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Changes in Hematological Markers Associated With Bone Turnover in Male Subjects

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Abstract: **We assessed the relationship of hemoglobin (Hb) levels with bone mineral density (BMD) by detected dual-energy X-ray absorptiometric (DXA) method in a large sample of men. The study conducted with 269 men, who were screened for osteopenia or osteoporosis by DXA. Patients categorized with osteopenia or osteoporosis (T score<-1.0 SD) were grouped as having low bone mass (LBM).Anemic patients were older and had significantly higher ratio of diabetes. In the study cohorts Anemic patients (n = 45) when compared with normal Hb subjects (n = 224), they had significantly higher ratio of patients with low bone mass (64.4% vs. 46.9%; *p* = 0.031, respectively). We found no statistically significant difference of femur T-score, femur BMD, femur Z-score, spinal T-score, spinal BMD and spinal Z-score between groups. There were significant correlations between Hb values and spine T- score, spine BMD values of the anemic patients in bivariate correlation analysis (*r* = 0.319; *p* = 0.033, *r* = 0.310; *p* = 0.038, respectively). In conclusion, we have shown that anemic men had significantly high prevalence of subjects with low bone mass. This means that anemia has a rule as a risk factor in changes of bone turnover leading to decrease bone density.**

Keywords: **Bone turnover- osteopenia- osteoporosis-hematology.**

1. INTRODUCTION

Many factors play a role in the etiology of osteoporosis. Aging, low body weight and lack of exercise are highly-risk factors for low bone density [1-3].Identify risk factors that increase the incidence of osteoporosis in the elderly age is important for their optimum management. Anemia represents a common condition in older populations, which prevalence has been found in approximately 13% of persons older than 70 years[4]. Additionally, hypoxia has been determined to be a risk factor for osteoporosis in animal and human and animal models [5-7].

Many studies have been conducted to find out the relationship between anemia, mostly sickle cell anemia (SCA), and secondary osteoporosis. All these studies confirmed the high prevalence of osteopenia and osteoporosis in patients with anemia [8,9].Four consecutive studies conducted at King Fahd University Hospital, Al Khobar, Saudi Arabia by Sadat-Ali et al. between 2006 and 2010 to discuss the relationship between SCA and low bone mass [10-13].

The relationship between hemoglobin levels and bone mineral density has been studied by three researches [14-16].Firstly, Cesari et al. (2005)concluded that anemia and low hemoglobin levels are negatively and independently associated with bone mass and density mesured by peripheral quantitative computerized tomography (pQCT) scan of the right calf and hemoglobin levels in men and women of Italian population based on data from the ‘‘Invecchiare in Chianti’’ (Aging in the Chianti area, In CHIANTI) study [14].Similarly, Laudisio et al. (2009) have found that Haemoglobin is independently associated with all ultrasound- derived (UD)-BMD parameters in all 358 subjects aged >75 years living in Tuscania [15]. In the latest study, Korkmaz et al. (2012) found that have shown that anemic postmenopausal Turkish women had significantly lower bone mass detected by dual-energy X-ray absorptiometric (DXA) method of the femur or spine [16].

Osteoporosis is common in Saudi Arabia and the burden of management in an aging population will increase in coming decades [17]. Osteoporosis and osteopenia occurs with high frequency in Saudi men [18,19]. n the current study we will explore the relationship between anemiaand bone health for men older than 50 years in Saudi's population. To our best knowledge, this relationship has not been studied yet. We aimed to make a comparison of bone health in anemic patients and healthy subjects with normal Hb values. The patients will be screened for osteopenia or osteoporosis.

2. SUBJECTS AND METHODS

The current study was carried out in the Center of Excellence for Osteoporosis Research, King Fahd Medical Research Center, King Abdul-Aziz University, Jeddah, Saudi Arabia. A 300 men above 50 years randomly selected during 2014, healthy and those with low BMD, subjected to study after the signature on consent form.In the final analytic sample, 269 men (with a mean age of 61.8 ± 7.8 years) after exclusions. Exclusion diseases were known chronic infectious or inflammatory disease, thyroid disease, and severe liver or renal disease. In addition, DXA scan results of patients had any metal in their femur and spine, known to affect BMD, were also excluded. The scores were reported from their screening records for osteopenia or osteoporosis for the cortical BMD (femoral neck) and the trabecular BMD (L1–L4 spine) values detected by dual-energy X-ray absorptiometry (DXA) methodusing a GE Lunar iDXA (ME+200672). BMD results for the femur neck and lumbar spinal were classified into 3 groups according to World Health Organization criteria: normal (T score> -1.0 SD), osteopenia (T score -1.0 to -2.5 SD) and osteoporosis (T score< -2.5 SD). Patients with osteopenia or osteoporosis (T score<-1.0 SD) were grouped as having low bone mass (LBM). Body mass index (BMI) computed as weight divided by height squared (kg/m^2).

