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Low Hemoglobin Is Associated With Low Bone Mineral Density and High Risk of Bone Fracture in Male Adults: A Retrospective Medical Record Review Study

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Abstract

The aim of this study was to examine the association between serum hemoglobin level, bone mineral density, and fracture risks based on the estimated score of the Fracture Risk Assessment Tool (FRAX) in Asian male adults. The medical records of 662 male patients who underwent health examinations at a regional teaching hospital in southern Taiwan were reviewed. The medical history, demographic characteristics, clinical laboratory results, and bone mineral density of the patients were ascertained from their medical records. Simple and multiple linear regression analyses were conducted to evaluate the association of hemoglobin levels with bone mineral density, the 10-year risk of hip fracture, and the 10-year risk of major osteoporotic fracture (clinical spine, forearm, hip, or shoulder fracture) as assessed by FRAX. The mean age of the patients was 53.1 years. Results from simple linear regression analysis indicated that hemoglobin was positively associated with bone mineral density but inversely associated with both hip fracture risk and major osteoporotic fracture risk. Similar results were obtained when potential confounding variables were adjusted using multiple linear regression analysis. Low serum hemoglobin levels might be an important indicator for predicting bone mineral loss and the risk of both major osteoporotic fracture and hip fracture in male patients. Bone mineral density should be closely monitored in patients receiving treatment for anemia.

Keywords

hemoglobin, bone mineral density, fracture, FRAX

A decrease in bone mass, as measured by bone mineral density (BMD) loss, is an important public health problem because of its consequences of bone fractures, subsequent morbidity and disability, as well as social costs (Bliuc et al., 2015). The causes and prevalence of osteoporosis in men are different from those in women. While women experience pronounced bone loss during perimenopause and after menopause, bone loss is observed throughout life in men (Warming, Hassager, & Christiansen, 2002). Although secondary osteoporosis is common in both men and women, three causes are of particular concern in men, namely, alcoholism, chronic glucocorticoid therapy, and hormonal suppressive therapy for the treatment of prostate cancer (Khosla, Amin, & Orwoll, 2008).

Previous studies have reported that the prevalence of osteoporosis in men was 1% in the United Kingdom, 4% in Japan, 3% in Canada, and 8% in France (Wade, Strader, Fitzpatrick, Anthony, & O'Malley, 2014). Based on an analysis of the Taiwan's population-based National Health Insurance claims database, the prevalence of osteoporosis for males in 2013 was 1,400 and 6,227 per 100,000 persons in those aged 60–69 years and ≥80 years, respectively (Wang et al., 2017). A nationwide osteoporosis survey conducted in Taiwan reported that the prevalence of male osteoporosis was 9.7%, and the factors associated with male osteoporosis were aging, lower body weight, and a history of fracture (Ko et al., 2018). In Taiwan, osteoporosis in men is still underrecognized and undertreated. Wang et al. (2017) estimated that in men with osteoporosis aged 70–79 and ≥80 years, only approximately 23% of them were under anti-osteoporosis treatment in 2012 and 2013, a proportion about half of that in women.

Previous research reported that the mortality associated with hip fracture in males was two to three times greater than that in females (Heidari et al., 2017). A study conducted on hip fracture in nine Asian Federation of Osteoporosis Societies members found that the incidence rate of hip fracture in males was higher in Taiwan than that in China, Hong Kong, India, Japan, South Korea, Malaysia, Singapore, and Thailand, across all age groups from 50 to over 80 years. (Cheung et al., 2018). Wang et al. (2017) reported that the prevalence of hip fracture was 2,675 per 100,000 men aged ≥80 years.

The BMD value, acquired with dual-energy X-ray absorptiometry (DXA), is an estimation of the quantity of bone mass (Kanis et al., 2005). A low BMD value is inversely proportional to an increase in the risk of fracture (Kanis et al., 2008). To improve the prediction of 10-year hip and major osteoporotic fracture risk (hip, clinical spine, distal forearm, and proximal humerus), a country-specific Fracture Risk Assessment Tool (FRAX) was developed by the University of Sheffield, United Kingdom, taking into account an individual's risk factor profile (Kanis et al., 2007). The National Osteoporosis Foundation (NOF) defined a patient as high risk if the FRAX score was ≥20% for major osteoporotic fractures or ≥3% for a hip fracture (Unnanuntana, Gladnick, Donnelly, & Lane, 2010).

