Frequency of Osteoporosis in patients with coronary heart disease (Case control study)

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ABSTRACT

Objective: The present study is concerned with seeking the relationship between coronary vascular disease and osteoporosis.
Design: Case control study.
Setting: The study was conducted at catheterization unit of Ebn-Sena teaching hospital and the DEXA unit of Al-Zahrawy teaching hospital in Mosul during the period between Nov. 2011 and Jun. 2012. **Patients and methods**: 100 patients were enrolled in the study, 50 of them proved to have CVD, the other 50 persons who matched in sex and age considered as a control group. The age ranging from 41-65.

All the studied groups were send for catheterization and DEXA study to examine the CVD and osteoporosis respectively, and laboratory investigations were done, including thyroid function test, to exclude another causes of osteoporosis. The main source of data was obtained from all the studied subjects by the investigator himself during interviews with them.
Results and conclusion: Our study concluded that there was no significant relationship between CVD and occurrence of osteoporosis with (P value= **0.067**).
Aim of the study The present study was aimed to seek the possible relationship between coronary artery disease and osteoporosis in men and in postmenopausal women in comparison with healthy control individuals.

Keywords: **Osteoporosis, coronary heart disease**(CVD), postmenopausal women

Introduction

Cardiovascular disease (CVD) and osteoporosis are common age-related conditions, both possessing important effects especially on quality of life and policies about health systems all over the world. Although these two diseases are generally known as different entities and their coexistence was attributed to independent age-related processes, accumulating evidence indicates that there are similar pathophysiological mechanisms underlying both diseases (Anagnostis et al., 2009; Warburton et al, 2007; Sinnott et al., 2006).

Osteoporosis and atherosclerosis are major causes of morbidity and mortality in both women and men in the Western world, and the incidence is expected to rise. As both disease processes are common, both conditions are often seen in the same individual. These conditions progress silently until a fracture or

myocardial infarction occurs (Aronow and Silent, 2003).

In addition to advanced age, several hypotheses have been proposed to explain the link between osteoporosis and CVD including not only shared risk factors like dyslipidemia and diabetes (Demer, 2002; McFarlane et al., 2004; McFarlane, 2006), but also common pathophysiological mechanisms like oxidative stress, and inflammation (Koh et al., 2005; Kim et al., 2007; Manolagas, 2010).

In both cross-sectional and longitudinal epidemiologic studies, low bone mass has been related to increased frequency of CVD, myocardial ischemia, cardiovascular mortality, cardiovascular morbidity, and subclinical measures of atherosclerosis (Jørgensen et al., 2001; Mussolino et al., 2003; Marcovitz et al., 2005; Farhat et al., 2006).

Osteoporotic fractures and CVD-related events are key origins of morbidity and premature mortality in the elderly (Warburton et al, 2006; Braithwaite et al, 2003). Post-menopausal women appear to be particularly at risk for developing both osteoporosis and CVD. In fact, once a woman reaches menopause, the risk for both osteoporosis and CVD increases substantially. Moreover, CVD and osteoporosis are often observed in the same individual (Schulz et al, 2004).

The nature of the relationship between osteoporosis and vascular calcification is unclear. Previous studies have demonstrated an association between them in women (Ramsey-Goldman and Manzi, 2001); however, other studies have failed to show it (Aoyagi et al, 2001). Only a few studies have explored this association in men, and they have reported conflicting results (Van der Klift et al, 2002).

Studies have implicated several possible metabolic linkages between osteoporosis and vascular calcification: estrogen deficiency (Kiel et al, 2001) , vitamin D excess (Holick, 2007), and lipid oxidation products (Tintut et al, 2004). More recently, osteoprotegerin, a protein that regulates osteoclast activity and proliferation, has been implicated in both processes (Schoppet et al, 2003).

Atherosclerotic calcification and bone mineralization share a number of intriguing common features. It is now recognized that calcification of the arterial tissue is not merely a passive process of calcium phosphate precipitation or adsorption in end-stage atherosclerosis, but instead is a highly organized process that is regulated by mechanisms similar to those involved in bone mineralization (Vattikuti et al, 2004).

Despite previous results, it remains unclear whether osteoporosis and coronary arterial disease are related to each other or are independent processes, both related to aging process. Therefore, additional research is necessary to further characterize the relationship between these two common illnesses (Manolagas, 2010).

1. Osteoporosis

1.1. Definition

Osteoporosis is a systemic, chronic, progressive skeletal disease of multifactorial etiology characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility. It has been most frequently recognized in elderly white women, although it does occur in men and women, all races, and all age groups (Ahmed SF et al, 2009).

