Assessment of Bone Mineral Density in Primary Generalized Osteoarthritis

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Abstract: Background: Osteoarthritis is the most common musculoskeletal disorder. The relation with osteoporosis is under-examined. **The aim of the present study** is to assess bone mineral density in primary generalized osteoarthritis. **Patients and methods:** 100 patients with primary generalized osteoarthritis were included. All fulfilled ACR Criteria for diagnosis of osteoarthritis. 20 healthy subjects were included as control group. All were subjected to history taking, clinical examination and laboratory investigations. Pain was assessed by visual analogue scale. Western Ontario and McMaster Universities questionnaire was used to evaluate a patient's functions when diagnosed with rheumatic diseases. All radiographs were examined using and graded according to the Kellgren and Lawrence criteria. Finally, Osteoporosis was assessed by dual-energy X-ray absorptiometry scanning. **Results:** Both study and control group were comparable as regard to age, sex, residence and height. The intensity of pain in the study group was significantly increased when compared to control group. There was statistically significant decrease of bone mineral density in the study group when compared to control group at lumber spine and forearm. There was statistically significant increase of C - reactive protein and erythrocyte sedimentation rate in study group, and there was statistically significant decrease of calcium and significant increase of alkaline phosphatase in study group. **Conclusion:** there was statistically significant decrease of BMD in the study group when compared to control group at lumber spine and forearm. However, the difference at femur was statistically non-significant.
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1. Introduction

Osteoarthritis (OA) a very common form of arthritis. It leads to a significant chronic pain and disability and confers an enormous load on both people and health economies **(Barr et al., 2015).** It is a primary inflammatory degenerative disease affecting joints and is marked by an inequality between production and degeneration of articular cartilage leading to classic pathologic change of wearing away and destruction of cartilage **(Brandt et al., 2009).** OA also has a multifactorial pathophysiological changes due to the interaction of genetic, mechanical, biochemical, metabolic, endocrine, and environmental factors that lead to cartilage breakdown and many changes in subchondral bone, which may lead to chronic pain, swelling of the joints, deformity and whole joint abnormalities resulting in disability **(Meulenbelt, 2012).**

All over the world estimates indicated that 9.6 % of males and 18 % of females ≥ 60 years have symptomatic OA **(Peláez-Ballestas et al., 2011).** The knee is the joint most affected by OA**.** Knee OA is the most frequent cause for joint replacement **(Sanghi et al., 2013).**

Osteoporosis (OP) is a systemic disorder characterized by reduced bone mineral density (BMD) and high fracture risk. It increases bone fragility by reduction of bone strength and causing fractures with minimal trauma during living activities **(Tuncer, 2011).**

The relationship between OA and OP is controversial. A review of the literature proposed that OA is inversely correlated with OP in general when studied cross-sectionally and systematically. However, when analyzed in individual bones, the BMD of the appendicular skeleton in OA-affected joints may decline, particularly in the upper extremities. The risk for osteoporotic fracture does not seem to be reduced despite increased BMD in people with OA, probably due to postural instability and muscle strength. Reduced BMD at the lumbar spine is linked with a lower incidence of knee OA although it does not arrest the progression of knee OA **(Im and Kim, 2014).**

In clinical practice, dual energy X-ray absorptiometry (DEXA) is the corner stone for

evaluating bone mass in vivo **(Blake and Fogelman, 2009).** This methodology involves measurement of the attenuation of two monochromatic X-ray beams (with a high and low energy) by bone and soft tissues. The bone mineral is accountable for X-ray attenuation allowing the evaluation of the bone mineral content (BMC). The measure of the bone mineral density (BMD) is derived by normalizing BMC by the area of the 2D bone projection and results into a real BMD (a BMD). Because of the 2D projection, DEXA allows for a global evaluation of the mineral phase of the bone as an organ including the marrow spaces, the vascular channels and the Haversian canals **(Mabilleau et al., 2015).**

The aim of the present study is to assess bone mineral density in primary generalized osteoarthritis.

Patients and methods

This prospective study was carried out on 100 patients with primary generalized OA. All of them fulfilled ACR Criteria for diagnosis of OA **(Wu et al., 2005).** They were recruited from the outpatient clinic of Rheumatology Department, Al-Azhar University. Other 20 apparently healthy subjects were included as a control group. Patients with secondary or primary localized osteoarthritis were excluded from the study.

