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RESEARCH ARTICLE

MANDIBULAR BONE CHANGES IN POST MENOPAUSAL OSTEOPOROTIC PATIENT AFTER TREATMENT WITH ZOLEDRONIC ACID - A PILOT STUDY

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ABSTRACT

The consequences of aging involve the risk of osteoporosis, leading to an impaired quality of life in the elderly patient, especially post menopausal women. Osteoporosis is the leading cause of morbidity and mortality in postmenopausal women. Aim of this study was to see mandibular bone changes in post menopausal osteoporotic patient after treatment with Zoledronic acid. 150 postmenopausal osteoporotic patients were selected and divided into two groups: first group was freshly diagnosed osteoporotic patients and second group one year after treatment with Zoledronic acid. All patients were evaluated by dual-energy X-ray absorptiometry (DXA), orthopantomograph (OPG) and radiovesiograph (RVG). Significant improvement of mandibular alveolar bone occurred in treated group measured by RVG. 83% and 84% of mandibular cortical index were eroded (C2&C3) in osteoporosis and treated osteoporosis respectively. Horizontal bone resorptions of mandibular alveolar bone were less in treated group vs non-treated group (88% and 97 %). The vertical bone resorptions were not significantly different in treated and non treated group (12% and 3%). In post menupousal osteoporotic patients, treatment with Zoledronic acid (Bisphosphonate) significantly improved mandibular alveolar bone in parameter of pixel intensity determines by RVG and cortical index by OPG. Post menopausal osteoporosis patient had eroded mandibular cortex.

INTRODUCTION

Osteoporosis is a medical disorder characterized by a generalized low bone mess and fragility with a consequent increase in fracture risk, particularly of vertebrae; hip and wrist (Rizzoli *et al*., 2009). There are two types of osteoporosis: 1. Primary osteoporosis and 2. Secondary osteoporosis. Primary osteoporosis caused by cessation of estrogen production and characterized by spinal fracture and secondary osteoporosis that affect the older population and results in proximal femur fracture (Riggs and Melton, 1986). Charles Dent said that "senile osteoporosis is a pediatric disease," meaning that failure to achieve adequate peak bone mass during adolescence increase the risk of osteoporosis in later life (Arneson *et al*., 1965-1984). Osteoporosis may arise in the context of other disease such as inflammatory bowel disease or primary biliary cirrhosis, as the result of medication, most commonly steroids or as a consequence of postmenopausal aging (Harderslev *et al*., 2000; Zein *et al*., 2005 and Jonasson *et al*., 2006). Alveolar bone is a unique tissue representing the most viable part of the tooth-supporting apparatus. The alveolar process consists of an external plate of cortical bone, the inner socket of thick compact bone, and cancellous trabeculae interposed. Alveolar bone is intra membranous in origin (Cooper and Melton, 1996) and undergoes continuous remodeling by osteoblast and osteoclast activity (Kanis, 1994). Loss of alveolar bone (metabolic disease/ osteoporosis/ aging/ periods of inactivity) is always accompanied by loss of periodontal fibers. Periodontal disease is one of oral problems that most extensively affect human population, being one of the major causes for adult tooth loss (Marcelo *et al*., 2003).

The gold standard of osteoporosis diagnosis is done by dual energy X ray absorptiometry which determine bone mineral density of femoral neck and lumbar spine. Fracture Risk Assessment Toll (FRAX) was develop by World Health Organization (WHO) tax force in 2008 to proved prediction tool for assessing and individual risk of fracture in order to provide general clinical guidance for treatment decision. WHO has been an established the diagnostic level of bone mineral density less than -2.5 to defined osteoporosis (Von Muhan *et al*., 1999). Suggestion have been made that panoramic radiograph or OPG that show progressive periodontal disease, alveolar bone, tooth loss and endosteal resorption of the mandibuler inferior cortex (MIC) may indicate general osteoporosis (Cooper and Melton, 1996 and WHO, 2003). The uses of OPG are common in dental sitting. Radiovesiography (RVG) is an increasingly popular option in the clinic. Such images are composed of pixel with a specific numerical value for each one. Two important methods of evaluating the pixel in these images are Fractal dimension (FD) and Pixel Intensity

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(PI) (WHO, 2003 and Taguchi *et al*., 1995). Pixel Intensity is a grayscale measure, ranging from zero (black) to 256 (white) in an digital image. Areas of bone lose represented as darker areas, while areas of bone gain represented as lighter area (WHO, 2003 and Klemetti *et al*., 1994). Bisphosphonates are approved to treat osteoporosis and are frequently used to treat osteopenia as well (WHO, 2003 and Delmas, 2005). Zoledronic is the most potent among all Bisphosphonate. Zoledronic acid at a dose of 5mg yearly for three years is most potent, safe and effective in osteoporotic patient (Nakayama and Mori, 2012; Brodeur *et al*., 1993 and Delmas, 2005). Morphology and functional oral sequel of aging are well documented in dental literature, but not those resulting from osteoporosis. Many studies have cited the possible correlation between age, systemic osteoporosis, periodontal disease, tooth loss and changes in quantity and quality of bone of the maxillae and mandible (Marcelo *et al*., 2003; Bone *et al*., 2004 and Haster *et al*., 2011). The restoration of occlusion for partially and totally edentulous patient often requires adequate bone therapy. Consequently, the frequent use of an implant supported prosthesis for the elderly patient or potentially osteoporotic patient demand a better understanding of the relationship between osteoporosis and the stomatognatic system. The aim of this study was to see the mandibular bone changes in postmenopausal osteoporotic patients after Zoledronic acid treatment.