1.2. Pathophysiology

Bone is continually remodeled throughout our lives in response to microtrauma. Dense cortical bone and spongy trabecular or cancellous bone differ in their architecture but are similar in molecular composition. Both types of bone have an extracellular matrix with mineralized and non-mineralized components. The composition and architecture of the extracellular matrix is what imparts mechanical properties to bone (Bono CM et al, 2003).

Bone strength is determined by collagenous proteins (tensile strength) and mineralized osteoid (compressive strength). The greater the concentration of calcium, the greater the compressive strength. In adults, approximately 25% of trabecular bone is resorbed and replaced each year, compared with only 3% of cortical bone (Bono CM et al, 2003).

Osteoclasts and osteoblasts are dependent on each other for production and linked in the process of bone remodeling. Osteoblasts not only secrete and mineralize osteoid but also appear to control the bone resorption carried out by osteoclasts. Osteocytes, which are terminally differentiated osteoblasts embedded in mineralized bone, direct the timing and location of bone remodeling (Raisz LG, 2005).

Furthermore, in periods of rapid remodeling (e.g., after menopause), bone is at an increased risk for fracture because the newly produced bone is less densely mineralized, the resorption sites are temporarily unfilled, and the isomerization and maturation of collagen are impaired (Seeman E et al, 2006).

The receptor activator of nuclear factor-kappa B ligand (RANKL)/receptor activator of nuclear factor-kappa B (RANK)/osteoprotegerin (OPG) system are the final common pathway for bone resorption. Osteoblasts and activated T cells in the bone marrow produce the RANKL cytokine. RANKL binds to RANK expressed by osteoclasts and osteoclast precursors to promote osteoclast differentiation. Osteoprotegerin is a soluble decoy receptor that inhibits RANK-RANKL by binding and sequestering RANKL (Sandhu et al, 2011).

1.3. Etiology

1.3.1. Hormones and cytokines:

Estrogen deficiency not only accelerates bone loss in postmenopausal women but also plays a role in bone loss in men. Estrogen deficiency can lead to excessive bone resorption accompanied by inadequate bone formation. Osteoblasts, osteocytes, and osteoclasts all express estrogen receptors (Sandhu et al, 2011).

In the absence of estrogen, T cells promote osteoclast recruitment, differentiation, and prolonged survival via IL-1, IL-6, and tumor necrosis factor (TNF)–alpha. Estrogen inhibits IL-6 secretion and that IL-6 contributes to the recruitment of osteoclasts from the monocyte cell line, thus contributing to osteoporosis (Ringe JD et al, 2007; Cummings SR et al, 2002).

T cells also inhibit osteoblast differentiation and activity and cause premature apoptosis of osteoblasts through cytokines such as IL-7. Finally, estrogen deficiency sensitizes bone to the effects of parathyroid hormone (Neer RM et al, 2001; Dempster DW et al, 2001; Body JJ et al, 2002).

1.3.2. Aging

In contrast to postmenopausal bone loss, which is associated with excessive osteoclast activity, the bone loss that accompanies aging is associated with a progressive decline in the supply of osteoblasts in proportion to the demand. This demand is ultimately determined by the frequency with which new multicellular units are created and new cycles of remodeling are initiated (Sandhu et al, 2011).

1.3.3. Calcium deficiency

Calcium, vitamin D, and PTH help maintain bone homeostasis. Insufficient dietary calcium or impaired intestinal absorption of calcium due to aging or disease can lead to secondary hyperparathyroidism. PTH is secreted in response to low serum calcium levels. It increases calcium resorption from bone, decreases renal calcium excretion, and increases renal production of 1,25-dihydroxyvitamin D (1,25[OH]^2 D)—an active hormonal form of vitamin D that optimizes calcium and phosphorus absorption, inhibits PTH synthesis, and plays a minor role in bone resorption (Dempster DW et al, 2001; Body JJ et al, 2002; Cosman F et al, 2005; Tang BM et al, 2007).

1.3.4. Vitamin D deficiency

Vitamin D deficiency can result in secondary hyperparathyroidism via decreased intestinal calcium absorption. Interestingly, the effects of PTH and 1,25[OH]^2 D on bone are mediated via binding to osteoblasts and stimulating the RANKL/RANK pathway. Osteoclasts do not have receptors for PTH or 1,25[OH]^2 D (Holick MF, 2007; Seeman E et al, 2006; Tang BM et al, 2007).

