Effect of Alendronate Treatment on Salivary Levels of Osteoprotegrin and TNF-α in Postmenopausal Woman with Osteoporosis and Periodontal Diseases

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ABSTRACT

Background: All diseases concerning bone destruction such as osteoporosis and periodontal diseases share common pattern in which the osteoclast cells are absolutely responsible for bone resorption that occurred when osteoclast activity exceeds osteoblast activity. Osteoprotegrin (OPG) considered as novel soluble decoy receptor known as "bone protector" since it prevents extreme bone resorption through inhibition of differentiation and activity of osteoclast by competing for binding site. It binds to receptor activator of nuclear factor kappa-B ligand (RANKL) and prevent its interaction with receptor activator of nuclear factor kappa-B (RANK), thus inhibits osteoclast formation. TNF-a is a pro-inflammatory cytokines having a broad range of important roles in regulation of immune system and bone resorption through the stimulation of osteoclastogenesis. Alendronate (ALN) diminishes the expression of osteoclast activating factors and cytokines such as RANKL and enhances the production of decoy receptor osteoprotegerin in osteoblast cells. Moreover, it decreases the production of proinflammatory cytokines such as TNF-a by macrophage, stimulates apoptosis of monocyte-macrophage cell lines derivative and reduces inflammatory response.

Aims of the Study: 1. To assess the effect of alendronate treatment on salivary levels of osteoprotegrin and TNF-a in postmenopausal women with osteoporosis and periodontal disease 2. To find any possible correlation between salivary levels of osteoprotegrin and TNF-a in control and study groups.

Materials and Methods: Total sample of 90 female subjects (55-65 years) were divided into 3 groups, (30 subjects in each group): first control group involved systemically healthy subjects with healthy periodontium, second group involved postmenopausal women with osteoporosis under alendronate treatment for(3-6)months (alendronate group), third group involved postmenopausal women with osteoporosis without alendronate treatment(osteoporosis group). The last two groups were sub- divided in- to two sub –groups (15 subjects in each sub-group) of gingivitis and periodontitis subjects respectively. Salivary samples were collected from all subjects and salivary levels of osteoprotegrin and TNF- a were determined by enzyme –linked immune sorbent assay (ELISA).

Results: Highest median value of salivary (OPG) was found in alendronate group followed by control group while the lowest value was found in osteoporosis group. Highest median value of TNF- a was found in osteoporosis group followed by control group and alendronate group respectively with highly significant differences between them. Spearman correlation between salivary levels of TNF-a and OPG showed non- significant correlation at all subgroups.

Conclusion: Subjects with osteoporosis in this study had greater levels of TNF-a and decrease in the level of OPG comparing with patients under alendronate treatment. Alendronate treatment for women with osteoporosis and periodontal disease may have beneficial outcome.

Keywords: periodontal diseases, Osteoporosis, Alendronate, Osteoprotegrin, TNF-a. **(J Bagh Coll Dentistry 2018; 30(2): 17-22)**

INTRODUCTION

Estimation of the association between osteoporosis (OP) and periodontal disease (PD) is confused by the truth that both conditions are caused by incorporation of multiple etiological factors for disease initiation and progression [1]. It was found that periodontal disease destruction might be greatly affected by the systemic loss of bone associated with osteoporosis [2]. Discovery of OPG/ Receptor activator of nuclear factor kappa-B (RANK)/ and receptor activator of nuclear factor kappa-B ligand (RANKL) system develops the perception about molecular system concerned with the balancing of bone turnover. Binding of RANKL to RANK on pre- osteoclast and osteoclast (OC) cells is crucial for their maturation and activity [3].

Osteoprotegrin (OPG) and receptor activator of nuclear factor kappa-B ligand (RANKL) act as negative and positive regulators in osteoclastogenesis and bone resorption. OPG is a soluble molecule that inhibits osteoclast differentiation. It binds to RANKL and inhibits its interaction with RANK leading to neutralization and inhibition of OC formation [4], as well as provoking apoptosis of matured OC [5, 6, 7] . Involvement of the RANKL/OPG system is well recognized in the pathogenesis of bone diseases and mineral metabolism, such as postmenopausal osteoporosis, [8]. Biological analysis of RANKL and OPG for periodontitis patients may provide information about periodontal disease status, however may not be capable to expect the activity of disease prospectively [9]. Periodontitis is related to increase RANKL and decreased OPG levels in gingival tissue and biological fluids including saliva and gingival crevicular fluid (GCF), In other words, periodontitis is related to increase

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RANKL/OPG ratio. Evidence obtained from experimental studies advocated that increase bone resorption after menopause may be due to excessive activation of osteoclast (OC) by increase proinflammatory cytokines production such as TNF-α due to decrease estrogen secretion, which considered as critical factor in the pathogenesis and development of PD as well as osteoporosis [10].