All participants were subjected to full history taking (personal, present, and past history), full clinical examination (general and musculoskeletal examinations). In general examination, all body systems were reviewed, blood pressure was measured and body mass index was calculated as weight in kilograms divided by the square of height in meters. In addition, a thorough musculoskeletal examination was performed where the system was inspected for bony deformity or swelling, palpated for range of motion, crepitus, tenderness of the joints or muscle weakness. Subsequently, pain was measured using a 10 cm Visual Analogue Scale (VAS). Pain intensity is classified using a range from 0 to 10, in which 0 = no pain at all and 10 = the worst possible pain. Patients were asked to sign the place on the VAS scale that corresponded to their pain level.

Westren Ontario and McMaster Universities (WOMAC) questionnaire was used to evaluate a patient's functions when diagnosed with rheumatic diseases. The WOMAC is a 24-item questionnaire with three subscales measuring pain (five items), stiffness (two items), and physical function (17 items). Answers to each of the 24 questions are scored on five-point Likert scales (none = 0, slight = 1, moderate = 2, severe = 3, extreme = 4), with total scores ranging from 0 to 96. So, the maximum possible scores for WOMAC, pain, stiffness, and function are 96 (most severe), 20, 8, and 68, respectively. Higher scores indicate greater disease severity **(McConnell et al. 2001).**

As regard to radiologic grading of joints, a single observer examined and interpret all radiographs using the Kellgren and Lawrence criteria (0 – 4, 0 = none, 4 = sever) **(Meulenbelt, 2012).** Grade 1: doubtful narrowing of joint space and possible osteophytic lipping; Grade 2: definite osteophytes, definite narrowing of joint space; Grade 3: moderate multiple osteophytes, definite narrowing of joints space, some sclerosis and possible deformity of bone contour; Grade 4: large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone contour. Only definite osteophytes were classified as present, with absent or possible osteophytes classified as not present.

Osteoporosis was assessed by dual-energy X-ray absorptiometry (DEXA) scanning: DEXA was done by Lunar DPX DEXA system, manufactured by GE healthcare (USA). Finally, laboratory test were done for each patient included CBC, ESR, CRP and bone turnover markers (Serum calcium, Serum phosphorus and Serum alkaline phosphatase).

Statistical analysis of data:

The collected data organized, tabulated and statistically analyzed using statistical package for social science (SPSS) version 22 (IBM®SPSS® Inc, USA). For numerical variables, mean, standard deviation, minimum and maximum were calculated, and for comparison between two groups, the independent sample's (t) test was used. Categorical variables were expressed as relative frequency and percent distribution, and for comparison between groups Chi square or Mann-Whitney test were used. P value < 0.05 was considered significant.

3. Results

In the present study, 100 patients with primary generalized osteoarthritis were included. In addition, 20 healthy subjects were included as control group. Both study and control group were comparable as regard to age, sex, residence and height. On the other hand, patients in study group had significant increase of both weight and BMI when compared to control group (80.86±5.97, 29.05±2.11 vs 69.75±3.17 and 27.70±0.69 respectively) (Table 1).

In the study group, symptoms were in the form of stiffness in 39%, limited motion in 47% and no deformity was reported. Past history of hypertension was reported in 14% of studied patients and no cases had diabetes or surgery. Clinical examination revealed swelling in 20%, decreased ROM in 81%, crepitus in 26%, tenderness in 87% and muscle weakness in 15%. Disease duration ranged from 12 to 48 months, the mean duration was 34.47 weeks.

As regard to pain intensity in the study group, it ranged from 3 to 7 with a mean of 4.85±0.94; while in control group, it ranged from 0 to 2.0 with a mean of

0.65±0.58; and there was statistically significant increase of VAS score in study when compared to control group. In addition, there was statistically significant decrease of BMD in the study group when compared to control group at lumber spine and forearm. However, the difference at femur was statistically non-significant (Table 2).

As regard to CBC findings, there was no significant difference between study and control groups as regard to hemoglobin, RBCs and platelets; while there was statistically significant increase of WBCs in study group when compared to control group (9.64±1.47 vs 5.70±1.26). In addition, there was statistically significant increase of both ESR and CRP in study group when compared to control group (34.32±4.91, 178.64±34.31 vs 11.90±3.21, and 61.55±15.09 respectively) (Table 2).

As regard to bone turn over markers, there was statistically significant decrease of calcium and significant increase of alkaline phosphatase in study when compared to control group (8.13±0.44, 79.56±9.35 vs 9.72±0.67 and 63.25±10.39 respectively) (Table 2). Total WOMAC score ranged from 23 to 39; the mean value was 30.82. The percentage ranged from 23.96 to 40.63, the mean value was 32.10±3.10 (Table 3).