Blood samples were collected between 8:00 am and 11:00 am after an overnight fast (preferred). Serum samples were stored at -20 ^oC until analysis. Complete blood count (CBC), serum calcium (mg/dl),serum phosphorus (mg/dl), Serum alkaline phosphatase (U/L),and serum level of 25-hydroxy vitamin D (ng/ml) were measured using standard laboratory procedures.Anemia defined by the World Health Organization (WHO) criteria as hemoglobin levels lower than 13 g/dl for female participants [20].

Values were presented as mean ± standard deviation. Student's *t*-test was used to compare continuous variables. Categorical data were compared with Chi-square analysis. Firstly, correlations between Hb values and femur t score, femur BMD, spine t score and spine BMD values of Anemic patients were investigated by bivariate correlation analysis (Pearson). Afterwards, multivariate logistic regression analysis with enter method was used to assess the independent association of low bone mass (femur BMD or spine BMD) with the presence of anemia. Significant parameters obtained from comparisons of groups which composed femur BMD or spine BMD values included to logistic regression analysis. Statistical analyses were carried out using SPSS 22.0 for Mac, and a p-value < 0.05 was considered significant.

3. RESULTS

In total, 269 subjects (average age of 61.8 ± 7.8 years, BMI of 29.6 ± 4.9 kg/m^2) were analyzed after exclusions. Exclusion diseases were known chronic infectious or inflammatory disease, thyroid disease, and severe liver or renal disease. In addition, DXA scan results of patients had any metal in their femur and spine, known to affect BMD, were also excluded. Thirty-nine percent of study populations were Saudi and 61% were Non-Saudi. Demographic, clinical, and laboratory variables of the subjects with normal and low hemoglobin levels were shown in (**Table 1**). Anemic patients were older and had significantly higher ratio of diabetes. As expected, anemic patients at examination (n = 45) when compared with normal Hb subjects (n = 224), they had significantly higher ratio of patients with low bone mass (64.4% vs. 46.9%; p = 0.031, respectively). We found no statistically significant difference of femur T-score, femur BMD, femur Z-score, spinal T-score, spinal BMD and spinal Z-score between groups (**Table 1**). Additionally, the ratio of subjects with spine and femur LBM were high in anemic patients but not significant (28.9% vs. 23.2%, 53.3% vs. 43.3%, respectively).

Serum 25-OH Vitamin D means contribute insufficiency values and not significant between groups (32.8 ± 18.3 vs. 31.1 ± 16.9 nmol/L, respectively). Also, Serum calcium, alkaline phosphatase, smoking status ratio, physical activity level ratio and hypertensive ratio with no difference (2.41 ± 0.13 vs. 2.42 ± 0.22 mmol/L, 78 ± 30.1 vs. 86 ± 42.2 U/L, 13.3% vs. 16.1%, 80% vs. 74.1% for sedentary to low; 20% vs. 25.9% for moderate to high, 44.4% vs. 41.5%, respectively). Serum phosphorus values were slightly high with no statically difference between groups (1.57 ± 0.7 vs. 1.78 ± 1.21 mmol/L,

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respectively). The ratio of diabetic patients was significantly higher in anemic group (71.1% vs. 44.6%; $p \leq 0.001$, respectively) (**Table 1**).

Table 1: Comparison of demographic, clinical and laboratory characteristics of groups according to hemoglobin value