Anemia is a common and multifactorial condition with an estimated prevalence of 5.6% in the U.S. population (Le, 2016). A low hemoglobin level is associated with poor general health and adverse outcomes in a wide range of diseases (Patel, 2008). It was suggested that hypoxia induced by anemia could lead to bone mass loss (Fujimoto, Fujimoto, Ueda, & Ohata, 1999). Chronic blood loss was found to be associated with the development of osteoporosis in an animal study (Gurevitch, Khitrin, Valitov, & Slavin, 2007). A study in older postmenopausal women reported that anemia was an independent risk factor for low BMD (Korkmaz et al., 2012). Rutten, Franssen, Spruit, and Wouters (2013) also reported that anemia was a significant independent determinant for lower BMD in patients with chronic obstructive pulmonary disease. A study on 358 Italian adults aged 75 years or older reported that hemoglobin levels were independently and significantly associated with ultrasound-derived T-score, based on regression models that adjusted for age, sex, protein consumption, body mass index (BMI), and physical activity (Laudisio, Marzetti, Pagano, Bernabei, & Zuccalà, 2009). However, the study did not report sex-stratified results. Another study on older Italian adults reported that hemoglobin levels were inversely and independently associated with peripheral quantitative computerized tomography bone measures of total bone density and cortical bone density in men (Cesari et al., 2005). Moreover, according to a cross-sectional study based on data from the Korea National Health and Nutrition Examination Survey, hemoglobin level was significantly associated with femoral neck and lumbar spine BMD in men (Oh, Moon, & Cho, 2017). Nevertheless, a prospective longitudinal study in community-dwelling older adults revealed no significant associations between hemoglobin level and total hip or lumbar spine BMD in men (Valderrábano et al., 2019). The aim of the present study was to explore the association of hemoglobin levels with BMD and the 10-year probability of hip fracture or major osteoporotic fracture in men between 20 and 70 years of age.

Materials and Methods

Participants

Male patients who had received health examinations at the center of preventive medicine of a regional teaching hospital in southern Taiwan between June 2014 and December 2017 were retrospectively identified from the computerized medical record system. Health history (by interview or questionnaire), basic characteristics, and laboratory data, including renal function (estimated glomerular filtration rate, eGFR; eGFR = $\text{creatinine}^{-1.154} \times 186 \times \text{age}^{-0.203}$), were recorded. Patients diagnosed with diabetes, hyperparathyroidism, or hypercortisolism, or who had a

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Table 1. Demographic and Clinical Characteristics of Study Participants.

Variable	Total $N = 662$	Normal $n = 263$	Osteopenia $n = 350$	Osteoporosis $n = 49$	p value
Age (years)	53.1 (10.1)	50.6 (10.2)	54.3 (9.7)	57.4 (9.4)	<.001
Height (cm)	168.5 (6.4)	170.2 (6.4)	167.6 (6.2)	165.9 (5.1)	<.001
Weight (kg)	70.6 (10.4)	74.8 (10.6)	68.6 (9.1)	62.5 (8.6)	<.001
Body mass index (kg/m^2)	24.84 (3.19)	25.79 (3.32)	24.41 (2.84)	22.77 (3.31)	<.001
Vegetarian dietary habit, *n* (%)	126 (19.0)	41 (15.6)	74 (21.1)	49 (22.4)	.182
Coffee or tea consumption, *n* (%)	621 (93.8)	250 (95.1)	326 (93.1)	45 (91.8)	.552
Smoking, *n* (%)	206 (31.1)	84 (31.9)	103 (29.4)	19 (38.8)	.391
Hemoglobin (gm/dl)	15.57 (1.82)	15.78 (1.74)	15.49 (1.88)	15.01 (1.68)	.012
eGFR (ml/min/1.73 m^2)	79.31 (15.44)	79.05 (14.98)	79.50 (15.09)	79.33 (20.06)	.940
BMD (g/cm^2)					
Lumbar spine	0.997 (0.145)	1.098 (0.111)	0.953 (0.113)	0.775 (0.095)	<.001
Right hip (neck area)	0.750 (0.126)	0.858 (0.010)	0.695 (0.073)	0.561 (0.067)	<.001
Right hip (total area)	0.875 (0.144)	0.986 (0.110)	0.823 (0.100)	0.659 (0.110)	<.001
Left hip (neck area)	0.756 (0.128)	0.865 (0.103)	0.700 (0.715)	0.563 (0.103)	<.001
Left hip (total area)	0.866 (0.142)	0.978 (0.109)	0.814 (0.092)	0.644 (0.103)	<.001
T-score					
Lumbar spine	−0.3 (1.3)	0.6 (1.0)	−0.7 (0.9)	−2.4 (0.8)	<.001
Right hip (neck area)	−0.9 (1.0)	0.1 (0.8)	−1.3 (0.6)	−2.5 (0.5)	<.001
Right hip (total area)	−0.4 (1.0)	0.4 (0.7)	−0.7 (0.6)	−1.8 (0.7)	<.001
Left hip (neck area)	−0.8 (1.1)	0.1 (0.8)	−1.3 (0.6)	−2.5 (0.5)	<.001
Left hip (total area)	−0.4 (1.0)	0.3 (0.7)	−0.8 (0.6)	−2.0 (0.6)	<.001
FRAX (%)					
Right MOF	3.7 (2.4)	2.3 (1.1)	4.1 (2.0)	7.9 (3.8)	<.001
Right HF	1.1 (1.5)	0.3 (0.4)	1.3 (1.1)	4.3 (2.8)	<.001
Left MOF	3.6 (2.4)	2.3 (1.1)	4.0 (2.0)	7.8 (3.7)	<.001
Left HF	1.1 (1.5)	0.3 (0.4)	1.2 (1.1)	4.3 (3.1)	<.001

Note. Data were expressed as mean (standard deviation) unless otherwise specified. BMD = bone mineral density; eGFR = estimated glomerular filtration rate; FRAX = Fracture Risk Assessment Tool; HF = hip fracture; MOF = major osteoporotic fracture.

history of vertebral fracture or total hip replacement were excluded. This study protocol was approved by the Institutional Review Board of the Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation (No. B10703014).

Bone Mineral Density

BMD was assessed by DXA using the Discovery Wi DXA system (Hologic Inc., Boston, MA, USA). Absolute BMD values and T-scores were calculated for all patients. The measured areas included the lumbar spine and the hip areas. The same densitometer was used for all patients to ensure consistent comparisons. All measurements were carried out by three technicians who have obtained formal certification from the International Society for Clinical Densitometry.

FRAX Calculations

The 10-year probability (expressed as a percentage) of hip fracture and major osteoporotic fracture were calculated for all patients. All fracture risk factors included in the FRAX (age, sex, weight, height, previous fracture history, parental hip fracture history, current smoking, glucocorticoid usage, rheumatoid arthritis, secondary causes of osteoporosis, and alcohol intake of three or more units/day) were assessed, as well as right and left hip femoral neck BMD data. Secondary causes of osteoporosis assessed in this study included type I diabetes mellitus, hyperthyroidism, osteogenesis imperfecta, chronic liver disease, and chronic malnutrition. The country-specific (Taiwan) FRAX algorithm (Web Version 4.0) was utilized and calculated using an online tool available at https://www.sheffield.ac.uk/FRAX/tool.aspx?country=26.

Statistical Analysis

Results are expressed as mean and standard deviation (*SD*) or frequency (%). Differences in means and frequency distribution of the variables in Table 1 were compared using t test and χ^2 test, respectively. Simple linear regression analysis was performed for BMD (including lumbar spine, right femoral neck, right total hip, left femoral neck, and

Table 2. Simple Linear Regression Analysis of Hemoglobin Level With Bone Mineral Density, T-Score, and Fracture Risk.

Variable	β	95% CI	Standardized β	*p* value
BMD (g/cm^2)				
Lumbar spine	0.007	[0.001, 0.013]	0.085	.029
Right femoral neck	0.010	[0.005, 0.015]	0.147	<.001
Right total hip	0.009	[0.003, 0.015]	0.116	.003
Left femoral neck	0.007	[0.001, 0.012]	0.097	.013
Left total hip	0.008	[0.002, 0.014]	0.104	.007
T-score				
Lumbar spine	0.062	[0.009, 0.115]	0.089	.021
Right femoral neck	0.084	[0.041, 0.127]	0.148	<.001
Right total hip	0.063	[0.023, 0.103]	0.119	.002
Left femoral neck	0.058	[0.014, 0.102]	0.100	.010
Left total hip	0.057	[0.017, 0.097]	0.109	.005
FRAX (%)				
Right MOF	−0.230	[−0.330, −0.130]	−0.173	<.001
Right HF	−0.152	[−0.215, −0.090]	−0.183	<.001
Left MOF	−0.151	[−0.251, −0.052]	−0.115	.003
Left HF	−0.104	[−0.169, −0.040]	−0.123	.002

Note. BMD = bone mineral density; CI = confidence interval; FRAX = Fracture Risk Assessment Tool; HF = hip fracture; MOF = major osteoporotic fracture.

left total hip), T-score (including lumbar spine, right femoral neck, right total hip, left femoral neck, and left total hip), and FRAX (including left and right major osteoporotic fracture and hip fracture) with hemoglobin as the independent variable. In addition, multiple linear regression analyses were conducted to assess the independent association between hemoglobin and the four fracture risk variables, adjusting for age, BMI, eGFR, vegetarian dietary habit, coffee or tea consumption, and smoking. All statistical analyses were performed using the PASW Statistics for Windows, Version 18.0 (SPSS Inc., Chicago, IL).

Results

Patient Characteristics

A total of 764 male subjects received DXA studies during this study period. After excluding cases with major causes for osteoporosis, 662 subjects were included in the final analysis. Demographic and clinical characteristics of the subjects are presented in Table 1. The mean age of the study population was 53.1 years (*SD* 10.1 years) with a range from 30.0 to 70.4 years.

Bone Mineral Density and FRAX

Mean lumbar spine BMD value on DXA was 0.997 (*SD* 0.145 g/cm^2). The mean BMD value was 0.750 (*SD* 0.126 g/cm^2) for the right femoral neck, 0.875 (*SD* 0.144 g/cm^2) for the total right hip, 0.756 (*SD* 0.128 g/cm^2) for the left femoral neck, and 0.866 (*SD* 0.142 g/cm^2) for the total left hip. The major osteoporotic fracture risk was 3.7% (*SD* 2.4%) for the right hip and 3.6% (*SD* 2.4%) for the left hip. The hip fracture risk was 1.1% (*SD* 1.5%) for the right hip and 1.1% (*SD* 1.5%) for the left hip (Table 1).

Association of Hemoglobin With BMD and FRAX

Serum hemoglobin level showed a significant association with both the BMD value and the FRAX score. Simple linear regression analysis showed that the hemoglobin level was significantly associated with BMD value and T-score in the lumbar spine and right and left hip (both the femoral neck area and total area) and was inversely and significantly associated with the FRAX score (Table 2).

The results of the multiple regression analyses of the four fracture risk variables adjusting for potential confounders are reported in Table 3. When age and BMI were included in the model, only the risk of right hip fracture and that of major osteoporotic fracture were significantly associated with hemoglobin (Model 1). The inclusion of additional potential confounding variables (Model 2), including eGFR, vegetarian dietary habit, coffee or tea consumption, and smoking, did not materially change the results of Model 1.

Discussion

In the present study, the association of hemoglobin level with BMD value and the risk of osteoporotic fracture was analyzed. A low hemoglobin level was found to be

Table 3. Multiple Linear Regression Analyses of Hemoglobin Level and Fracture Risk.

Fracture risk variable	β	95% CI	standardized β	*p* value
Model 1: adjusted for age and body mass index				
Right MOF	−0.130	[−0.203, −0.057]	−0.098	<.001
Right HF	−0.096	[−0.151, −0.041]	−0.115	.001
Left MOF	−0.050	[−0.124, 0.023]	−0.038	.180
Left HF	−0.048	[−0.105, 0.010]	−0.056	.104
Model 2: adjusted for age, body mass index, eGFR, vegetarian dietary habit, coffee or tea consumption, and smoking				
Right MOF	−0.124	[−0.197, −0.051]	−0.093	.001
Right HF	−0.092	[−0.147, −0.037]	−0.110	.001
Left MOF	−0.048	[−0.122, 0.026]	−0.037	.204
Left HF	−0.045	[−0.103, 0.012]	−0.053	.124

Note. CI = confidence interval; eGFR = estimated glomerular filtration rate; HF = hip fracture; MOF = major osteoporotic fracture.

significantly and independently associated with decreased BMD. It was inversely associated with the 10-year probability of hip fracture and major osteoporotic fracture as measured by FRAX.

Our findings suggested that a diminished hemoglobin level was associated with bone mineral loss, which could lead to an increased risk of osteoporotic fracture. Previous research suggested that chronic hypoxia due to long-term anemia could interfere with bone metabolism (Dimai, Domej, Leb, & Lau, 2001; Fujimoto et al., 1999). When serum hemoglobin levels are decreased, the oxygen supply to the tissue and organs is reduced. Oxidative stress and extracellular acidification could develop under hypoxic conditions and influence bone formation and remodeling. Moreover, inflammation has been suggested to play an important role in both the development of anemia and osteoporosis. Autoimmune diseases, chronic infection, and chronic pulmonary diseases were associated with the anemia of inflammation. The proinflammatory cytokine, interleukin-6, and the ferroportin–hepcidin axis were thought to be implicated in the anemia of inflammation (Fraenkel, 2017). Various inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease were also found to be associated with increased bone resorption and decreased bone formation (Amarasekara, Yu, & Rho, 2015; Hardy & Cooper, 2009). Another hypothesis suggested that diseases, such as sickle cell anemia (Sarrai, Duroseau, D'Augustine, Moktan, & Bellevue, 2007) and thalassemia (Voskaridou & Terpos, 2008), that continuously affect hematopoietic function might increase the number of hematopoietic cells. These cells, which include hematopoietic growth factors and osteoclasts, could stimulate bone resorption.

The present study has several limitations. First, this was a cross-sectional study based on a review of medical records, and therefore a causal relationship could not be established. Second, serum markers, such as ferritin, were not available for the identification of the type of anemia. Third, although a number of potential confounding variables were adjusted in the multiple linear regression models, the presence of other unmeasured ones could not be completely ruled out.

Despite these limitations, there are also important strengths of this study. Studies on male osteoporosis are fewer than those on female osteoporosis, and studies on the association between anemia and BMD and osteoporotic fractures are even fewer. Moreover, this study focused on not only the association between hemoglobin level and BMD in male patients but also the risk of future fracture based on FRAX. Findings from the multiple regression models, adjusting for potential confounding variables, indicated that hemoglobin levels were only significantly associated with the risk for hip fracture and major osteoporotic fracture of the right side of the body. Since most Taiwanese people are right-hand dominant and assessing only the right side of the body is the routine clinical practice for BMD measurement in Taiwan, right hip measurement should be used for predicting fracture risks based on hemoglobin levels in male adults.

Conclusions

Serum hemoglobin levels could be used as an indicator of emerging bone mineral loss and for increasing clinicians' awareness of the potential for the development of osteoporotic fractures in male adults. BMD should be closely monitored in patients receiving treatment for anemia. Proactive therapy to reduce the risk of osteoporosis should be provided, where appropriate.

Authors' Note

This research was reviewed and approved by the Institutional Review Board of the Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation (No. B10703014).

Declaration of Conflicting Interests

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