Research Article

Bone mineral density is not related to angiographically diagnosed coronary artery disease

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Abstract
Based on data, there may exist an association between low bone mineral density (BMD) and atherosclerosis. *This study aimed* to investigate the association between BMD and coronary artery disease (CAD). *In this study the possible association* of BMD with CAD in 65 men with CAD and in 49 men with normal angiography as well as in 51 women with CAD and in 51 normal women was investigated. *Both spinal and femoral BMD* values for men were higher than those of women (P<0.05). Neither femoral nor spinal BMD values were different in patients with or without CAD. *In addition*, BMD values were not associated with the severity of CAD. Body mass index (BMI) was positively correlated with BMD both in men and women, whereas age and anti-diabetic treatment were linked with lower BMD in women. *In conclusion*, in this study CAD was not related to low BMD. However, BMI was an independent predictor of diminished BMD.

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Introduction

Although osteoporosis and coronary artery disease (CAD) share common risk factors, like inflammation, a direct relationship between the two is missing [1, 2]. Basic and clinical investigations have documented increased levels of osteoprotegrin (OPG) as well as receptor activator of nuclear factor kappa ligand (RANKL) in atherogenesis and bone loss [1]. Aortic calcification is shown to predict bone loss and fractures; bone resorption is also indicative of aortic calcification [2, 3]. Marcovitz et al. (2005) primarily described that low BMD (osteoporosis and/or osteopenia) is an independent predictive factor for CAD in ambulatory patients predominantly women [4]. Furthermore, according to angiography findings, low BMD in men is associated with CAD complications [5]. On the other hand, some reports have failed to demonstrate a direct relationship between low bone mineral density (BMD) and CAD or cardiovascular risk factors in post-menopausal women [6]. Likewise, risk of death due to CAD or stroke was not linked to low BMD among men and an increased risk of CAD and stroke in women with low BMD was suggested, but without significant associations between variables [7].

We aimed to undertake this study in order to add our experience on whether there is an association between BMD and CAD in a population of men and women.

Materials and methods

This study was performed on patients, who referred to our Institution for angiography, suspicious of CAD. Patients with hyperparathyroidism, renal failure, active inflammatory disease or malignancy, hormone replacement treatment or menopause and those under treatment with corticosteroids, anticoagulants or anticonvulsants were excluded. Overall, we studied 114 men and 102 women.

All subjects filled a detailed questionnaire about demographic and behavioral status as well as a medical history of conditions that could affect bone mass and metabolism. The study was approved by the Ethical Committee of Bushehr University of Medical Sciences, and written informed consent was obtained from all subjects studied.

Bone mineral density

Bone mineral density was determined for the lumbar spine (L2-L4) and femoral neck using dual-energy X-rays absorptiometry on an Osteocore II bone densitometer (Osteocore II, France). To eliminate the inter-observer errors, the same operator tested all subjects and results were confirmed by a nuclear medicine specialist. The precision errors were measured using the mean square method. The coefficients of variation (CV) of calculations of the lumbar spine and femoral neck were 0.9% and 1.8%, respectively.

The BMD values for the regions of interest (ROI) were measured by T and Z score values. T scores are measured by taking the difference between a patient's BMD and the mean BMD value in healthy young adults, which is matched for sex and ethnic group, and presenting the difference relative to the young adult population standard deviation (SD) [8].
The participants were considered as normal (T score>-1SD), osteopenic (-1SD< T <-2.55SD) and osteoporotic (T score <-2.5SD) according to the World Health Organization criteria for osteoporosis [8].

Coronary angiography was performed with the standard Judkin's method [9] using angiography device (Siemens Axiom Artis, Germany). Stenosis of more than 50% was considered as CAD.

Statistical analysis

Linear regression analysis was performed to ascertain the association of BMD results as a dependent variable and other independent variables and beta as the regression coefficient. T-test was applied to analyze the difference between the normal and abnormal groups. One-way ANOVA was used to analyze BMD values in patients with different degrees of CAD involvement, and Kruskal-Wallis was used for interquartile comparison of end diastolic volume (EDV), systolic volume (ESV) and ejection fraction (EF). SPSS V. 18 was used for statistical analysis and P<0.05 was considered as significant.