Alendronate (ALN) an aminobisphosphonate is an individual of the second generations of bisphosphonates which are chemical analogs of pyrophosphate (a result of human metabolism) established to be capable of inhibition of bone resorption by osteoclast through modulation of bone mineralization. Various studies confirmed that the systemic use of ALN in humans and some animal models reduced bone loss and increased bone density. It was also proved that treatment with ALN in postmenopausal women with osteoporosis carries a considerable improvement in bone mass [11]. The aims of this study were to assess the effect of alendronate treatment on salivary levels of OPG and TNF-α in postmenopausal women with osteoporosis and periodontal disease and to find any possible correlation between salivary levels of OPG and TNF-α in control and study groups.

MATERIALS AND METHODS

Total sample of 90 female subjects (55-65years) were selected to take part in this study. The subjects recruited for this study were attending to the branch of Rheumatology of Baqubah teaching hospital in Baqubah city. Salivary sample collection was started from 7th December 2016 till 2th April 2017.Each subject was informed about the aims and protocol of the study and they were permitted to accept or reject to participate in the study. All subjects were divided into three groups:-

1-First group **(Control group):** 30 healthy (Systemically and periodontally) postmenopausal women.

2-Second group **(ALN group):** 30 post postmenopausal osteoporosis women under ALN treatment for a period of 3-6 months. They were further divided into two subgroups of 15 gingivitis (**ALNg**) and 15 periodontitis (**ALNp**).

3-Third group **(OP group):** 30 post postmenopausal women with osteoporosis without alendronate treatment. They were further divided into two subgroups of 15 gingivitis (**OPg**) and 15 periodontitis (**OPp**). About five ml of unstimulated salivary sample were collected from all subjects in to a sterile disposable test tube; the samples were placed in a cooling package for inhibition of microorganism growth. Each donor number and group was written on each corresponding tube, and then salivary samples were centrifuged for 20 minutes at 3000 rpm. The supernatant was separated using micropipette in to two eppendorf tubes and stored at -20°C in deep freeze for later analysis by Enzyme Linked Immunosorbent Assay (ELISA) kit for quantitative determination of salivary OPG and TNF- α. The laboratory tests were done in the laboratory of Baqubah teaching hospital. At the time of chemical analysis, all salivary samples were defreezed at room temperature before investigation [12]. Statistical analysis was done using Kruskal-Wallis H test, Mann-Whitney U test, Dun test for multiple comparisons with control, and Spearman's rank correlation coefficient test (r).

RESULTS

The results in this study showed that the highest median value of OPG found in ALN group (7.25) followed by control (3.35) then OP group (2.05) with highly significant difference between them. The median value for gingivitis and periodontitis in ALN group (7.20 and 7.30 respectively) were higher than the median value of gingivitis and periodontitis in OP group (2.20 and 2.00 respectively) with highly significant difference between them as illustrated in table 1. Multiple comparisons among groups were showed highly significant difference when compare between each two group (Table 2). Inter group comparison in table 3, showed non-significant difference between ALNg and ALNp and between OPg and OPp subgroups with nearly an equal median value between gingivitis and periodontitis in each group (7.20, 7.30, 2.20 and 2.00 respectively). Multiple comparisons of each subgroup with control group (Table 4) showed highly significant difference when compare each subgroup with control. Regarding TNF-α the highest median value was in OP group (281.90) followed by control then ALN group (144.80 and 113.45 respectively) with highly significant difference between them. When compared gingivitis and periodontitis in ALN and OP group the median value for OP group were higher than median value for ALN group in both gingivitis and periodontitis (281.40, 283.10, 112.50 and 114.50 respectively) with highly significant difference between them (Table 5). Multiple comparisons among groups were showed highly significant difference between each two group (Table 6). Inter group comparisons in table 7

showed nearly an equal median value between ALNg and ALNp (112.50 and 114.50) and between OPg and OPp (281.40 and 283.10 respectively) with non-significant difference between them. Multiple comparisons of each subgroup with control group (Table 8) showed highly significant difference when compare each subgroup with control. Spearman's rank Correlation Coefficient between salivary levels of TNF-α and OPG showed non-significant correlation at all subgroups.