1.4. Classification:

Osteoporosis is initially divided into localized and generalized categories, and these two main categories are further classified

further into primary and secondary osteoporosis.

1.4.1. Primary osteoporosis: Patients are said to have primary osteoporosis when a secondary cause of osteoporosis cannot be identified, including juvenile and idiopathic osteoporosis. Idiopathic osteoporosis can be further subdivided into postmenopausal (type I) and age-associated or senile (type II) osteoporosis**.**

Types of Primary Osteoporosis (Smith R, 2005; Schnatz PF et al, 2011; Geusens P et al, 2008; U.S. Preventive Services Task Force, 2011).

i. **Juvenile osteoporosis:** Usually occurs in children or young adults of sexes, normal gonadal function, and age of onset usually 8-14 years. Hallmark characteristic is an abrupt bone pain and/or a fracture following trauma

ii. **Idiopathic osteoporosis**

   a. **Postmenopausal osteoporosis (type I osteoporosis):** Occurs in women aged 50-65 years. Characterized by a phase of accelerated bone loss, primarily from trabecular bone**.** Fractures of the distal forearm and vertebral bodies common

   b. **Age-associated or senile osteoporosis (type II osteoporosis):** Occurs in women and men older than 70 years. Represents bone loss associated with aging. Fractures occur in cortical and trabecular bone. Wrist, vertebral, and hip fractures often seen in patients with type II osteoporosis

1.4.2 Secondary osteoporosis

Secondary osteoporosis occurs when an underlying disease, deficiency, or drug causes osteoporosis. Up to one third of postmenopausal women, as well as many men and premenopausal women, have a coexisting cause of bone loss, of which renal hypercalciuria is one of the most important secondary causes of osteoporosis and treatable with thiazide diuretics (Schnatz PF et al, 2011).

Causes of Secondary Osteoporosis in Adults (American Association of Clinical Endocrinologists: 2001 edition; Kelman A et al, 2005; U.S. Preventive Services Task Force, 2011):

1. Genetic/congenital: like renal hypercalciuria, cystic fibrosis, Ehlers-danlos syndrome, Gaucher disease and Marfan syndrome.
2. Hypogonadal states: like androgen insensitivity, anorexia nervosa/bulimia nervosa and hyperprolactinemia.
3. Endocrine disorders: like Cushing syndrome, diabetes mellitus, acromegaly, adrenal insufficiency and estrogen deficiency.
4. Deficiency states: like calcium, magnesium and vitamin D deficiency.
5. Inflammatory diseases: like inflammatory bowel disease, ankylosing spondylitis, rheumatoid arthritis and systemic lupus erythematosus.
6. Hematologic and neoplastic disorders: like hemophilia, leukemia, lymphoma, multiple myeloma, sickle cell anemia and thalassemia
7. Medications: like phenytoin, barbiturates, antiretroviral drugs, cyclosporine, tacrolimus, cyclophosphamide, furosemide, glucocorticoids and corticotropin.
8. Miscellaneous: like alcoholism, amyloidosis, chronic metabolic acidosis, congestive heart failure, depression, multiple sclerosis and sarcoidosis.

1. Coronary Artery Atherosclerosis

2.1 Background

Coronary artery atherosclerosis is the single largest killer of men and women in the United States. It is the principal cause of coronary artery disease (CAD), in which atherosclerotic changes are present within the walls of the coronary arteries. CAD is a progressive disease process that generally begins in childhood and manifests clinically in middle to late adulthood (Pencina MJ, 2009).

Atherosclerosis is a disease of large and medium-sized muscular arteries and is characterized by endothelial dysfunction, vascular inflammation, and buildup of lipids, cholesterol, calcium, and cellular debris within the intima of the vessel wall (Deo R, 2011).

Pathophysiology 2.2

Initially thought to be a chronic, slowly progressive, degenerative disease, atherosclerosis is a disorder with periods of activity and quiescence. Although a systemic disease, atherosclerosis manifests in a focal manner and affects different organ systems in different patients for reasons that remain unclear (Kolodgie FD et al, 2003).

Materials and Methods

The present study had approval from regional research committee of Mosul health administration, and the scientific research committee of collage of medicine, university of Mosul, Mosul, Iraq, and performed during the period between Nov. 2011 and Jun 2012 in the Rheumatology outpatient department in Ebn Sena teaching hospital.

