DOI Number: 10.5958/0976-5506.2019.02038.2

The Role of Inflammatory Markers in the Development of the Osteoporosis in Women after Menopausal

Rusul Ali Al-Masaoodi[1], Alaauldeen S.M. AL-Sallami[2], Hamadallah AL-Baseesee[3]

[1]Physiology and Endocrinology, Collage of Medical Techniques, The Islamic University, Iraq,
[2]Faculty of Science, University of Kufa, Iraq, [3]Faculty of Medicine, University of Kufa, Iraq

Abstract

Background: Osteoporosis is a porous bone. It is common disease of bones, and causes insufficient bone formation or loss of bone mineral density(BMD), making the bones more susceptible to fractures. The aim of the current study is to determine the role of inflammatory makers in women with osteoporosis after menopausal ,this biomarkers include the ; Interleukin-1β(IL -1β)and Resistin.

Patient and Method: According to case-control study. This study was conducted at DEXA (dual-energy x-ray absorptiometry) Unit in Radiology Department in Al-Sader teaching hospital in AL-Najaf province / Iraq from to know the prevalence of osteoporosis in Iraqi menopausal women. A total number of the study include (88) women involved in this studyp. IL -1β , Resistin and estrogen were measurement by using a solid phase enzyme-linked immunosorbent assay (ELISA).

Result: In current study showed a significant decrease ($p< 0.05$) in level of serum estrogen, calcium and phosphorus in menopausal women with osteoporosis compared with healthy group. The biomarker show a significant increase ($p< 0.05$) in the concentration of IL-1β and Resistin in menopausal women with osteoporosis compared with healthy group.

Conclusion: In this study found the role of immunity after menopausal and relation to osteoporosis through measured the level of IL-1β and Rsisten which increase after menopausal and activation of the bone resorpation.

Keyword*: resistin, Menopausal, estrogen (E2) , IL-1β, BMD.*

Introduction

Osteoporosis (OP) is a osteometabolic chronic, progressive disease characterized by a deterioration of bone microarchitecture and reduction in bone mineral density(BMD), which leading to mechanical fragility and ready to spontaneous and traumatic fractures[1]. The causes of osteoporosis is increase breakdown of bone structure, decrease in bone formation, or an imbalance between the activity of bone cells responsible for bone remodeling, which excessive the number or activity of osteoclasts and reduction in number or activity of osteoblasts[2]. Postmenopausal women considered most cases of osteoporosis due to estrogen deficiency. Fractures of osteoporosis occurs in spine and hip therefore considered high morbidity and mortality[3]. Fractures in osteoporosis affect the muscle and the skeletal systems, cause loss of functional capacity, chronic pain, and compromise quality of life[4]. Menopause is an irreversible and universal process, that result from loss of ovarian sensitivity to gonadotropin stimulation , this part of the overall aging process[5].

The immune system has a strong association with bone metabolism[6], For example, interleukin (IL)-6 promotes osteoclast differentiation and activation[7]. IL-1 is another potent stimulator of bone resorption[8]. The IL-1 family of ligands includes 11 members and among them IL-1β emerged as the primary therapeutic target for an expanding number of inflammatory conditions. The inactive IL-1β precursor is cleaved by caspase-1 via a protein complex called inflammasome into an active cytokine, IL-1β binds type I (IL-1RI) and type II (IL-1RII) specific receptors[9]. IL-1β is a strong stimulator of

in vitro and *in vivo* bone resorption[10]. IL-1β upregulates the production of RANKL enhancing its activity and stimulating osteoclastogenesis[11]. IL-1β also regulates the production of osteoprotegerin (OPG), a natural inhibitor of RANKL. OPG inhibits osteoclast differentiation by binding RANKL[12]. IL-1β increases prostaglandin synthesis in bone[13].

