al., Osteoporosis prevalence and associated factors in patients with COPD: a cross-sectional study, Respir. Care 56 (7) (2011) 961–968.
[69] L. Graat-Verboom, B.E. van den Borne, F.W. Smeenk, M.A. Spruit, E.F. Wouters, Osteoporosis in COPD outpatients based on bone mineral density and vertebral fractures, J. Bone Miner. Res. 26 (3) (2011) 561–568.
[70] U.A. Gurkan, O. Akkus, The mechanical environment of bone marrow: a review, Ann. Biomed. Eng. 36 (12) (2008) 1978–1991.
[71] D. Dickerson, E. Sander, E. Nauman, Modeling the mechanical consequences of vibratory loading in the vertebral body: microscale effects, Biomech. Model. Mechanobiol. 7 (3) (2008) 191–202.

[72] N.A. Zakai, R. Katz, C. Hirsch, et al., A prospective study of anemia status, hemoglobin concentration, and mortality in an elderly cohort: the cardiovascular health study, Arch. Intern. Med. 165 (19) (2005) 2214–2220.
[73] J.C. Silva, Z.V. de Moraes, C. Silva, et al., Understanding red blood cell parameters in the context of the frailty phenotype: interpretations of the FIBRA (Frailty in Brazilian Seniors) study, Arch. Gerontol. Geriatr. 59 (3) (2014) 636–641.
[74] B.W. Penninx, M. Pahor, M. Cesari, et al., Anemia is associated with disability and decreased physical performance and muscle strength in the elderly, J. Am. Geriatr. Soc. 52 (5) (2004) 719–724.
[75] M.S. Duh, S.H. Mody, P. Lefebvre, R.C. Woodman, S. Buteau, C.T. Viech, Anaemia and the risk of injurious falls in a community-dwelling elderly population, Drugs Aging 25 (4) (2008) 325–334.
[76] D. Mellström, O. Johnell, Ö. Ljunggren, et al., Free testosterone is an independent predictor of BMD and prevalent fractures in elderly men: MrOS Sweden, J. Bone Miner. Res. 21 (4) (2006) 529–535.
[77] H.A. Fink, S.K. Ewing, K.E. Ensrud, et al., Association of testosterone and estradiol deficiency with osteoporosis and rapid bone loss in older men, J. Clin. Endocrinol. Metab. 91 (10) (2006) 3908–3915.
[78] L. Ferrucci, M. Maggio, S. Bandinelli, et al., Low testosterone levels and the risk of anemia in older men and women, Arch. Intern. Med. 166 (13) (2006) 1380–1388.
[79] J.W. Eschbach, J.W. Adamson, Anemia of end-stage renal disease (ESRD), Kidney Int. 28 (1) (1985) 1–5.
[80] T.L. Nickolas, M.B. Leonard, E. Shane, Chronic kidney disease and bone fracture: a growing concern, Kidney Int. 74 (6) (2008) 721–731.
[81] K. Redlich, J.S. Smolen, Inflammatory bone loss: pathogenesis and therapeutic intervention, Nat. Rev. Drug Discov. 11 (3) (2012) 234.
[82] R. Hardy, M. Cooper, Bone loss in inflammatory disorders, J. Endocrinol. 201 (3) (2009) 309–320.
[83] V. Breuil, M. Ticchioni, J. Testa, et al., Immune changes in post-menopausal osteoporosis: the Immunos study, Osteoporos. Int. 21 (5) (2010) 805–814.