Table 1: The concentration of salivary OPG for study and control group with comparison of gingivitis and periodontitis between study groups.

Statistics	Groups			Gingivitis		Periodontitis	
	Control	ALN	OP	ALN	OP	ALN	OP
Median	3.35	7.25	2.05	7.20	2.20	7.30	2.00
Mean rank	45.50	75.50	15.50	23	8	23	8
Statistic	Kruskall-Wallis=79.185 p=0.000 HS			Z=4.670 p=0.000 HS		Z=4.675 p=0.000 HS	

Kruskall-Wallis H test, Z = Mann-Whitney U test

Table 2: Multiple comparison among groups for salivary OPG concentration.

Groups	Z	P	Sig.
(Control) X (ALN)	4.45	0.000	HS
(Control) X (OP)	4.45	0.000	HS
(ALN) X (OP)	8.899	0.000	HS

Table 3: Inter group comparisons of salivary OPG concentration.

Statistics	Inter groups comparisons			
subgroups	ALNg	ALNp	OPg	OPp
Median	7.20	7.30	2.20	2.00
Mean rank	13.30	17.70	15.77	15.23
Statistics	Z=1.372 P=0.174 NS		Z=0.167 P=0.870 NS	

Z = Mann-Whitney U test

Table 4: Dun test for multiple comparisons of subgroups with control for salivary OPG concentration.

Statistical Test	Comparison		Mean rank	Z	P-value	Sig.
Kruskall-Wallis= 79.695	Mean rank of Control =45.50	ALNg	73.30	3.360	0.0031	HS
Degree of freedom=4		ALNp	77.70	3.893	0.0004	HS
P=0.000 HS		OPg	15.77	3.594	0.0013	HS
		OPp	15.23	3.659	0.0010	HS

Z = Mann-Whitney U test

Table 5: The concentration of salivary TNF-α for study and control group with comparison of gingivitis and periodontitis between study groups.

Statistic	Group			Gingivitis		Periodontitis	
	Control	ALN	OP	ALN	OP	ALN	OP
Median	144.80	113.45	281.90	112.50	281.40	114.50	283.10
Mean rank	45.50	15.50	75.50	8	23	8	23
Statistic	Kruskall-Wallis=79.125 P=0.000 HS			Z=4.667 P=0.000 HS		Z=4.667 P=0.000 HS	

Kruskall-Wallis H test, Z = Mann-Whitney U test

Table 6: Multiple comparisons among groups for salivary TNF- α concentration

Groups	Z	P	Sig.
(Control) X (ALN)	4.45	0.000	HS
(Control) X (OP)	4.45	0.000	HS
(ALN) X (OP)	8.89	0.000	HS

Z = Mann-Whitney U test

Table 7: Inter group comparisons of salivary TNF-α concentration.

Statistics	Inter groups comparisons			
Subgroups	ALNg	ALNp	OPg	OPp
Median	112.50	114.50	281.40	283.10
Mean rank	14.30	16.70	13.53	17.47
Statistics	Z=0.747 P=0.461 NS		Z=1.224 P=0.233 NS	

Z = Mann-Whitney U test

Table 8: Dun test for multiple comparisons of subgroups with control for salivary TNF-α concentration.

Statistical Test	Comparison		Mean rank	Z	P-value	Sig.
Kruskall-Wallis = 79.358	Mean rank of control=45.50	ALNg	14.30	3.771	0.007	HS
Degree of freedom =4		ALNp	16.70	3.480	0.002	HS
P=0.000 HS		OPg	73.53	3.387	0.003	HS
		OPp	77.47	3.863	0.000	HS

Z = Mann-Whitney U test

Table 9: Spearman's Correlation Coefficient (r) between salivary concentration of OPG and TNFα in control and subgroups

Group	r	p	Significance
Control	0.112	0.554	NS
ALNg	0.125	0.656	NS
ALNp	0.128	0.650	NS
OPg	0.483	0.068	NS
OPp	0.038	0.894	NS

r= Spearman's rank correlation coefficient test

DISCUSSION

The result of this study indicate significant increase in the level of salivary OPG in ALN group when compared to control and OP group with highly difference between them and when compared gingivitis and periodontitis between two groups. Osteoporosis is one of the risk factors that have been implicated in the progression of periodontal disease [13]. A number of studies showed that there is a relationship between oral and systemic bone loss as well as an association of osteoporosis with periodontal diseases [14-16]. Estrogen hormone plays vital protective effect as antiresorptive agent on alveolar bone, since it improve OPG production and decrease RANKL expression, therefore estrogen deficiency after menopause considered as a key feature for development of osteoporosis[17], progression of periodontitis, alveolar bone resorption, and osteoporotic changes in the jaw[18]. Bone resorption and formation is regulated by the quantity of RANKL and RANK on the osteoclast surface and the presence of OPG [5] that inhibit osteoclast function and prevent bone resorption through binding to RANKL [19]. Any alteration to this regulation due to inflammatory conditions will lead to bone resorption like in case of osteoporosis [20], and periodontitis [21].Alendronate has been revealed as modulators of osteoclast function and bone metabolism as a result it may inhibit the development of OP due to reduction of bone loss [22]. Also it is able to produce mediators that inhibits osteoclastogenesis, moreover influences the RANKL/OPG system by increasing OPG and declining RANKL construction[23]. The median value of salivary TNF- α levels in this study showed significant increase in OP group when compared to control and ALN group with highly significant difference between them and in gingivitis and periodontitis between two group. TNF-α has an important role in increasing bone resorption following menopause, and the incidence of postmenopausal osteoporosis due to estrogen deficiency, since estrogen was reported to inhibit stimulation of osteoclast maturation by TNF- α[24]. Proinflammatory cytokines such as TNF-α play vital function in inflammation and bone loss in many conditions like osteoporosis and periodontal disease [25]. It was reported that TNF-α contributes to a basic responsibility in periodontal tissue destruction [26] and progression of periodontitis [27], also it is highly expressed in osteoporosis [28]. All medications that involve inhibition of osteoclast function such as alendronate may be useful in inflammatory conditions [27] through decreasing cytokines production [29], since these cytokines essential for stimulation of RANKL expression, which is crucial for osteoclastogenesis [30] and decreasing OPG production [9]. The cause of non-significant correlation in this study between salivary level of OPG and TNF- α may be due to reduced number of subject's distribution in each group and apparent variations in disease activity between subgroups, and could be attributed to limited changes in alveolar bone during gingivitis as compared to periodontitis. In conclusion the present study provides evidence of association between periodontal diseases and osteoporosis. Patients with osteoporosis had increased TNF- α and decreased OPG level compared to the patients under alendronate treatment, so these biochemical markers could be used for diagnosis and prediction of periodontal disease and osteoporosis.

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الخلاصة

الخلفية:ان جميع الامراض التي تتصف بحدوث نخر وامتصاص النسيج العظمي كمرض هشاشة العظام والتهاب اللثة وانسجة ماحول الاسنان تشترك بنمط عام والذي يتميز بكون الخلايا الملتهمة للعظم هي الخلايا المسؤولة بشكل مطلق عن ذوبان العظم والذي يحدث عندما يكون نشاط هذه الخلايا اكثر من نشاط الخلايا المسؤولة عن بناء العظم.يعتبر الاوستيوبروتجرين كمستلم وفخ يوجد بشكل ذائب ويعرف ب "حامي العظم" لكونه يمنع ذوبان العظم بشكل مفرط من خلال عمله كفخ للرانكل وبذلك يعمل على تثبيط نشاط الخلايا الملتهمة للعظم عن طريق احتلاله لمكان ارتباط الرانك.ان عامل تي ان اف –الفا يعتبر من السايتوكينات المؤدية لحدوث الالتهابات من خلال امتلاكه لدور مهم في تنظيم الجهاز المناعي وعملية ذوبان العظم عن طريق تحفيز تكون الخلايا الملتهمة للعظم.ان عقار الندرونيت يعمل على التقليل من تكوين العوامل والسايتوكينات المحفزة لنشاط الخلايا الالتهامية مثل الرانكل بالاضافة لتأثيره على زيادة افراز العامل المضاد للرانكل وهو الاوستيوبروتجرين من قبل الخلايا المسؤولة عن بناء العظم.بالاضافة لدوره في التقليل من انتاج السايتوكينات كعامل تي ان اف –الفا بواسطة الخلايا البلعمية وتحفيز موت الخلايا المشتقة من خط الخلايا الاحادية-البلعمية والذي يؤدي بدوره الى التقليل من الاستجابة للتاثير الالتهابي.

اهداف الدراسة:تهدف الدراسة الى تقييم تاثير العلاج بعقار الندرونيت على المستويات اللعابية للاوستيوبروتجرين وعامل تي ان اف-الفا في النساء المصابات بمرض هشاشة العظام مابعد سن اليأس والتهاب اللثة وانسجة ماحول الاسنان.كما تهدف الدراسة لايجاد اي احتمال ممكن للربط بين المستويات اللعابية للاوستيوبروتجرين وعامل تي ان اف-الفا في مجموعة الضبط ومجاميع الدراسة.

المرضى,المواد وطرق العلاج: 90 مشاركة من النساء فقط تم ادراجها في هذه الدراسة تتراوح اعمارهم مابين (55-65) سنة تم تقسيمهم الى ثلاثة مجاميع 30 شخص لكل مجموعةوكالاتي:اولا:مجموعة الضبط تتكون من 30 من النساع الاصحاء والحالة الصحية للثة وانسجة ماحول الاسنان صحية ايضا.ثانيا:مجموعة الندرونيت تتكون من 30 من النساء المصابة بهشاشة العظام تخضع لعلاج الندرونيت لمدة 3-6 اشهر(مجموعة الالندرونيت).ثالثا:مجموعة الهشاشة تتكون من 30 من النساء المصابة بمرض هشاشة العظم لاتخضع للعلاج بالالندرونيت او اي علاج اخر.تم تقسيم كل من المجموعتين الاخيرتين الى مجموعتين فرعيتين تتكون من 15 شخص لكلمجموعة فرعية وهي المجموعة الفرعية للالتهاب اللثة والمجموعة الفرعية للالتهاب الانسجة الرابطة للاسنان المزمن.تم تجميع عينات اللعاب من جميع المشاركات في الدراسة وتم تحديد المستويات اللعابية للاوستيوبروتجرين وعامل تي ان اف-الفا عن طريق نظام مقايسة الانزيم المرتبط الممتز المناعي.

النتائج:اظهرت نتائج هذه الدراسة بان القيم الوسطية للمستويات اللعابية للاوستيوبروتجرين في مجموعة الالندرونيت هي الاعلى بين المجاميع تتبعها مجموعة الضبط وبعدها مجموعة الهشاشة باقل قيم وسطية.اما فيما يخص عامل تي ان اف-الفا فقد كانت اعلى قيم وسطية للمستويات اللعابية في مجموعة الهشاشة تتبعها مجموعة الضبط ثم مجموعة الالندرونيت باقل مستويات لعابية.وكانت الفروق ذات دلالة احصائية معنوية عالية بين المجاميع الدراسية ومجموعة الضبط.باستخدام معامل سبيرمان للارتباط تم تقييم العلاقات بين المستويات اللعابية للاوستيوبروتجرين وعامل تي ان اف-الفا حيث اظهرت النتائج وجود علاقات غير معنوية في كل المجاميع الفرعية.

الاستنتاج:من الممكن الاستنتاج بان المريضات اللواتي يعانين من هشاشة العظام يملكن مستوى عالي من عامل تي ان اف مع انخفاض مستوى اوستيوبروتجرين بالمقارنة مع مجموعة الندرونيت والتي تكون ذات مستوى منخفض من تي ان اف مع ارتفاع مستوى اوستيوبروتجرين..بالاضافة لذلك فان العلاج بعقار الندرونيت من الممكن ان يكون ذات مردود فعال ومفيد في المريضات التي تعاني من هشاشة العظام والتهاب اللثة وانسجة ماحول الاسنان مابعد سن اليأس.