	Anemic patients (n = 45)	Subjects with normal hemoglobin (n = 224)	*P* value
Age (year)	64.1 ± 7.0	61.4 ± 7.9	≤ 0.001
Body mass index (kg/m^2)	28 ± 5.3	29.8 ± 4.8	NS
Serum 25-OH Vitamin D (nmol/L)	32.8 ± 18.3	31.1 ± 16.9	NS
Serum calcium (mmol/L)	2.41 ± 0.13	2.42 ± 0.22	NS
Serum phosphorus (mmol/L)	1.57 ± 0.7	1.78 ± 1.21	NS
Serum alkaline phosphatase (U/L)	78 ± 30.1	86 ± 42.2	NS
Hemoglobin (g/dL)	12.0 ± 0.87	15.1 ± 1.16	≤ 0.001
MCV (fL)	81.3 ± 10.0	88.2 ± 5.4	≤ 0.001
Spine BMD (g/cm^2)	1.1 ± 0.16	1.1 ± 0.16	NS
Spine T-score	- 0.26 ± 1.40	- 0.26 ± 1.34	NS
Spine Z-score	0.31 ± 1.42	0.00 ± 1.29	NS
Femur BMD (g/cm^2)	0.89 ± 0.14	0.92 ± 0.14	NS
Femur T-score	- 1.13 ± 1.04	- 0.88 ± 1.09	NS
Femur Z-score	0.11 ± 0.98	0.24 ± 1.06	NS
Low bone mass of spine (%)	28.9	23.2	NS
Low bone mass of femur (%)	53.3	43.3	NS
LBM of spine Osteopenia (%) Osteoporosis (%)	22.2 6.7	18.3 4.9	NS NS
LBM femur Osteopenia (%) Osteoporosis (%)	48.9 4.4	36.6 6.7	NS NS
Patients of LBM (%)	64.4	46.9	0.031
Smoking status (%)	13.3	16.1	NS
Physical activity level (%) Sedentary-Low Moderate-High	80 20	74.1 25.9	NS NS
Diabetic (%)	71.1	44.6	≤ 0.001
Hypertensive (%)	44.4	41.5	NS

Moreover, study population was divided into two groups as normal and group with low bone mass according to spine BMD and femur BMD values. When compared subjects with normal spine BMD and low spine BMD, low spine BMD group had lower BMI, femur T-score and ratio of diabetic patients (27.3 ± 4.8 vs. 30.3 ± 4.7 kg/m^2; $p \leq 0.001$, -1.73 ± 1.03 vs. -0.67 ± 0.98;$p \leq 0.001$, 35.4% vs. 53.4%; $p = 0.011$, respectively). However, their ratio of subjects with femur LBM and ALP value were higher than value of normal spine BMD group (78.5% vs. 34.5%; $p \leq 0.001$, 98 ± 61 vs. 79 ± 27 U/L; $p = 0.019$, respectively).

Also, when compared subjects with normal femur BMD (n = 124), and low femur BMD (n = 121), low femur BMD group had lower BMI and spine T-score (28 ± 4.6 vs. 30.9 ± 4.8kg/m^2; $p \leq 0.001$, -0.78 ± 1.37 vs. 0.16 ± 1.17; $p \leq 0.001$, respectively), but higher age and ratio of subjects with spine LBM (63.0 ± 7.7 vs. 60.9 ± 7.8years; $p = 0.024$; 42.1% vs. 9.5%; $p \leq 0.001$, respectively). Additionally, ratio of anemic patients was high but not significant in low spine and femur BMD groups (20% vs. 15.7%; 19.8 vs. 14.2, respectively).

There were significant correlations between Hb values and spine T- score, spine BMD values of the anemic patients in bivariate correlation analysis ($r = 0.319$; $p = 0.033$, $r = 0.310$; $p = 0.038$, respectively) (**Fig. 1**), (**Fig. 2**).