As regard to X-ray grading, it was zero in 12%, grade I in 27%, grade II in 45% and grade III in 16%.

In the present work BMD of lumbar spine was negatively correlated with each of VAS, BMI, ESR, CRP and alkaline phosphatase, and correlated proportionately with total WOMAC and calcium. Similar correlations were found between femur DEXA and the same variables as lumbar spine. Finally, no significant correlation was found between forearm DEXA and any of studied variables (Table 4).

Table (1): General characteristics of studied populations

Variable		Study	Control	Test	P value
Age (y)		55.40±7.17; 40-70	55.05±6.24; 45-63	0.20	0.84(ns)
Weight (kg)		80.86±5.97; 69-93	69.75±3.17; 64-75	***8.07***	***<0.001****
Height (m)		1.6685±0.03532; 1.62-1.75	1.6800±0.02248; 1.63-1.71	1.39	0.16(ns)
BMI		29.05±2.11; 24.62-34.16	27.70±0.69; 23.31-25.95	***9.08***	***<0.001****
Sex	**Male**	38(38.0%)	7(35.0%)	0.06	0.80(ns)
	Female	62(62.0%)	13(65.0%)		
Residence	**Rural**	73(73.0%)	12(60.0%)	1.36	0.24(ns)
	Urban	27(27.0%)	8(40.0%)		

Table (2): Pain intensity (VAS), BMD and laboratory investigations of studied populations

Variable		Study	Control	t	P value
VAS		4.85±0.94	0.65±0.58	***19.07***	***<0.001****
BMD	**Lumbar spine**	0.898±0.101	1.054±0.103	***6.26***	***<0.001****
	Femur	0.927±0.145	0.983±0.082	1.68	0.09(ns)
	Forearm	0.715±0.06	1.030±0.33	***8.98***	***<0.001****
Z score	**Lumbar spine**	-0.79 ± 0.59	0.475±0.483	8.97	***<0.001****
	Femur	-0.506±0.58	-0.276±0.514	1.64	0.10
	Forearm	-1.84±0.67	-0.20±0.18	***10.75***	***<0.001****
Hemoglobin		11.69±0.52	11.61±0.53	0.59	0.551
RBCS		4.00±0.31	3.88±0.27	1.57	0.117
WBCS		9.64±1.47	5.70±1.26	***11.16***	***<0.001****
Platelets		255.09±40.67	211.80±21.49	0.35	0.72
ESR		34.32±4.91	11.90±3.21	***19.53***	***<0.001****
CRP		178.64±34.31	61.55±15.09	***13.59***	***<0.001****
Calcium		8.13±0.44	9.72±0.67	***13.31***	***<0.001****
Phosphorus		3.44±0.21	3.52±0.18	1.39	0.167
Alkaline phosphatase		79.56±9.35	63.25±10.39	***6.98***	***<0.001****

Table (3): WOMAC values in patients of study group

		Mean	SD	Minimum	Maximum
Pain	Walking	1.35	0.83	0.00	3.00
	Stair climbing	2.10	1.05	0.00	4.00
	Nocturnal	1.18	0.70	0.00	3.00
	Rest	0.65	0.54	0.00	2.00
	Weight bearing	1.75	0.95	0.00	3.00
Stiffness	Morning	1.74	0.93	0.00	3.00
	Occur later in the day	0.55	0.69	0.00	3.00
Physical function	Descending stairs	0.44	0.57	0.00	2.00
	Ascending stairs	1.16	0.71	0.00	3.00
	Rising from sitting	1.79	0.88	0.00	3.00
	Standing	1.22	0.73	0.00	3.00
	Bending to floor	1.17	0.69	0.00	2.00
	Walking on flat surface	0.29	0.45	0.00	1.00
	Getting in/out of the car	0.85	0.52	0.00	2.00
	Going shopping	0.60	0.49	0.00	1.00
	Putting on socks	1.12	0.73	0.00	3.00
	Lying in bed	0.85	0.52	0.00	2.00
	Taking off socks	0.74	0.61	0.00	3.00
	Rising from bed	0.90	0.59	0.00	2.00
	Getting in/out of bath	1.52	0.80	0.00	3.00
	Sitting	1.06	0.23	1.00	2.00
	Getting on/off toilet	0.83	0.37	0.00	1.00
	Heavy domestic duties	1.79	0.86	0.00	3.00
	Light domestic duties	0.27	0.44	0.00	1.00
Total score		30.82	2.98	23.00	39.00
Percentage of total score		32.10	3.10	23.96	40.63