Study design

Case – control study

Subjects

1) **Patients group:** Fifty patients with ischemic heart diseases, with positive catheterization results whose ages range between 45 - 65 years old were enrolled in the study and referred as **Group A**.
   - **A. Exclusion criteria**
     1. Hyperthyroidism
     2. Steroid therapy for long period
     3. Alcoholism
     4. Chronic inflammatory diseases
     5. Patient under treatment for osteoporosis
2) **Control group:** Fifty aapparently healthy subjects, matched for age with the patients group , were kept as control group and referred as **Group B**.

Data collection

The main source of data was obtained directly from all the studied subjects by the investigator himself during interviews with them. A questionnaire form was designed to record the subject's information. It includes information on age, sex, body weight in (kg), height in (m), BMI and biochemical profile (Appendix No.1).

Instruments

The instruments used in this study were:

1. **Weight and height scale** (seca) made in Germany. Body mass index (BMI) was calculated according to the equation:

BMI = weight (kg) /height (m^2).

2. **Dual-Energy X-Ray Absorptiometry:** Bone mineral density (BMD) was obtained at lumbar vertebrae in all subjects using dual energy x-ray absorptiometry (the name of the apparatus).

T- Score classification as following:

Normal	**5.5 to -0.9**
Osteopenia	**-1 to > -2.5**
Osteoporosis	**≤ -2.5**

Statistical Analysis

IBM SPSS Statistics Version 20.0 was used to test study's result. Chi square and independent t-test was used to compare the results of various parameters among the studied groups. Some values expressed as Mean±SD. P value of <0.05 was considered to be statistically significant and P value of <0.001 was considered to be statistically highly significant.

The Results

Fifty patients in Group A their mean age±SD were 52.90 ± 5.33, 28 (56%) of them were males and 22 (44%) were females. Fifty patients in Group B their mean age±SD were 52.22 ± 6.36, 19 (38%) of them were males and 31 (62%) were females. No significant differences between mean age for studied groups by applying independent t-test for two means for each group (Table-1), and also there

is no significant differences between both groups regarding gender by applying chi square test (Table -2).

Table -1: The age of the studied groups.

Age	Group A	Group B	P value*
Mean±SD	**52.90 ± 5.33**	**52.22 ± 6.36**	**0.084**
Minimum	**42**	**41**	
Maximum	**62**	**65**	

*Independent t-test for two means was used.

Table -2: The gender of the studied groups.

Sex	Group A		Group B		P value*
	N	**%**	**N**	**%**	
Male	**28**	**56%**	**19**	**38%**	**0.054**
Female	**22**	**44%**	**31**	**62%**	
Total	**50**	**100%**	**50**	**100%**	

* Chi-square test was used.

The mean and standard deviation of Dexa results by using T- score for **Group A** were -0.38 ± 1.63, and for **Group B** were -0.35 ± 1.28. There was no significant differences (P value= **0.137**) between two groups by applying independant t-test (Table- 3).

Table -3: Dexa (T- Score) Mean±SD results for studied groups.

Bone density by Dexa (T-Score)	Group A	Group B	P value*
Mean±SD	**-0.38 ± 1.63**	**-0.35 ± 1.28**	**0.137**
Minimum	**-3.10**	**-2.5**	
Maximum	**5.50**	**3**	

*Independent t-test for two means was used.

The frequency of bone density by using Dexa (T-score) in studied subjects in Group A were normal (T-score= 5.5 to -0.9) in 34 (68%) subjects, osteopenia (T-score= -1 to -2.4) in 11 (22%) subjects, and osteoporosis (T-score ≤ -2.5) in 5 (10%) subjects. For Group B, 32 (64%) had normal Dexa results, 17 (34%) were osteopenic, and 1 (2%) had osteoporosis. There was no significant relationship between both groups by using chi square test (P value= 0.067) (Table- 4).

Table -4: Dexa (T- Score) frequency for studied groups.

Bone density by Dexa (T-Score)	Group A		Group B		P value*
	N	**%**	**N**	**%**	
Normal (5.5 to -0.9)	**34**	**68%**	**32**	**64%**	**0.067**
Osteopenia (-1 to -2.4)	**11**	**22%**	**17**	**34%**	

Osteoporosis (≤ -2.5)	**5**	**10%**	**1**	**2%**	
Total	**50**	**100%**	**50**	**100%**	

* Chi-square test was used.

There was no effect of gender on Dexa results in both groups by using independent t-test for two means for each group. In Group A, the mean±SD of T-score in males were -0.217 ± 1.798 and in females were -0.595 ±1.388 (P value=0.588) (Table- 5). In Group B, the mean±SD of T-score in males were -0.631 ± 1.505 and in females were -0.218 ± 1.163 (P value=0.1) (Table- 6).