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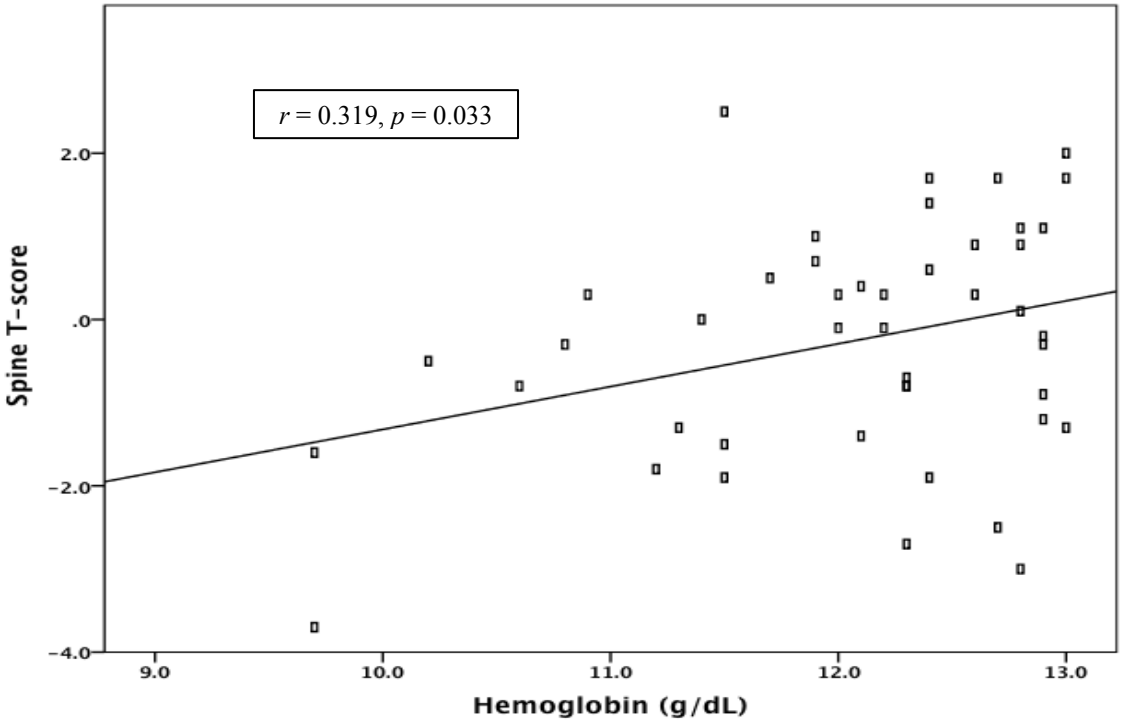

Fig. 1: The correlations between hemoglobin levels and spine T- scores in anemic patients (n = 45).

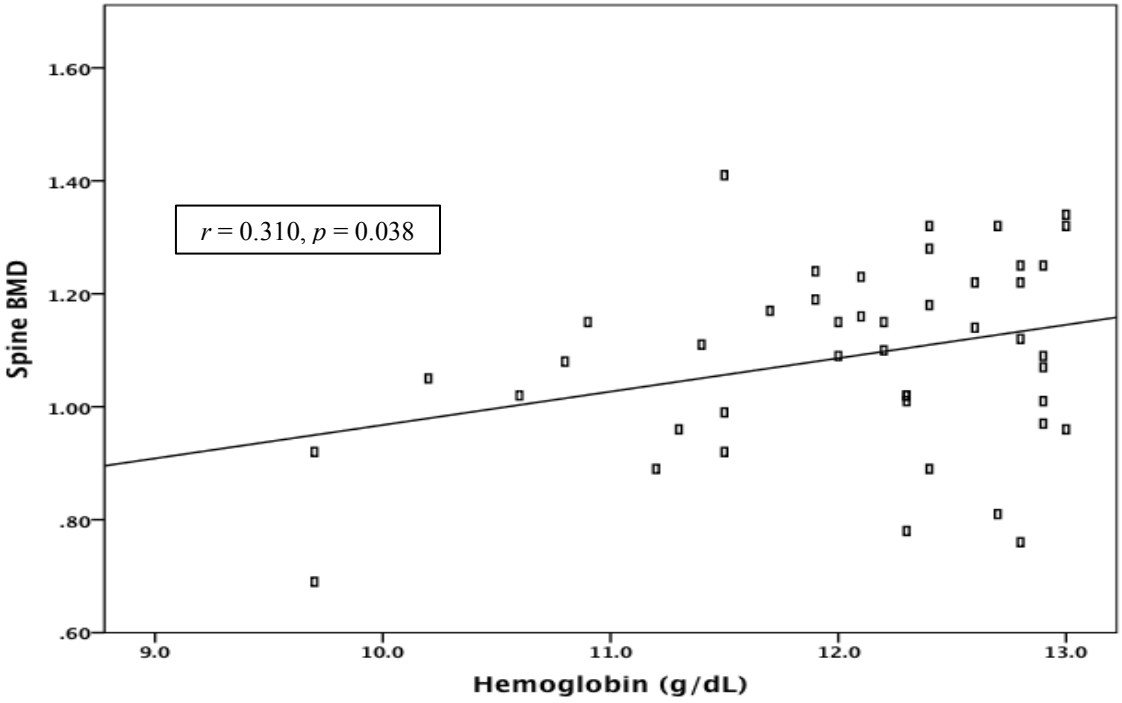

Fig. 2: The correlations between hemoglobin levels and spineBMD in anemic patients (n = 45).