Table (4): Correlation between BMD and other variables

	Lumbar spine DEXA		Femur DEXA		Forearm DEXA	
	r	p	r	p	r	p
X ray grading	0.063	0.535	0.085	0.400	-0.150	0.138
Total WOMAC	***0.293***	***0.003****	**0.264**	**0.008***	0.001	0.990
VAS	***-0.367***	***0.000****	**-0.570**	**0.000***	0.092	0.315
BMI	***-0.303***	***0.001****	**-0.560**	**0.000***	0.050	0.589
Hemoglobin	0.014	0.881	-0.124	0.177	-0.092	0.320
ESR	***-0.413***	***0.000****	***-0.645***	***0.000****	0.087	0.347
CRP	***-0.480***	***0.000****	***-0.590***	***0.000****	0.072	0.434
Calcium	***0.314***	***0.000****	***0.396***	***0.000****	-0.085	0.357
Phosphorus	0.006	0.948	0.084	0.362	-0.004	0.962
Alkaline phosphatase	***-0.192***	***0.036****	***-0.417***	***0.000****	-0.104	0.260
Age	0.076	0.410	-0.035	0.701	0.132	0.149
Duration	0.131	0.193	0.083	0.414	0.151	0.135

4. Discussion

The present study was designed to assess bone mineral density in primary generalized osteoarthritis. It included 100 patients with generalized primary osteoarthritis and 20 healthy controls. All were submitted to full history taking, clinical examination, laboratory investigations and determination of BMD by DEXA.

In the present work, females were higher in OA group representing 62.0% of included patients. This result is comparable to those reported by **O'Connor (2006)** who reported that, the incidence and severity of OA is greater in women than in men, suggesting a greater need for effective treatment and prevention of OA in women. Most population-based studies have demonstrated that women have a higher frequency of knee complaints along with higher prevalence of

radiographic and symptomatic OA compared to males. This has been usually observed at around menopause where hormones begin to fluctuate and their protective effects on OA are assumed to cease **(Bialog and Reginato, 2011).** On the other hand, **Edwards et al. (2017)** reported that, 58.2% of their participants were men and 37.8% of women. The possible explanation for this contradiction may be attributed higher age of patients included in their study, as the majority of their patients were in 70s while majority of our patients were in 50s; as at the higher age the degeneration may affect men more than women.

In the present study, patients in study group had significant increase of both weight and BMI when compared to control group. These results are in agreement with those reported in previous literature, where the association between OA and obesity is well known, although the exact pathophysiology of OA is unclear **(Chapple et al., 2011).** The biomechanical effect of increased body weight is one explanation for this association; especially in weight-bearing joints such as the knee joint **(Bennell et al., 2011).** In addition, the adipose tissue of obese patients is an endocrine organ that secretes various adipokines that contribute to the pathophysiology of OA **(Hui et al., 2012).**

In the study group, symptoms were in the form of pain in all patients, stiffness in 39%, limited motion in 47% and no deformity was reported. Past history of hypertension was reported in 14% of studied patients and no cases had diabetes or surgery. Clinical examination revealed swelling in 20%, decreased ROM in 81%, crepitus in 26%, tenderness in 87% and muscle weakness in 15%. Disease duration ranged from 12 to 48 months, the mean duration was 34.47 weeks. These results are comparable to **Felson (2005)** who reported that, pain is the most common presentation of an osteoarthritic joint. The nature of the pain is often described as dull and ill defined. Joint pain is typically accompanied by morning stiffness and generally lasts less than an hour. The origin of pain is poorly understood. Hyaline cartilage lacks nociceptors, but neighboring structures do possess them. Pain from articular cartilage lesions results from mechanical irritation of loose flaps of cartilage, from synovial and capsular inflammation, and from subchondral bone sclerosis that acts on the periarticular nerve endings. The stimuli causing pain are related to, but fundamentally different from, those produce cartilage loss.