Table - 5: The effect of gender on the Dexa results in Group A

Gender	**No.**	**T-score Mean±SD**	**P-value** *
Male	29	-0.217 ± 1.798	**0.588**
Female	21	-0.595 ±1.388	

* Independent t-test for two means was used.

Table -6: The effect of gender on the Dexa results in Group B.

Gender	**No.**	**T-score Mean±SD**	**P-value** *
Male	16	-0.631 ± 1.505	**0.1**
Female	34	-0.218 ± 1.163	

* Independent t-test for two means was used

Discussion

Osteoporosis is a major health problem worldwide that is associated with an increased risk of fractures and mortality. Vascular calcification is a well-defined independent risk factor for cardiovascular disease (CVD) and mortality (Christos E et al, 2012).

Both diseases were considered as unrelated diseases concomitantly occurring to aging process. One of common features of atherosclerotic plaques, calcification, have demonstrated similar regulatory mechanisms observed in bone metabolism (Laszlo B et al, 2005).

The nature of the putative link between osteoporosis and cardiovascular disease remains unclear. Traditionally, these two conditions were considered unrelated and their progression was attributed to independent age-related processes (Aoyagi K et al, 2001).

However, recent evidence from many studies points to a link between osteoporosis and cardiovascular disease that cannot be explained by age alone. While this evidence has been consistent in older populations, further support for the role of factors other than age is derived from observations in younger populations. (Aoyagi K et al, 2001; Bono CM and Einhorn TA, 2003).

Despite of high percent (10%) of patients with cardiovascular problem had osteoporosis in comparison with control (2%), statistically, there was no significant association between cardiovascular disease and osteoporosis, represented by low bone density. This finding was consistent with others reported by Frye et al. among women in Rochester, Minnesota (Frye MA et al, 1995), by Aoyagi et al. in Japanese-American women (Aoyagi K et al, 2001), and by Sinnott B et al who found that osteoporosis and coronary atherosclerosis are independent processes that occur as part of the aging process both in postmenopausal women and in men (Sinnott B et al, 2006).

Also there was no significant association between osteoporosis and sex in this study, although the present study showed that females had a low mean of bone density than males, but still statistically not significant. This can be explained as women generally have lower levels of physical activity than men, and overweight and obesity are more common among women as well as the sample size of this study was not enough to show this relation.

Furthermore, the association between cardiovascular disease and osteoporosis has been observed almost only in women (Samelson EJ et al, 2004; Kiel DP et al, 2001; Van der Klift M et al, 2002; Hirose K et al, 2003), raising further uncertainty whether the two disease processes are truly linked.

Moreover, both osteoporosis and cardiovascular diseases increase with age (Aoyagi K, et al, 2001) and, in some studies, an association between bone mineral density (BMD) and cardiovascular diseases was lost once age was adjusted for (Vogt MT et al, 2004; Frye MA et al, 2004).

The present study showed normal mean level for T4 and TSH in both women and men regardless the result of T-score and was statistically not significant in both males and females. This result inconsistent with other studies that showed a positive relation between osteoporosis in postmenopausal women with hyperthyroidism (Kim DJ et al, 2006; Bassett JH et al, 2007; Hye Won Chung et al, 2012)

Several hypotheses have been proposed to explain the link between the two conditions. The results of our study may be affected by method of selection of the patient which is differing from other studies. The other studies may use other parameter in diagnosing the osteoporotic patient e.g. ultrasound technique or using DXA study measurements in the radius, phalanx, or heel, while in our study using DXA study in spine.

Conclusion & Suggestion

1. There was no relationship between osteoporosis and cardiovascular diseases.
2. Gender had no effects on osteoporosis.
3. Further studies are needed to investigate this association in men and in women with larger sample size and more diagnostic measurements for osteoporosis and atherosclerosis of coronary arteries.

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Frequency of osteoporosis in patient with ischemic heart disease

Name	Age	Sex
Address	Date	Occupation

Inclusion criteria: patients diagnosed as Ischemic heart disease by catheterization at age 45-65 years old.

Exclusion criteria:
1-Hyperthyroidism
2-Steroid therapy for long period
3-Alcoholism
4-Chronic inflammatory diseases

CAD: Yes No Duration:

Smoking: Yes ☐ No ☐ Duration: ☐ No:

Hypertension: Yes ☐ No ☐

Diabetes mellit Yes ☐ No ☐

Dyslipidemia: Yes ☐ No ☐

ECG changes:

Serum createnin: Pre catheterization: Post catheterization:

Cath. Finding: N= ☐ Abn= ☐

DEXA finding: