



## Alendronate Sodium in Osteoarthritis: Effects on Lipid Profile, Circulating Leptin and the Clinical Activity

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### ABSTRACT

**Objective:** Osteoarthritis (OA) is a most common arthritic disease and responsible for more of disability in all world. OA affects all joint and characterized by degredation of cartilage, subchondral bone turnover and osteophytes formation.

**Aim of the study:** To evaluate the effectiveness of alendronate sodium (ALN) on disease activity and physical function, evaluate the lipid profile and study the impact of ALN on circulating leptin marker and myeloperoxidase (MPO) and to determine its effectiveness in slowing progression of disease.

**Patients and Methods:** 116 OA patients over 45 years old with X-ray grade II and more of Kellgren and Lawrence grading were enrolled in our study. Base line assessment was done, Kellgren and Lawrence X-ray grading, WOMAC scoring, body mass index and the lipid profil with enzyme-linked immunosorbent assay (ELISA) analysis of serum leptin and MPO. They were instructed to take ALN 10 mg daily. Reassessment was done after 3 months.

**Results:** A significant symptomatic improvement in WOMAC scoring (pain, stiffness) were observed associated with significant reduction in serum leptin and no significant reduction in MPO. A nonsignificant changes in lipid profile, joint space width and function were also reported.

**Conclusion:** ALN in patients with OA has clinical efficacy in reducing suffering especially pain probably through inhibition of leptin with no significant joint structural improvement, and may help delay and prevent further disease progression probably through inhibition of leptin activity.

### Introduction

Osteoarthritis (OA) is a progressive degeneration of articular cartilage with subsequently joint space width (JSW) narrowing (Blagojevic *et al.*, 2010),

a most common form of joint disorders (Bijlsma *et al.*, 2011). OA occurrence includes reduction in mineralization of the trabecular structure, associated with destruction in the subchondral

bone, defects in bone marrow and subchondral plate sclerosis (Karsdalet *et al.*, 2014). This resulted in a reduction in JSW leading to immobile, and disabling joint (Kon *et al.*, 2012). OA can be classified as primary (idiopathic) if its cause is not well defined and secondary when there is a certain events causing OA.(Brandt *et al.*, 1986). The initiation of OA may occur under influence of many factors like genetic, local, systemic and environmental factors (Brandt *et al.*, 2009). OA affected group of joint as joint of end of finger, base of thumb, neck, knee, base of big toe, lower back and hip (Hochberg, 2001). Healthy lifestyle measures in women are essential to permit healthy ageing, and the antioxidants lead to pain relief and functional improvement in knee OA, in many things, were based on avocado-soya bean and curcumin (Grover and Samson, 2016).

OA is a degenerative joint abnormality (Blagojevic *et al.*, 2010) which may associated with inflammatory events (Berenbaum, 2013). Pathophysiological changes in the synovial fluid may also occur, as well as subchondral bone and other joint structures (Suri *et al.*, 2012).

Recently OA associated with increased activity of different cytokines in the joints (Loeser *et al.*, 2012) which lead to production of enzymes that mediate destruction of cartilage (Goldring and Goldring, 2007). The synovium is a main part for gross and microscopic inflammatory changes (Sellam and Berenbaum, 2010). Increasingly recognized is the presence of synovitis in a significant value in primary OA (Jeremy and Christin, 2013). Synovitis is occur following cartilage destruction and shows a critical link in the processes of initiation and progression of OA (Scanzello and Goldring, 2012).