Human resistin is a 12.5 kDa cysteine rich peptide with a mature sequence composed of 108 amino acid. The site of resistin gene found on chromosome 19[14], Human resistin plays important role in the regulatory of inflammatory response[15], during which macrophages, peripheral blood mononuclear cells (PBMC), and vascular cells are the primary targets of resistin[16]. Resistin regulation of expression of pro-inflammatory cytokines such as TNF-α, IL-6, IL-12, and monocyte chemoattractant protein (MCP)-1 in PBMCs, macrophages, and hepatic stellate cells via the nuclear factor-κB (NF-κB) pathway[17]. Resistin expression has also been identified in the non-adipocyte fibrotic livers and atherosclerotic lesions[18]. Moreover, circulating resistin concentration are associated with inflammatory and fibrinolytic markers such as C-reactive protein (CRP)[19].

Material and Method

This study was conducted in the research from Al-Sader teaching hospital in AL-Najaf province from DEXA unit in the Radiology Department , Fractures and Joints Department and in laboratories of Biology Department/ Faculty of Sciences/ University of Kufa , during the period from.The samples tested were 88 samples which divided to control group were 20 samples, 68 samples from menopausal women patients .

Biochemical Parameters

Specific kit for measuring human Calcium and phosphate concentrations in serum by spectrophotometer was supplied by Biolabo SA, France. Another specific kits were using to measuring Interleukin-1β level and Resistin level by ELISA technic supplied by Elabscience Biotechnology, while serum estradiol level supplied by CALBIOTECH, China.

Statistical Analysis:

The well- known statistical system (Graph Pad prism ver. 5) was adopted, and the analysis of variance table one – way anova (by Tukey´s multiple comparisons test) was used for the comparison among subdivided groups in the measured parameters. The results were expressed as (Mean ± Stander Error). The comparison between subgroups was analysed by t-test.

Results

The results in figure 1 and 2 reveal statistically significant differences of menopausal women with osteoporosis compared with Healthy group , there was significant decreased ($p<0.05$) in BMD and t-scores in (MO) compared with Healthy group in menopausal women.

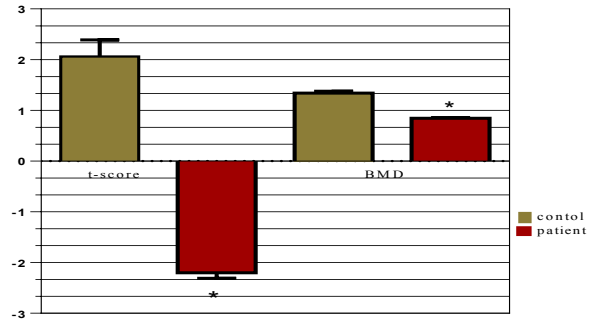

Figure (1) : BMD and T-scores in spin between menopausal women with osteoporosis group and healthy group.

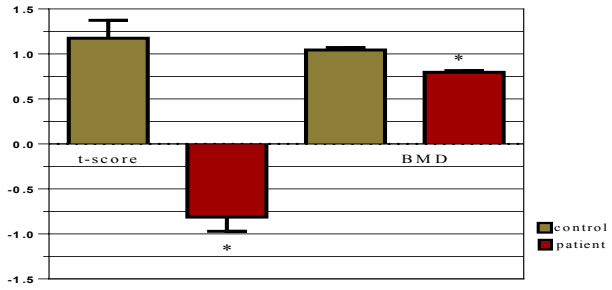

Figure 2: BMD and T-scores in right femur between menopausal women with osteoporosis group and healthy group.

Table 1 revealed significant differences in minerals and hormonal between MO and healthy groups, that show significant decrease in the E2, Ca and Pi. The significant was found (the mean values ± the standard errors) in the serum. The results in figures 3 and 4 exhibit significant increase ($p<0.05$) in serum levels of RETN and IL-1β in POM group compared with in HT group.