In the present study, there was statistically significant decrease of BMD in the study group when compared to control group at lumber spine and forearm. However, the difference at femur was statistically non-significant. These results are in agreement to those reported by **Zholdoshova and Yalcin (2013)** who reported that, osteoarthritis and osteoporosis (decreased bone mineral density) are the most common societal diseases. In addition, it was reported that, the relationship between OA and OP varies between primary generalized OA and localized OA. The coexistence of OA and OP in the hand joints has been previously shown **(Hochberg et al., 2004).**

Blake and Fogelman (1992) measured the femoral BMD of 50 primary hip OA patients with DXA and found high BMD values at the femoral neck and Ward's triangle. Despite numerous studies on this subject, there are conflicting results. These contradictions suggest that there is a very complicated relationship between these two diseases. Both have a multifactorial etiology, which might explain the varying research conclusions. In fact, genetic, metabolic, mechanical, and endocrine factors show both differences and similarities between OA and OP **(Tuncer, 2011).**

As regard to ESR and CRP, there was statistically significant increase in study group when compared to control group. **Schett et al. (2006)** demonstrated that low-grade inflammation, as estimated by the high-sensitivity C-reactive protein level, is a significant and independent risk predictor of Non-traumatic fractures in healthy individuals. This finding is in line with the hypothesis of a tight link between low-grade inflammation and bone quality. In addition, **Bultink and Lems (2013)** confirmed the link between inflammation and development of OA (increased inflammatory markers such as cytokines). They added, the recognition that low-grade inflammation contributes to the development of OA and OP provides the opportunity to develop new, anti-inflammatory therapeutic interventions.

Although OA is commonly described as a non-inflammatory disease and, strictly speaking, should be termed "osteoarthrosis," inflammation does play a role. In healthy individuals, the joint space is filled with synovial fluid that contains abundant hyaluronic acid (HA) acting as lubricant. In OA patients, hyaluronan is smaller in size, diminished in concentration, and provides less efficient lubrication, and the joint space narrows. This decrease in joint lubrication can be remedied to some extent by intraarticular visco-supplementation **(Tehranzadeh et al., 2005).** Synovitis (inflammation of the synovial membrane) can either be the result of an acute inflammatory "flare" or of a chronic, but subclinical inflammation. Synovitis may be the primary event, that is, to initiate or propagate OA, or it may be a secondary result, perhaps due to the accumulation of cartilage breakdown products in the joint space **(Bonnet and Walsh, 2005).**

As regard to bone turn over markers, there was

statistically significant decrease of calcium and significant increase of alkaline phosphatase in study when compared to control group. These results are in agreement with **Li et al. (2016)** who reported that, a negative association between serum calcium concentration and radiographic OA of the knee was observed in a model after adjustment for age, sex, and BMI, and also in a multivariable model adjusted for age, BMI, sex, educational level, smoking status, activity level, alcohol drinking status, diabetes, and hypertension. **Yazmalar et al. (2013)** found that serum calcium levels were not significantly different between 74 knee osteoarthritis patients and 70 controls. The authors state that there were statistically significant differences between groups in terms of age, sex, and BMI ($P<0.05$). However, these potential confounding factors were not adjusted, which may compromise the accuracy of the research results.

In the present study we found no significant correlation between BMD and x-ray grading. Several studies have shown the presence of a relationship between the radiological grade of OA of the knee and BMD **(Zhang et al., 2000).** However, these results were not always consistent **(Iwamoto et al., 2002). Iwamoto et al. (2002)** reported that, BMD was higher in radiological grade 3 than in grades 1 and 2, but BMD was lower in grade 3 than in grade 4. The most severe radiological grade of OA showed a lower BMD than moderate grade. The reason for this remains uncertain. However, these findings suggest that, although BMD may increase with OA of low to moderate radiological grades, a severe grade OA of the knee may not always develop from moderate grade OA. Some cases of severe grade OA of the knee may be associated with low BMD. The X-ray finding of severe joint-space narrowing is included in radiological grade 4. Thus, one possible explanation for the lower BMD in grade 4 than in grade 3 is that severe joint-space narrowing in the medial femorotibial joint with severe varus deformity could result from low bone mass. That is, patients with OA of the knee with low bone mass may show a radiological course different from that observed in those with high bone mass. These results can explain the non-significant correlation found between BMD and x-ray grading in the present work.

Although, the present study did not follow up patients to know whether BMD decreased or not with advanced primary generalized OA; **Hart et al. (2002)** examined a cohort of 830 white women from the Chingford study (a suburb of London). Bone mineral density measurements of the lumbar spine and hip and radiographs of the knees and hands were obtained at baseline, and the knee radiographs were repeated 48 months later. Hart et al. found that baseline bone mineral density at the lumbar spine and hip was significantly higher in women who subsequently developed incident knee osteophytes. Low bone mineral density at the hip appeared weakly related to progression. These results support the results of the present work.

Although we had some encouraging results, none of them provided conclusive evidence regarding the relationship between these two diseases. To clarify this issue, further studies with larger patient groups are needed, and separate information should be included for each joint and there should also be a long-term follow-up period.

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