Results

Overall, we included 114 men (65 with angiography-confirmed CAD and 49 with normal angiography), as well as 102 women (51 with CAD and 51 normal). Demographic information of the patients is described in Table 1. Fifty nine subjects (36 men, 23 women) had hypertension, 104 (59 men, 45 women) were smokers, and 53 (23 men, 30 women) had diabetes mellitus (DM). There was no significant difference between men and women regarding smoking, hypertension or DM.

The BMD values of men and women with or without CAD are presented in Tables 2 and 3. Overall the femoral neck (0.891±0.187) and the lumbar (0.893±0.192) BMD values for men were higher than for women (0.84±0.13 and 0.80±0.18, respectively) (P<0.05). Femoral neck and lumbar BMD in CAD patients (0.87±0.14 and 0.85±0.21, respectively) was not significantly different from those of normals (0.86±0.2 and 0.85±0.18). In addition, there was not a notable difference when the BMD values were compared between CAD patients and normals in both men and women. Moreover, the frequency of CAD was not different between men and women.

A linear regression analysis showed that only body mass index (BMI) was positively correlated with lumbar (β=0.28, P<0.05) and femoral neck (β=0.36, P<0.01) BMD in men (Table 4). In addition, BMI (positively) and age (negatively) were associated with lumbar and femoral neck BMD in women (P<0.05). Treatment with antidiabetic drugs had also a negative impact on femoral neck BMD in women (β=-0.458, P<0.001). Increase of age was also associated with increase of CAD risk (β=0.254, P<0.01). Finally, we could not detect a significant correlation between coronary artery disease and BMD neither in men (β=0.157, P=0.139 for femoral neck and β=-0.017, P=0.886 for lumbar) nor in women (β= 0.076, P=0.526 for femoral neck and β= 0.135, P=0.304 for lumbar).

Table 1. *Gender, age and CAD in the subjects studied*

	Gender		Age	
	Men	Women	Men	Women
CAD	65	51	58.32±10.17	59.53±8.92
No CAD	49	51	53.65±9.58	52.59±9.56

Table 2. *Subjects with normal or abnormal BMD and CAD*

Femoral Neck BMD						
	Osteoporosis		Osteopenia		Normal	
	Men	Women	Men	Women	Men	Women
CAD	0	0	0	14	65	37
No CAD	0	0	0	16	49	35

Lumbar BMD						
	Osteoporosis		Osteopenia		Normal	
	Men	Women	Men	Women	Men	Women
CAD	35	15	7	16	23	20
No CAD	31	12	4	29	14	10

There was no significant difference in BMD values among the patients with different values of CAD involvement (Table 5, P>0.05). In addition, when the data of BMD was categorized into quartiles, we did not find a notable difference in end diastolic volume, end systolic volume or in ejection fraction.

In Figures 1-3 a one normal and two abnormal angiography tests are shown. In Figures 4 and 5 a normal BMD and an abnormal BMD are shown.

Discussion

Although an inflammatory process is evident for both osteoporosis and CAD, a direct relationship between the two is missing. A negative correlation between the BMD and serum

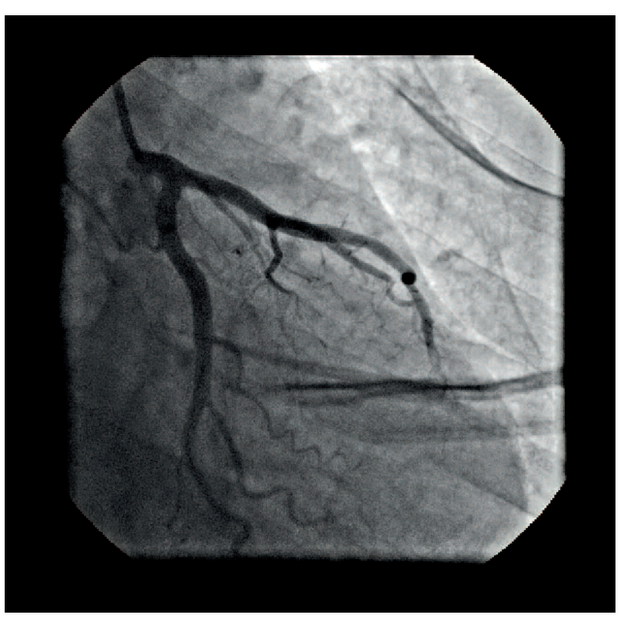

Figure 1. Normal angiography.

***Table 3**. BMD values between subjects with CAD and without CAD*

Gender	BMD	Group	N	Mean±SD	Mean difference (95% CI)	P
Men	Femoral Neck	CAD	65	0.91±0.13	-0.04 (-0.11 - 0.03)	0.25
		No CAD	49	0.87±0.24		
	Lumbar	CAD	65	0.91±0.21	-0.03 (-0.1 - 0.04)	0.43
		No CAD	49	0.88±0.16		
Women	Femoral Neck	CAD	51	0.81±0.12	0.04 (-0.01 - 0.01)	0.12
		No CAD	51	0.86±0.14		
	Lumbar	CAD	51	0.78±0.17	0.05 (-0.02 - 0.12)	0.18
		No CAD	51	0.83±0.19		

***Table 4.** Linear regression of different variables as predictors for BMD*

	BMD							
	Men (79 patients)				Women (48 patients)			
	Femoral neck		Lumbar		Femoral neck		Lumbar	
Parameter	Beta	P value	Beta	P value	Beta	P value	Beta	P value
Constant		.215		.035		.000		.003
Age	-.160	.192	.031	.816	-.392	.002*	-.440	.001*
HTN	.159	.16	.066	.599	.042	.723	.163	.215
Smoking	-.008	.937	.054	.635	.053	.635	.054	.66
Anti-diabetics	-.001	.994	-.082	.475	-.458	.000*	-.21	.098
CAD	.157	.139	-.017	.886	.076	.526	.135	.304
BMI	.362	.002*	.277	.03*	.209	.089	.283	.037*

** Significant effect of the variable on BMD, BMI: body mass index, HTN: hypertension, Beta: regression coefficients, constant: y intercept*

***Table 5.** The BMD values of subjects with different levels of CAD involvement*

			BMD (mean±SD)			
Involved vessels	Number of subjects	Age	Femoral neck		Lumbar	
			Men	Women	Men	Women
0	114	53.70±9.73	0.88±0.23	0.85±0.14	0.91±0.21	0.83±0.18
1	22	56.35±10.73	0.92±0.13	0.8±0.16	0.89±0.19	0.79±0.12
2	25	56.96±8.96	0.99±0.13	0.82±0.12	0.9±0.17	0.81±0.16
3	54	61.11±8.88	0.89±0.12	0.82±0.13	0.87±0.18	0.74±0.22
4	1	72.00	0.72±0	0	0.83±0	0
P value			0.44	0.49	0.94	0.34

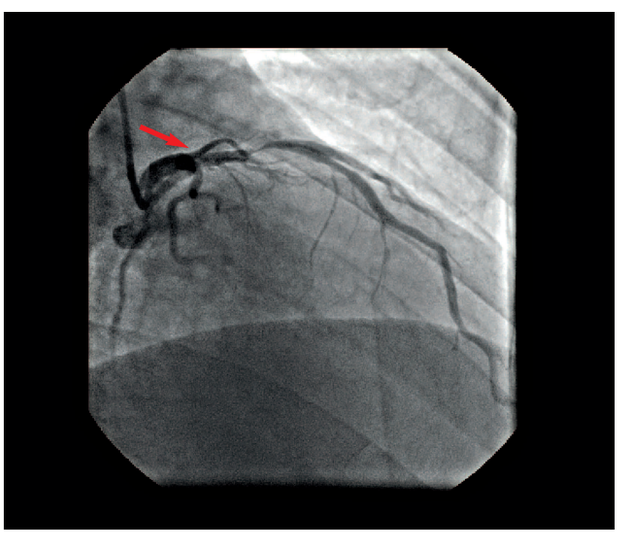

Figure 2. Abnormal angiography. Arrow indicates 99% stenosis in left anterior descending artery (RAO- cranial view).

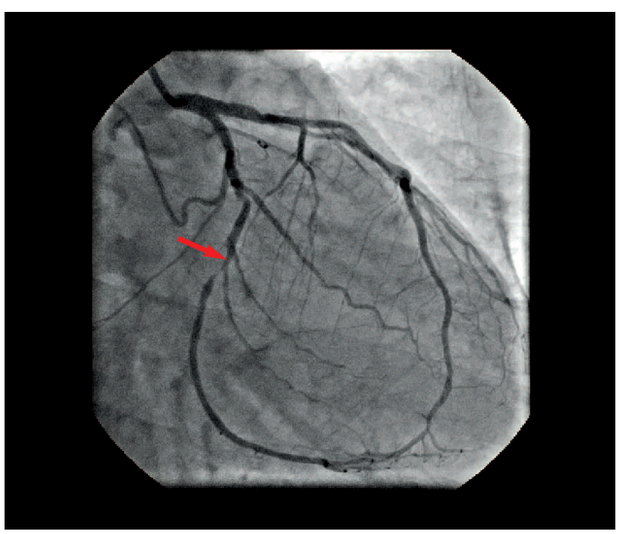

Figure 3. An abnormal angiography. Arrow indicates 99% stenosis in mid-left circumflex artery (RAO-caudal view).

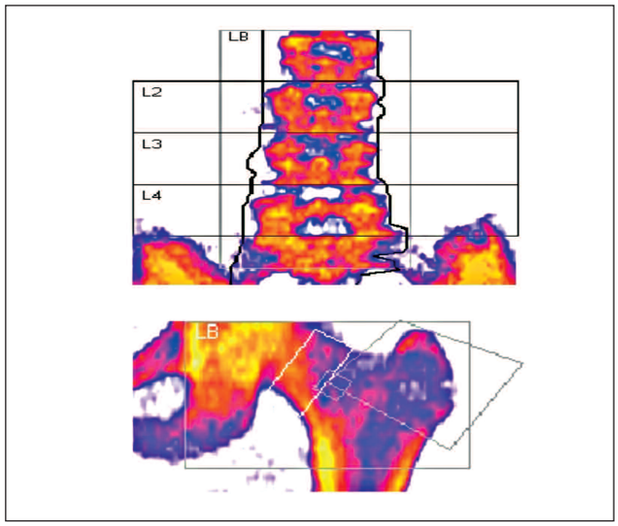

Figure 4. A normal BMD value in either the lumbar (T score= -0.67) or the femoral region (T score= 0.46).

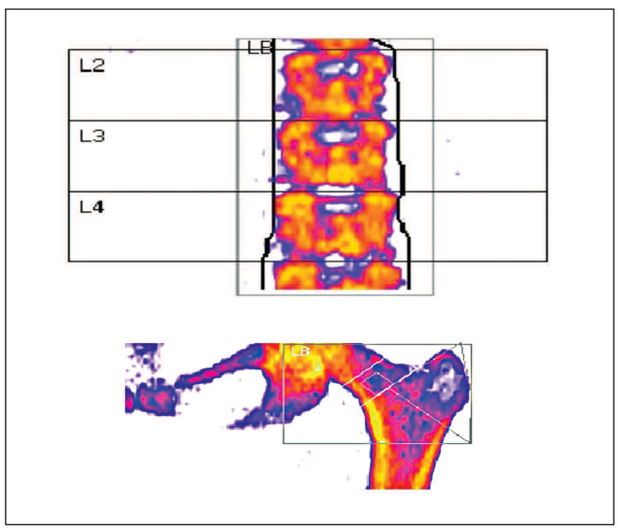

Figure 5. An abnormal BMD. It showed osteopenia in the lumbar region (T score= -2.35) but normal BMD value in the femoral region (T score= -0.92).

levels of osteoprotegerin (OPG) in postmenopausal women without hormone replacement treatment (HRT) has been reported. However, such a relationship could not be established for men, premenopausal women, or postmenopausal women with HRT [10].

In accelerated atherosclerosis inflammatory process is supported by enhanced endothelial cell activation and the RANKL/OPG/RANK axis [1, 11, 12]. Osteoprotegrin (OPG) inhibits osteoclast differentiation through inhibition of the interaction between receptor-activator of nuclear factor kappa-B (RANKL) and its membrane receptor (RANK). In addition, this system is also involved in atherosclerosis through promotion of cellular inflammatory response, matrix metaloproteases, or prothrombotic activity [1]. Elevated levels of OPG are also associated with acute coronary symptoms and coronary calcification [1, 13]. Bakhireva et al. (2008) noted that increased BMD was associated with a lower risk of coronary artery calcification [12-17].

We did not find a significant difference between the BMD values in patients with or without CAD (Table 2). In addition, linear regression analysis revealed that the presence of CAD could not significantly influence BMD (Table 4). Other researchers described that low BMD could be an independent predictive factor for CAD [4]. In contrast, we did not find a significant relationship between low BMD and CAD in both women and men. In addition, cardiovascular risk factors such as hypertension and smoking did not show a notable influence on our BMD findings. However the risk for both CAD and osteoporosis was higher with increased age. Absence of direct relationship between low BMD and CAD or cardiovascular risk factors was also reported by others in post-menopausal women [6]. Likewise, the risk of death due to CAD or stroke was not attributed to low BMD among men [7]. Low BMD was found by others to be associated with increased thickness of carotid intima-media as well as carotid atherosclerosis in post-menopausal women [14, 15]. Subclinical cardiovascular disease was also reported to be related with increased bone loss as well as with a fracture risk [16]. As the above indicate, the shared pathophysiological mechanisms for bone loss and coronary CAD are not fully clarified; yet, age, estrogen deficiency and inflammation appear to be the most significant factors that might explain this association [17-20].

Other researchers reported that patients with advanced coronary stenosis (three-vessels) showed a lower BMD in the femoral neck but not in the spine [17]. In contrast, we did not observe a difference in the BMD values, either in the lumbar area or the femoral head, among our patients with different levels of coronary artery involvement (Table 5). The above researchers also described that CAD patients with low BMD had a lower level of testosterone and testosterone/estradiol ratio but similar levels of estradiol, estrone and dehydroepiandrosterone sulfate (DHEA-S) [17]. Furthermore, in osteoporotic or osteopenic women a higher prevalence of atherosclerotic vascular disease, including CAD was suggested [18].

We also noticed that administration of anti-diabetic drugs was associated with low BMD in women. Insulin deficit and hyperglycemia in diabetic patients can alter bone metabolism, thereby produce a higher risk of fractures. Imbalance of the AGE/RAGE axis as described above and oxidative stress can alter osteocalcin production and osteoblastic activity. In addition, Peroxisome proliferator-activated receptor (PPAR) agonists including the anti-diabetic agents thiazolidinediones are thought to significantly influence bone density and increase the risk of osteoporosis, especially in older women [19-21].

In addition, we found a wide discrepancy between BMD values of lumbar and femur regions. This discordance may be associated to the skeleton's natural adaptive reaction to normal external and internal conditions and forces, eg, overweight, or to the dissimilarity in bone loss velocity between the trabecular and the cortical bone, eg, during menopause or after the use of steroids; secondarily to a disease yielding a falsely increased lumbar T score, like in vertebral osteophytosis, facet sclerosis or syndesmophytes; artefactual; and lastly, to technical errors, technicians variability or movements of the subjects tested [22-25]. Others [26] have de-

tected that ^{18}F-FDG uptake in aortic segments increases with age irrespective of genders. In this study, we did not investigate a possible correlation between BMD, hormones and aortic calcification. As osteoporosis and CAD share molecular risk factors like RANKL, an association between BMD scores and coronary calcium score seems to be relevant even before the involvement of vessels becomes detectable in angiography.

In conclusion, there was not a significant difference between the BMD values of subjects with or without CAD. In addition BMD values of patients with different degrees of CAD were not notably different. Furthermore, BMI was positively correlated with BMD in men and women. Treatment with anti-diabetic drugs and age were negatively associated with BMD in women.

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The authors declare that they have no conflicts of interest.

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