Table (1): Comparisons of hormonal evidence between osteoporosis and healthy

Groups Aspect	Mean ±S.E.		p- value
	PMO n=68	Healthy group n=20	
E2 (pg/ml)	15.46 ± 1.747*	22.70 ± 2.687	<0.05
Ca mg/dl	8.19 ± 0.076*	9.15 ± 0.124	<0.05
Pi mg/dl	2.059 ± 0.04423*	2.985 ± 0.1203	<0.05

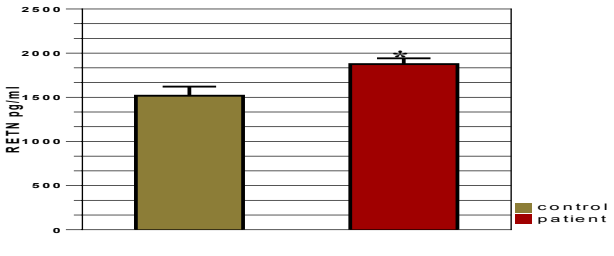

Figure 3 : Comparison of serum RETN level between POM and HT group in menopausal women.

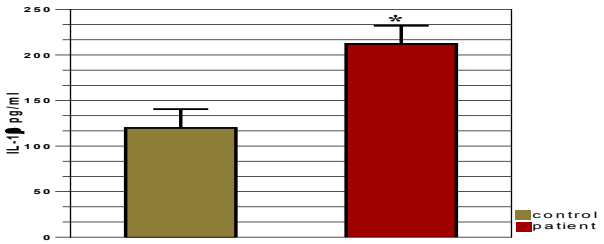

Figure 4 : Comparison of serum IL-1β level between POM and HT group in menopausal women

The results of figure 5 when compare with different age groups indicated there was a significant increase ($p<0.05$) in serum IL-1β concentration in the ages(<65y) and(55-64) than (45-54y), but no significant difference ($p>0.05$) between the age (<65y) and(55-64) in menopausal women with osteoporosis.The result in figure 6 show no significant increase ($p>0.05$) in serum RETN concentration when compare between different age groups in menopausal women with osteoporosis.

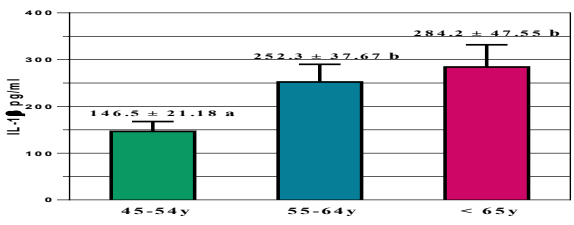

Figure 5: Comparison of serum IL-1β level at different Ages groups in MO.

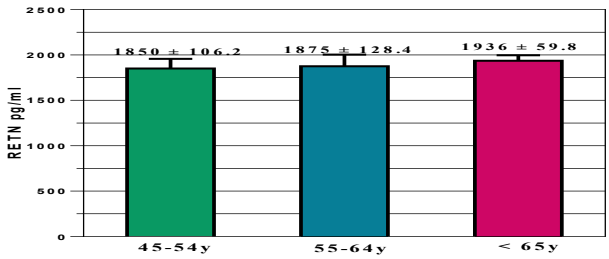

Figure 6: Comparison of serum RETN level at different ages groups in MO.

Discussion

The result of the study revealed that the bone density data from a DEXA scan are reported as decrease in BMD and T-scores in menopausal women with osteoporosis when compared to healthy women. In this study shown an age-dependent decrease in BMD was seen in women in age groups and most in postmenopausal age were found to have low BMD of osteoporotic range; This result is similar to[20,21]. The study of [22] showed the major determinant of bone strength was bone mass and, after reaching peak values in the third decade of life, bone mass and density begins to decline until age 60-65[22].

The age 56–60 and 46–50 years which notice in women a quick reduced in BMD, with a maximum bone reduction occurring at 51–55 years, and a decelerated reduced in BMD after 56–60 years[23]. This study noticed that the DEXA, which gives criteria for the diagnosis of osteoporosis and the related with risks fractures[24]. In this study show the DXAE most common test to diagnosis of the osteoporosis but not show the reason of the osteoporosis, therefore; suggest using the biochemical test. The results of this study have revealed a significant decrease ($P<0.05$) in serum estrogen in menopausal women with osteoporosis more than healthy women. This result agree with [25, 26,27].

In the menopause, estrogen concentration rapidly decrease, therefore women have a hypo-estrogenic state[28]. consequently, the exposure to estrogen during these key periods may dramatically affect a woman's bone health [29]. The estrogens are able to block bone resorption through two mechanisms: both by direct interaction with osteocytes and osteoclast and by regulation of T-cell and osteoblast formation and activity [30,31], The common effects of estrogen deprivation lead to an obvious induced of bone resorption and a period of quick bone loss that is major for the beginning of osteoporosis in postmenopausal[32]. Combined effects of estrogen deprivation cause a marked stimulation ,the role of estrogen in regulation of calcium and phosphorous in the kidney to the well-recognized effect of PTH in elderly women[33]. The results of this study have revealed a significant increase ($P<0.05$) in serum IL-1β . Pro-inflammatory cytokines (IL-1b and IL-6) were significantly elevated in patients than controls, consistent with other studies that induct the associated between osteoporosis and inflammation [34].

Inflammatory cytokines produce from the Innate and adaptive immunity cells which not only perpetuate inflammation but also may activate bone degradation and inhibit bone formation and causes diseases in women before menopause [43], the degree of the inflammation correlates with the extent of local and systemic bone loss [35]. Pro-inflammatory cytokines may participate to bone loss by osteoclasts which activated by receptor activator of nuclear factor kB ligand (RANKL) leading to osteoporosis[36]. Target cell for IL 1β is the osteoclast that provides an important stimulus the formation and activity of osteoclasts, resulting to elevated bone resorption, found of osteoblast and stromal cells was critical in the formation of osteoclasts by IL-1β [37]. IL-1β may also act in the formation of osteoclasts by nuclear factor kappa-light-chain-enhancer of activated B cells and prevents its apoptosis[38].Resistin play a role in bone remodeling [39]. The study have observed moderate correlations between resistin and a marker of increased osteoclast activity[40]. Resistin have important role in bone metabolism by stimulating osteoblast and osteoclast differentiation, possibly through the nuclear factor kappa B (NF-jB) pathway [41].

The loss of ovarian function lead to deficiency estrogen in postmenopausal women which promote signaling and gene expression cascade of major pro-inflammatory cytokines that directly induce early osteoclast precursor formation[42].

Significance Statements

In this study found the role of immunity after menopausal and relation to osteoporosis through measured the level of IL-1β and Rsisten which increase after menopausal and activation of the bone resorpation. This study is the first clinical study in Iraq.

Conflict of Interest: There was no any conflict of interest in this study.

Funding: There was no fund in this study.

Ethical was according to the Declaration of Helsinki issued by the world Medical Association, formulated in experimental protocols and independent (ethics committees approval university of kufa /collage of Medicine).

References

1. Khajuria DK, RazdamR and MahapatraDR. Medicamentos paraprevenc¸ão da osteoporose: revisão. Rev Bras Reumatol. 2011;51(4):365–82.

2. ReidIR. Overview of pathogenesis. In: Rosen CJ, editor. Primer on the metabolic bone diseases and disorders of mineral metabolism. Washington, DC: Wiley-Blackwell. 2013 p: 357–60.

3. Chao AS, Chen FP, Lin YC, Huang TS, Fan CM and Yu YW. Application of the World Health Organization Fracture Risk Assessment Tool to predict need for dual-energy X-ray absorptiometry scanning in postmenopausal women. Taiwanese Journal of Obstetrics & Gynecology. 2015; 54 :722-725.

4. National Osteoporosis Foundation (NOF). Clinician's Guide to Prevention and treatment of Osteoporosis. 2010.

5. Maturana MA, Irigoyenm MC. and Spritzer PM. Menopause, estrogens, and endothelial dysfunction. current concepts Clinics. 2007; 62(1):77-86.

6. Walsh MC, Kim N, Kadono Y, Rho J, Lee SY, Lorenzo J and ChoiY. Osteoimmunology: interplay between the immune system and bone metabolism. Annu. Rev. Immunol. 2006; 24: 33-63.