Leptin is a nonglycosylated protein encoded by ob (obese) gene express in OA, is secreted by adipose tissue, so it is higher in over weight persons (de Boer *et al.*, 2012). It represent a causative a link between obesity and osteoarthritis (Scotece and Mobasher, 2015) and act as a body weight homeostasis, immune and inflammatory process-

ses, including increase MMP production, regulator (Otero *et al.*, 2006). Leptin with its receptor are present in chondrocytes, synovium, osteophytes and infrapatellar fat pad (Presle *et al.*, 2006). It has a biphasic activity, it contributing to cartilage synthesis when leptin is low and facilitates cartilage degradation at high level (Pottie *et al.*, 2006). Leptin induces chondrocytes apoptosis (Huang *et al.*, 2016). It has been discovered that leptin mediated the associations between adiposity measures and cartilage thickness, and it may have a key role in cartilage thinning (Oliver *et al.*, 2015). Such findings have concluded the importance of leptin as a therapeutic target for the treatment of OA in the overweight population (Zhang *et al.*, 2016 ; Huang *et al.*, 2016).

Myeloperoxidase (MPO) is a peroxidase enzyme , express in humans neutrophil, oxidatively damaging host tissue (Klebanoff, 2005). MPO may be present in the synovial fluid of OA (Steinbeck *et al.*, 2007). In OA serum, MPO level reduced after joint replacement (Deberg *et al.*, 2008). Thus MPO may serve as diagnostic marker for detection of early OA (Steinbeck *et al.*, 2007).

OA sign and symptoms, including pain, tenderness, decrease flexibility, stiffness, harsh sensation and bone overgrowth, often increase slowly and get worse over time and vary among OA patients (Srikulmontree, 2012 ; Zhang *et al.*, 2010). Use-related pain in OA is frequent but rest pain and pain at night also occur, and a many patterns of pain can be seen, varying from a dull ache to sharp, stabbing pain (Hawker *et al.*, 2008), The Western Ontario and McMaster Universities Arthritis Index (WOMAC) scores were more in the diffuse compared to anterior-medial patterns OA pain (Gincke *et al.*, 2016).

Routine laboratory investigations, in patient with OA, appear to be within normal ranges. Primary OA is typically diagnosed according to clinical and radiographic imaging findings (Hunter, 2008). Kellgren and Lawrence (KL) system is the most often used (Kellgren and Lawrence, 1957) in form of following grading

Grade	Score	Description
None	0	clear-cut absence of x-ray changes
Doubtful	1	possible osteophytic lipping
Minimal	2	clear-cut osteophytes and possible tightening of joint space
Moderate	3	moderate numerous osteophytes, clear-cut tightening of joints space, a few sclerosis and possible abnormality of bone contour
Severe	4	great osteophytes, obvious narrowing of joint space, rigorous sclerosis and clear-cut deformity of bone contour

It has been discovered that a combination of both pharmacological and non-pharmacological therapies exert a more beneficial role in treating patients with knee osteoarthritis (Alshami, 2014). many drugs is used in treatment of OA like acetaminophen, NSAID, calcitonin, glucosamine and more with not so clear advantages as disease modifying activity. Alendronate sodium the antiresorptive drug appears in the field now a day. It is anonhormonal therapeutic agent, synthetic analogs of pyrophosphate attach to the hydroxyapatite, one of bone contents. It considered as a member of bisphosphonates. ALN interfere with normal bone formation and turnover cycle in the body by slowing bone loss with elevating bone mass by interfering with osteoclast (Kosuke *et al.*, 2010). The bisphosphonate inhibitory action on bone resorption is resulted from accumulation of bisphosphonate in osteoclasts after released from bone surfaces during bone resorption. Bisphosphonates inhibit farnesyl pyrophosphate synthase (Michael *et al.*, 2011). It has been demonstrated that ALN has the ability to protect chondrocyte from OA events induced by IL-1beta (Wang *et al.*, 2011) by increasing Collagen II and reduction of MMP-13 within chondrocytes (Wang *et al.*, 2011).ALN is used in osteoporotic postmenopausal lady (Nijset *al.*, 2006), male osteoporosis (Orwollet *al.*, 2010),corticosteroid-associated osteoporosis (Nijs *et al.*, 2006), paget's disease (Reid and Hosking., 2011) and treatment for osteogenesis imperfecta (Atsuko *et al.*, 2016). More recent clinical study,

early starting of treatment with anti-resorptive agent gives better outcome which play a valuable role in pain reduction and disease modification of osteoarthritis (Laslett *et al.*, 2014).