Logistic regression analysis was performed to examine the independent association between Hb levels and low bone mass according to femur and spine BMD. Other parameters, which are obtained from comparisons of BMD groups, were included in logistic regression analysis (**Table2**). Body mass index and diabetes were significant as Independent predictors of low bone mass for spine (OR=0.857; $p \leq 0.001$, OR= 2.373; p =0.009, respectively) while age and Body mass index were significant as Independent predictors of low bone mass for femur (OR = 1.037; $p = 0.025$, OR = 0.883; $p \leq 0.001$, respectively) in study population.

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Table 2: Independent predictors of low bone mass according to spine or femur BMD values.

	OR	95% confidence interval		*P* value
		lower	upper	
Independent predictors of low bone mass for spine				
Age	0.987	0.947	1.028	0.531
Body mass index	0.857	0.799	0.920	≤ 0.001
Anemia	1.470	0.664	3.254	0.342
Diabetes	2.373	1.246	4.519	0.009
Hypertension	1.029	0.547	1.935	0.930
Smoking status	0.886	0.393	1.994	0.769
Physical activity	0.632	0.304	1.313	0.219
Independent predictors of low bone mass for femur				
Age	1.025	0.990	1.060	0.156
Body mass index	0.883	0.833	0.935	≤ 0.001
Anemia	1.232	0.614	2.469	0.557
Diabetes	0.925	0.542	1.579	0.776
Hypertension	1.156	0.677	1.976	0.595
Smoking status	0.749	0.370	1.516	0.422
Physical activity	0.616	0.337	1.124	0.114

4. DISCUSSION

The results obtained from this study revealed that when compared the anemic subjects with normal Hb subjects, anemic patients had significant higher ratio of low bone mass. However, they were older and had significantly higher ratio of diabetes. Additionally, the ratio of subjects with femur and spine LBM were high in anemic patients but not significant. Similarly, number of anemic patients was higher in LBM groups according to femur and spine BMD but not significant. In bivariate correlation analysis, we found significant correlations between Hb values and spine T- score, spine BMD values of the anemic patients.

Previously, several studies have directly or indirectly suggested an association of hemoglobin levels and bone density in selected conditions, such as sickle-cell anemia, chronic inflammatory conditions or renal failure [2, 8, 21, 22]. Hypoxemia has been determined to be a risk factor for osteoporosis in clinical and experimental studies [5–7, 23]. Also, the relationship between hemoglobin levels and bone mineral density has been clarified in a population-based studies [14,15]. In general population only one study has been done to discuss this relationship in women [16].Therefore, our study was carried out among men, 224 subjects with normal Hb values and 45 anemic subjects, and bone status was estimated using DXA as trabecular and cortical at the lumbar spine and femoral neck.

In a large Italian cohort, the mean age of the sample population was 75±6.9 years Cesari et al. (2005) studied the relationship between bone mass and hemoglobin levels in 420 men and 530 postmenopausal women in this cohort (56 anemic females).They have found that hemoglobin levels and anemia were negatively and independently associated with bone mass and density assessed by pQCT scan of the right calf. Moreover, they have suggested that the bone loss associated with Hb levels occurs mainly in the cortical bone [14].However, the bone density measurements considered in their study were from tibial pQCT scans and, therefore, the generalization of their findings to the entire skeleton might be difficult. Likewise, Laudisio et al. (2009) have reported that there is a significant association of hemoglobin levels with ultrasound- derived (UD) T score, Z score and the stiffness index in all 358 subjects (173 females with normal Hb and 24

anemic females) aged 75+ living in Tuscania [15].Anemia was detected in 43/358 (12%) participants; osteoporosis was found in 153/358 (43%) participants. They searched for the hemoglobin cutoff levels that might best identify participants with osteoporosis. They have shown that hemoglobin levels < 14 g/dl in men and < 13 g/dl in women was the best predictor of osteoporosis in linear discriminate analysis. Also hemoglobin is independently associated with all UD-BMD parameters. In this way, linear discriminant analysis was used in separate models to identify hemoglobin levels which best predicted T score levels diagnostic of LBM (i.e., <−1.0) in men.On the contrary, in our study there was no specific hemoglobin cutoff level that might best identify participants with LBM.