7. Manolagas SC. Birth and death of bone cells: basic regulatory mechanisms and implications for the pathogenesis and treatment of osteoporosis. Endocrine reviews. 2000; 21(2): 115-137.

8. Wei S, Kitaura H, Zhou P, Ross FP and Teitelbaum SL. IL-1 mediates TNF-induced osteoclastogenesis. The Journal of clinical investigation. 2005; 115(2): 282-290.

9. Garlanda C, Dinarello C and Mantovani A. The interleukin-1 family: back to the future. Immunity. 2013; 39(6): 1003-1018.

10. Lorenzo J, Horowitz M and Choi Y. Osteoimmunology: interactions of the bone and immune system. Endocrine reviews. 2008; 29(4): 403-440.

11. Nakamura I and Jimi E. Regulation of osteoclast differentiation and function by interleukin-1. Vitamins & Hormones. 2006; 74 : 357-370.

12. Polzer K, Joosten L, Gasser J, Distler JH, Ruiz G, BaumW and Schett G. Interleukin-1 is essential for systemic inflammatory bone loss. Annals of the rheumatic diseases. 2010; 69(01), 284-290.

13. Redlich K and Smolen JS. Inflammatory bone loss: pathogenesis and therapeutic intervention. Nature reviews Drug discovery. 2012; 11(3); 234.

14. Steppan CM Bailey ST, Bhat S, Brown EJ, Banerjee RR, Wright CM, Patel H R, Ahima RS and Lazar, M. A.The hormone resistin links obesity to diabetes. Nature. 2001; 409: 307–312.

15. Filková M, Haluzík M, Gay S and Šenolt L. The role of resistin as a regulator of inflammation: Implications for various human pathologies. Clinical immunology. 2009; 133(2): 157-170.

16. Jamaluddin MS, Weakley SM, Yao Q and Chen C. Resistin: functional roles and therapeutic considerations for cardiovascular disease. British journal of pharmacology .2012; 165(3): 622-632.

17. Bokarewa M, Nagaev I, Dahlberg L, Smith U and Tarkowski A. Resistin, an adipokine with potent proinflammatory properties. The Journal of Immunology. 2005; 174(9): 5789-5795.

18. Jung HS, Park KH, Cho YM, Chung SS, Cho HJ, Cho SY and Park KS. Resistin is secreted from macrophages in atheromas and promotes atherosclerosis. Cardiovascular research. 2006; 69(1): 76-85. Park, H. K. and Ahima, R. S. (2013). Resistin in rodents and humans. Diabetes & metabolism journal, 37(6): 404-414.

19. Sharma S and Khandelwal S. Effective risk assessment tools for osteoporosis in the Indian menopausalfemale. 2010;Journal of mid-life health, 1(2): 79.

20. Mishra S, Manju M, Toora, BD, Mohan S and Venkatesh, BP. Comparison of bone mineral density and serum minerals in pre and post-menopausal women. 2015; International Journal of Clinical Trials, 2(4): 85-90.

21. Kabenkama JMK, Ilunga LB, Tshikwela ML, Tshibola JM, Rahma T and Muamba JMM. Multidetector CT in Quantitative Morphometric Assessment of Post-Menopausal Vertebral Fractures in Black Women of Central Africa. 2017; Research in Health Science, 2(4): 335

22. Sambrook P and Cooper C. Osteoporosis. Lancet . 2006; 367

23. Cipriani C, Pepe J, Bertoldo F, Bianchi G, Cantatore FP, Corrado A and Porcelli T. The epidemiology of osteoporosis in Italian postmenopausal women according to the National Bone Health Alliance (NBHA) diagnostic criteria: A multicenter cohort study. Journal of Endocrinological Investigation. 2010 : 1-8.

24. Cauley JA. Estrogen and bone health in men and women. Steroids. 2015; 99: 11-15

25. Lindsay R. Estrogens, progestins, serms, and osteoporosis. In Nutrition and Bone Health. 2915; (pp. 57-63). Springer New York.

26. Lerner UH. Bone remodeling in post-menopausal osteoporosis. Journal of dental research. 2006; 85(7): 584-595.

27. Trémollieres F. Impact of oral contraceptive on bone metabolism. Best Practice and Research Clinical Endocrinology and Metabolism. 2013; 27(1): 47-53.

28. Jackowski SA, Baxter-Jones AD, McLardy AJ, Pierson RA. and Rodgers CD. The associations

of exposure to combined hormonal contraceptive use on bone mineral content and areal bone mineral density accrual from adolescence to young adulthood: a longitudinal study. Bone reports. 2016; 5: 333-341.

29. Pacifici R. The immune system and bone. Arch Biochem Biophys. 2010; 503 : 41-53. : 2010-18.

30. Khosla S, Oursler MJ and Monroe DG. Estrogen and the skeleton. Trends in Endocrinology& Metabolism. 2012; 23(11): 576-581.

31. Faienza MF, Chiarito M, D'amato G, Colaianni G, Colucci S, Grano M and Brunetti G. Monoclonal antibodies for treating osteoporosis. Expert Opinion on Biological Therapy. 2017; 1-9.

32. Dick IM, Devine A, Beilby J and Prince RL. Effects of endogenous estrogen on renal calcium and phosphate handling in elderly women. American Journal of Physiology-Endocrinology and Metabolism. 2005; 288(2): 430-435.

33. Al-Daghri NM, Yakout S, Al-Shehri E, Al-Fawaz H, Aljohani N and Al-Saleh Y. Inflammatory and bone turnover markers in relation to PTH and vitamin D status among Saudi postmenopausal women with and without osteoporosis. International journal of clinical and experimental medicine. 2014; 7(9) : 2812.

34. Redlich K and Smolen JS. Inflammatory bone loss: pathogenesis and therapeutic intervention. Nature reviews Drug discovery. 2012; 11(3): 234–250.

35. Teitelbaum SL. Osteoclasts: what do they do and how do they do it?. The American journal of pathology. 2007; 170(2): 427-435.

36. Lee YM, Fujikado N, Manaka H, Yasuda H and Iwakura Y. IL-1 plays an important role in the bone metabolism under physiologicalconditions. International immunology. 2010; 22(10): 805-816.

37. Knowles HJ and Athanasou NA. Canonical and non-canonical pathways of osteoclast formation. Histology and histopathology. 2009; 24(3): 337-346.

38. Thommesen L, Stunes AK, Monjo M, Grøsvik K, Tamburstuen MV, Kjøbli E and Syversen U. Expressio and regulation of resistin in osteoblasts and osteoclasts indicate a role in bone metabolism. Journal of cellular biochemistry. 2009; 99(3): 824-834.

39. Forsblad d'Elia H, Pullerits R, Carlsten H and Bokarewa M. Resistin in serum is associated with higher levels of IL-1Ra in post-menopausal women with rheumatoidarthritis. Rheumatology. 2008; 47(7), 1082-1087.

40. Almehed K, d'Elia HF, Bokarewa M and Carlsten H. Role of resistin as a marker of inflammation in systemic lupus erythematosus. Arthritis research & therapy. 2008; 10(1): R15.

41. Zupan J, Jeras M and Marc J. Osteoimmunology and the influence of pro-inflammatory cytokines on osteoclasts. Biochemia medica: Biochemia medica. 2013; 23(1): 43-63.

42. Zhang Z, Xing X, Hensley G, Chang LW, Liao W, Abu-Amer Y and Sandell LJ. Resistin induces expression of proinflammatory cytokines and chemokines in human articular chondrocytes via transcription and messenger RNA stabilization. Arthritis & Rheumatism. 2010;62(7): 1993-2003.

43. Aljelawy Z H. and Al-Sallami, ASM. Role of kisspeptin in polycystic ovary disease in patients of ALNajaf ALAshrif City, Iraq. J. Pharm. Sci. &amp. (2019). Res. Vol. 11(1):169-173.