A potential benefit of antiresorptive agents, bisphosphonates, results from experimental studies have shown promising results in treatment of OA (Spector, 2003). ALN intake, in symptomatic hip OA, is effective in pain reduction (Nishii *et al.*, 2013). ALN, in randomized controlled trial, was associated with less spinal osteophyte and joint space narrowing progression (Neogi *et al.*, 2008).ALN, in animal model of severe OA study, reduced subchondral bone turnover, reduced osteophyte formation and suppression of articular cartilage degeneration, so ALN reduces OA progression, with suggestion ALN has chondroprotective effects in OA (Siebelt *et al.*, 2014; Mohan *et al.*, 2013). Both in vitro and in vivo studies, it has been found that ALN has the ability to protect chondrocytes by decreasing MMP-13 expression (Hu *et al.*, 2009).

Preclinical trail of rabbit model of OA, has found that ALN prevented periarticular loss of bone (Shirai *et al.*, 2011), decrease the expression of matrix metalloproteinase-13 and interleukin-1 $\beta$  and it has been suggested that ALN had a chondroprotective effect in OA (Shirai *et al.*, 2011).

### Patients and Method

116 OA patients over 45 years old with Kellgren and Lawrence X-ray grade 2 and more, the male patients were 32 while the female were 84 giving the male to female ratio of 1:2.63 and mean BMI (kg/m<sup>2</sup>) was 30.21 $\pm$ 5.91, were enrolled in this study. The patients were habitants of the city of Al-Diwanyhia and Baghdad and had the Iraq nationality.Laboratory equipment and reagents were of the highest available grades.Base line assessment were done in form Kellgren and Lawrence X-ray grading (Kellgren and Lawrence, 1957), WOMAC scoring (Falk *et al.*, 2008), body mass index and the biochemical parameters. Reassessment was done after 3 months of

treatment. Measurement of serum lipid profile, MPO (ELISA), leptin(ELISA), WOMAC and KL were done. Numeric variables were expressed as mean standard deviation. Comparison was done using pared t-test.

Results : Table (1) Demographic characteristic of the study population

Characteristic	N	Mean±SD	Range
Sample size	116		
Age (years)		54.68±5.16	45-65
Gender (m/f)	32/84 (1:2.63)		
BMI (kg/m <sup>2</sup> )		30.21±5.91	21.87-37.81

n: number of cases; m/f: male to female ratio; BMI: Body Mass Index

The results were as follows: mean serum cholesterol showed no significant change, 188.97±44.36 versus 186.27±42.78 (P=0.131); mean serum TG showed no significant change (elevation), 132.45±64.19 versus 131.72± 56.66 (P=0.829); no significant alteration in mean serum HDL, 40.27±6.63 versus 40.12± 6.86 (P=0.693); no significant change(reduction) in mean serum LDL, 122.39±40.06 versus 123.42± 34.19 (P=0.768), as shown in table (2) and figures (1) through (4).

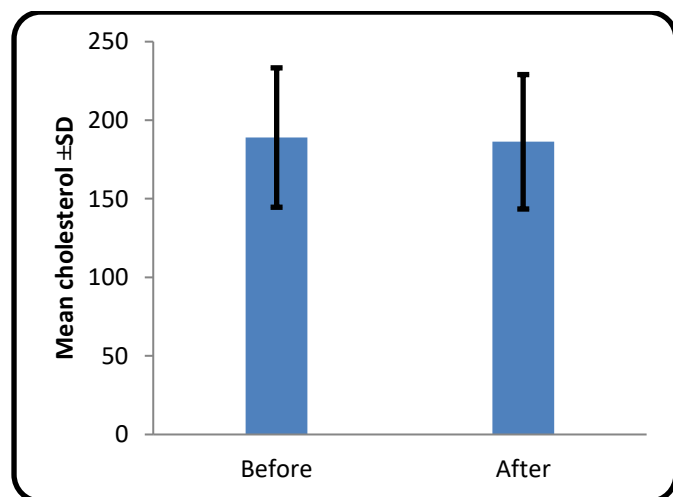


Figure (1): Mean cholesterol level before and after treatment with ALN

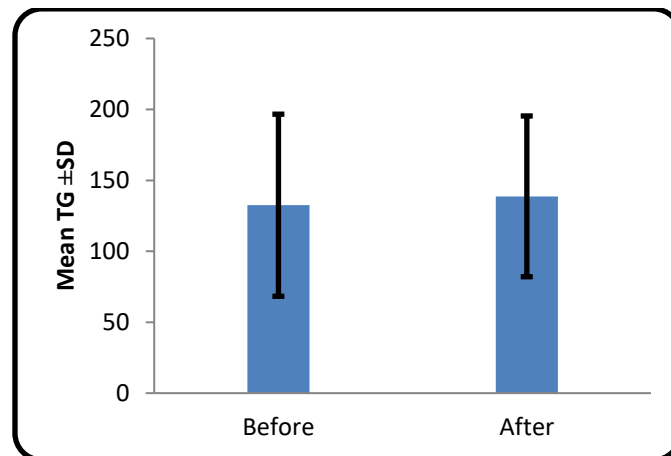


Figure (2): Mean TG level before and after treatment with ALN

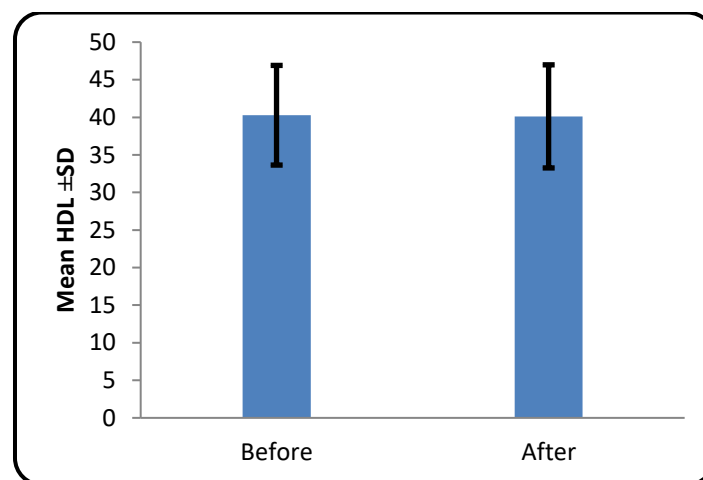


Figure (3): Mean HDL level before and after treatment with 10 mg ALN

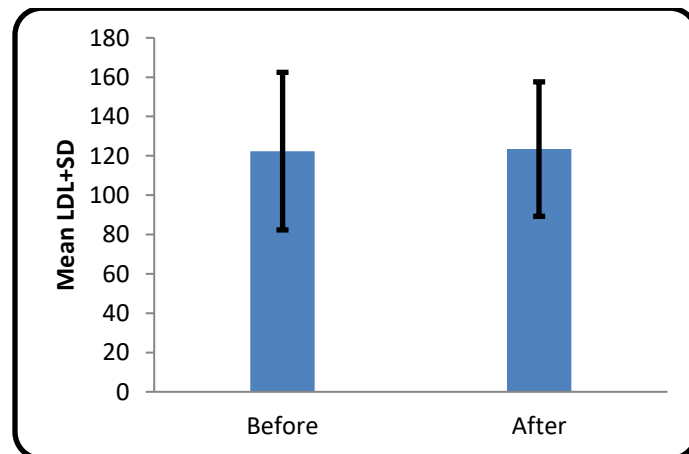
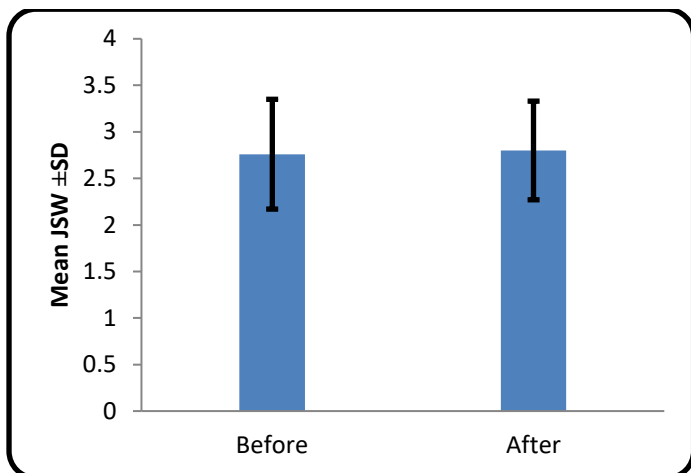


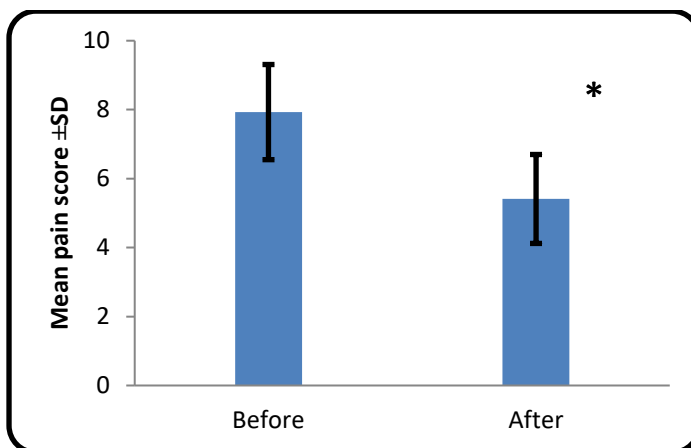
Figure (4): Mean LDL level before and after treatment with 10 mg ALN

Mean JSW score was not significantly changed after treatment, 2.76±0.59 versus 2.80±0.53 (P=0.295). The mean score of pain showed highly significant reduction from 7.93 ± 1.38 to 5.41 ±

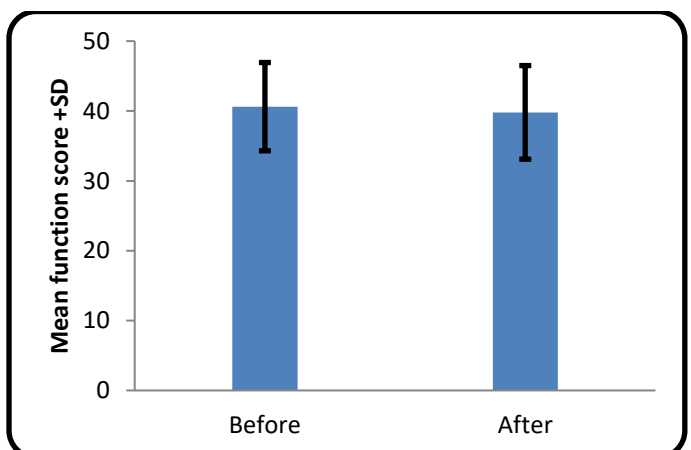
1.29 (<0.001); the same was observed for function score which was reduced, insignificant, from  $40.39 \pm 6.10$  to  $39.54 \pm 6.51$  ( $P=0.661$ ). On the other hand Stiffness score was shown to be reduced (highly significant reduction) from  $3.90 \pm 1.20$  to  $2.22 \pm 1.14$  ( $P<0.001$ )



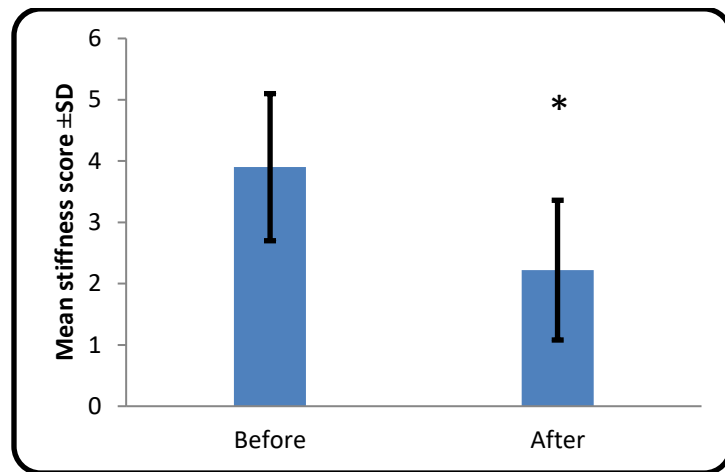
**Figure (5):** Mean JSW before and after treatment with ALN



**Figure (6):** Mean pain score level before and after treatment with ALN



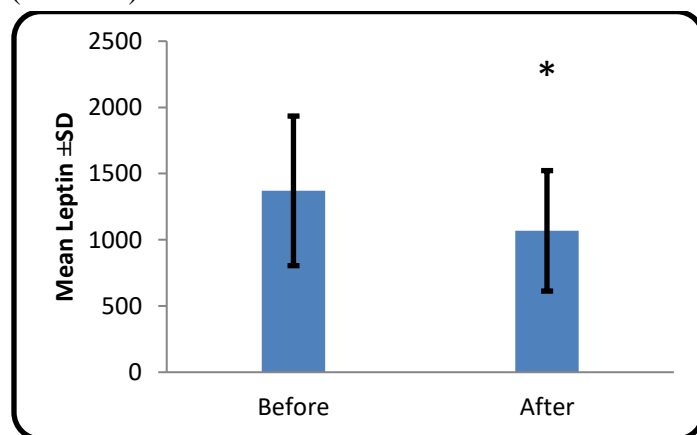
**Figure (7):** Mean function score level before and after ALN



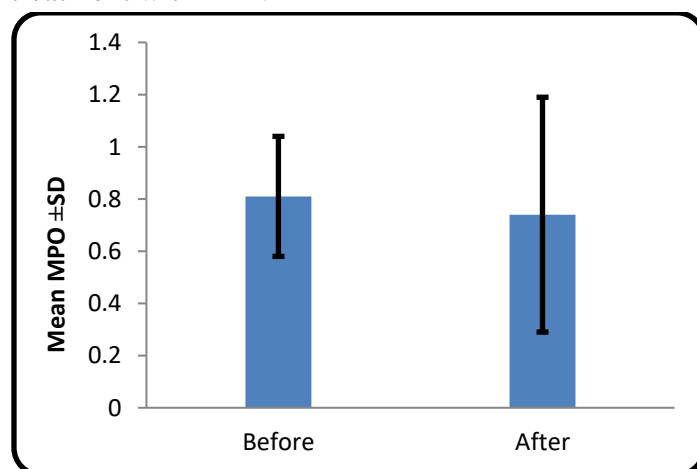
**Figure (8):** Mean stiffness score level before and after with ALN.

(\*) means significant

Mean serum leptin showed highly significant reduction,  $1369.50 \pm 564.90$  versus  $1067.60 \pm 454.89$  ( $P<0.001$ ). On the other hand mean MPO was no significantly changed before and after treatment,  $0.81 \pm 0.23$  versus  $0.74 \pm 0.45$  ( $P=0.100$ ).



**Figure (9):** Mean Leptin level before and after treatment with ALN



**Figure (10):** Mean MPO level before and after treatment with ALN



## Discussion

The importance of pharmacological therapy of OA is reducing pain and cartilage protection. we demonstrated that there was clinical improvement with no observed radiological improvement. Significant alteration in Western Ontario and McMaster Universities (WOMAC) scores together with no significant changes in Kellgren-Lawrence grade (KL) joint space width (JSW) were obtained by the current study. WOMAC gives an acceptable measure of the degree of knee pain affected by (Jinks *et al.*, 2002). The present study showed that ALN use was associated with reduced knee pain severity as assessed by WOMAC scores. In agreement with our finding, Carbone and coworkers in 2004 reported significant change in pain according to WOMAC score in patients with OA after 3 years treatment with ALN. In agreement with current results, placebo control trial has found that there was a substantial improvement in total WOMAC score (Jokar *et al.*, 2010). Nishii and coworkers in 2013 suggested that 2 years ALN intake is effective in pain reduction associated with no significant observation obtained in OA changes as precluded by radiological JSW. All of the trials have stated that there was significant reduction in urinary CTX-II levels in all enrolled groups. Pain suppression in OA may be also due to suppression of Matrix metalloproteinase (MMP) -13, a cytokine not involved in our study, by ALN (Hu *et al.*, 2009).

The alteration in serum lipid profile (Tc, TG, HDL and LDL) was not significant in the current study after treatment with ALN. The lack of significant alteration in serum lipid profile is an indicator that dyslipidemia is not a problem with the use of ALN and that there is no significant increase in cardiovascular and cerebrovascular risk in patients using it for OA. In agreement with the results reported by several other observational studies on human and several experimental studies on experimental animals (Sanadet *et al.*, 2011; Iwamoto *et al.*, 2008; Sookvanichsilpet *et al.*, 2014). According to the result of the present study, the

serum leptin was significantly reduced following treatment with ALN. Following the discovery of leptin receptors in osseous tissue several studies have been carried out to investigate its involvement in osseous metabolism. Some researchers have shown that leptin is expressed and secreted from human osteoblasts primary cultures during the period of mineralization, and that it may activate osteogenesis in human bone marrow in vitro (Reseland *et al.*, 2001). Recent study in OA has recorded that progression of Kellgren-Lawrence grade and high levels of plasma leptin were found to increase knee OA severity (Calvet *et al.*, 2016; Staikos *et al.*, 2013). Other study has demonstrated that severe pain was significantly correlated with high synovial fluid content of leptin in hip and knee OA (Bas *et al.*, 2014).

The synovial fluid and plasma leptin might be a markers correlated with the severity of knee OA (Staikos *et al.*, 2013). Authors has found that in addition to leptin levels in the joint; leptin sensitivity in the cartilage are also increased in over weight patients with OA (Vuolteenaho *et al.*, 2014). This findings referring to leptin as a causative bridge between OA and obesity and that lowering of leptin is a target to the formation of disease-modifying therapeutics for OA (Vuolteenaho *et al.*, 2014). It has been found that joint pain correlated with increased synovial fluid leptin concentrations and raised pre-operative pain seen in obese may be linked to high intra-articular leptin concentrations (Lübbecke *et al.*, 2013). In contrast to current study, other authors observed, after 12 months ALN treatment, that serum leptin was not affected by treatment; however this study included a sample of postmenopausal women treated for osteoporosis (Sebastián-Ochoa *et al.*, 2012). Pre-clinical studies have demonstrated that leptin administration to Ovariectomized rats resulted in reduced bone turnover, playing role in OA, and they concluded that leptin can inhibit or at least delay osteoporosis (Abdel-Sater and Mansour, 2013). Based on these observations, targeting leptin may play a role in treating OA

patients.

The present study showed that myeloperoxidase MPO was not affected by ALN treatment. It was shown in other clinical study that serum MPO is higher in patients with erosive OA than patients with non-erosive subtype (Punzi, 2012) and patients with erosive type may not benefit completely from ALN treatment and targeting MPO may be considered using other modality of treatment for that subset of patients.

### Conclusion

The use of Alendronate in patients with osteoarthritis has clinical efficacy in reducing symptoms especially pain probably through inhibition of leptin, and MMP-13 with no structural improvement and may help delay and prevent further disease progression probably through inhibition of leptin activity. Alendronate proved to be safe in old patients with dyslipidemia since there is no associated lipid disturbances.

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