Trabecular bone (lumbar spine, os calcis) has been shown to be more sensitive to metabolic changes than cortical bone (femoral neck, distal radius) [24]. Marked disparity between trabecular and cortical bone loss with age in healthy men. The fact that radial cortical bone mineral content falls much less rapidly than vertebral trabecular content with age and is also associated with surface area indicates that trabecular and cortical bone compartments may be independently modulated [25]. As there are essential differences in response to environmental factors (including hormonal or nutritional) between the trabecular (lumbar spine) and cortical (femoral neck) part of bone structure, it would seem more logical that measurements of both cortical and trabecular bone is necessary.

The study, which brought together screening the femoral neck (cortical) and lumber spine (trabecular) bones was conducted by Korkmaz et al. (2012)in Turkish postmenopausal women. They investigated the association of bone mineral density (BMD) by detected dual-energy X-ray absorptiometric (DXA) method and hemoglobin (Hb) levels in a large sample. A total of 371 women subjects (average age of 59.8±8.5 years, BMI of 31.5 ± 5.4 kg/m2) were analysed. Anemic patients at examination were 82. They have shown that anemic women had significantly lower bone mass of the femur or spine. Their analysis was restricted to postmenopausal women; therefore, their findings are not generalizable to men. Another limitation of this study is the lack of measurement of serum vitamin D level [16].

Overall results of this study are in agreement with the finding of previous studies in terms of a relationship between anemia and low hemoglobin levels are negatively associated with high prevalence of low bone mass and density. Unlike the Turkish study, we have found that the bone loss associated mainly in the cortical (femoral neck) bone. In the other two Italian studies, it has been reported that relationship between BMD and anemia and/or Hb levels was found after controlling for body mass index and other potential confounders (age, smoking, physical activity and so on). Otherwise, number of subjects who have been taking antihypertensive and hormone replacement therapy (HRT) which could positively or negatively interfere calcium metabolism were not definitely represented in the analysis of Cesari et al.and our study. Like the study of Korkmaz et al., we also controlled for many significant parameters which obtained from comparisons of groups and potential confounders, including BMI, smoking, physical activity etc. On the other hand, analysis of the other two Italian studies were restricted to elderly Italian population and the findings may not be to other ethnic groups and age groups. In addition, when compared with our study (n = 45), number of anemic men in Laudicio et al. (2009) study were limited (n=19). Thus, statistical power of their results might be accepted weaker than ours. Moreover, bone mass was determined by impractical and/or expensive methods in these studies.In comparing withpQCT and UD, we can say that the DXA is the best modern technology for measuring bone density [26,27].

Furthermore, a strong and independent relationship between LBM for spine and diabetes were found after controlling for BMI and other potential confounders (smoking, hypertension, physical activity etc.) in the applied logistic regression analysis. Most of the diabetic patients who underwent the study were type 2 and this relationship between LBM for spine and diabetes type 2 is confirmed by the study conducted by Adil et al [28].The classification of BMI mean for our study population, anemic patients, Low BMD of Spine group and Low BMD of Femur group is overweight. Most likely, the studies ofCesari et al., Laudisio et al. and Korkmaz et al. had the same classification of BMI for anemic groups. Obese individuals often present comorbidities while they appear protected against the development of osteoporosis [29].

The relationship between Weight, Body Mass Index, and Bone Mineral Density in men by Salamat et al. explained such relation and confirmed the previous studies for the positivecorrelation between weight and bone menial density [30].

The conflicting results with some previously reported studies might be explained at least in part by different patient selections such as age, ethnicity, sample size, inclusion of patients with comorbidity, study design, statistical analyses, sites of bone measured, and different diagnostic methods or criteria. In the present study, we performed rules in the selection of the study population and excluded patients with confounding diseases such as thyroid, hepatitis B, Hepatitis C, Inflammatory diseases especially affecting bone mass.

5. POTENTIAL LIMITATIONS

Our analysis was restricted to men aged 50 years and older; therefore, our findings are not generalizable to women or younger men. Another limitation of this study is the lack of measurement of serum parathormone and ferritin levels. Therefore, prospective designed studies with larger sample size including the measurement of biochemical indices of bone mineral metabolism are needed to evaluate more detailed the relationship between Hb and BMD.

6. CONCLUSION

In conclusion, we have shown that anemic men had significantly high prevalence of subjects with low bone mass. This means that anemia has a rule as a risk factor in changes of bone turnover leading to decrease bone density. We also found high prevalence of low bone mass In Saudi population.

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