MATERIALS AND METHODS

Total 150 postmenopausal osteoporotic patients were selected for the study. 100 postmenopausal osteoporotic patients who were not treated with Zoledronic acid or any Bisphosphonates were in group A. Another 50 patients who were treated with Zoledronic acid were in group B. All treated postmenopausal osteoporotic patients took Zoledronic acid (Inj. Aclasta) infusion 5mg before 1 year. Postmenopausal women more than 50 years of age with BMD -2.5 or less, with written conscent, not having secondary factors related to osteoporosis and postmenopausal osteoporotic patients those treated by Zoledronic acid were included in this study. Patients with secondary osteoporosis were excluded from this study. All procedure was followed for both groups.

Primarily osteoporosis was diagnosed by determining BMD at the lumbar spine and femoral neck by Dual- energy X-ray absorptiometry (DEXA) scanner. But for treatment and follow-up purpose in osteoporotic patients, bone mass is calculated as gm/cm^2. The cut of margin of T-score of BMD was -2.5 or less at any site either lumber vertebra or femoral neck. All OPG were obtained simultaneously with DEXA scan from Comilla Medical College and Hospital, Comilla. OPG showed the direction of bone resorption of bone loss was suggested on the films, either 'horizontal' or 'vertical' in character. Horizontal bone loss is determined when the bone loss interproximally on two adjacent tooth, vertical bone loss is determined when the bone crest is more apical to the cemento enamel junction (CEJ) adjacent to one tooth than to other. OPG was analyzed for mandibular cortical index. According to Klemitti *et al.* (1994) "MCI is classification of appearance of the mandibular inferior cortex distal to the mental foramen, which includes the following criteria (Klemetti *et al*., 1994). C_1- the endosteal margin of the cortex is even sharp on both sides of the mandibule.C_2- the endosteal margin has semilunar defects (resorptive cavities) with cortical residues one to three layers thick on one or both sides.C_3- the endosteal margin consists of thick cortical residues and is clearly porous. Mandibular bone changes like sclerosis, loss of cortical line were evaluated in follow up panoramic radiograph (Jonasson *et al*., 2001). Moreover, clinical history and oral examination was done to evaluate the unexplained symptoms, infection, pathological fracture or fistula.

After the previous procedure a periapical radiograph were taken by using RVG. RVG machine, manufactured by Gendex, USA. Vixwin Platinum image processing software was used for the measurement of gray level of mandibular bone. Digital periapical radiograph by RVG was used due to their minimal radioactive emission and high image quality that are not lost upon digitalization. Pixel intensity of mandibular alveolar bone was determined by the mean gray level values of the alveolar bone on digital radiograph. The region of interest (ROIs) were set on the apical radiograph of the individual on the 6mm step of the reference radiograph with "rectangular tool" avoiding the lamina dura and the most crestal locations. No apical bone was included (Zein *et al*., 2005). Than the gray value were measured from low level to high level (by assigning the value zero to black 256 to white). Areas of bone loss represent as darker, while areas of bone gain represented as lighter areas (Klemetti *et al*., 1994). This obtained data was posted to data sheet for statistical analysis. Calculation of mean and standard deviation as well as correlation and difference were performed using SPSS 11.5 for windows XP. A p-value <0.05 were considered statistically significant. All the authors vouch for the completeness and accuracy of data and analyses presented.

RESULTS

The mean age of an osteoporotic patient and treated osteoporotic patient are statistically non-significant (table-1). The lumbar spine and femoral neck BMD were 0.706±0.11 gm/cm^2 and 0.723±0.12 gm/cm^2, 0.743±0.15 gm/cm^2 and 0.694±0.11 gm/cm^2 respectively in non-treated osteoporotic patient (group A), treated osteoporotic patient (group B). Those were statistically non-significant. Minimum level of pixel intensity in group A and Group B was statistically significant (table-2). The mean pixel intensity (min) were 62.28±26.37 gm/cm^2 and 77.14±31.65 gm/cm^2 in group A and group B. Maximum level of pixel intensity in both groups was also statistically significant (table-2). The mean pixel intensity (max) was 102.82±30.03 gm/cm^2 and 118.6±34.44 gm/cm^2 in group A and group B. The number of present teeth in group A and group B was statistically non-significant. It was 26.44±6.93 gm/cm^2 in group A and 23.88±9.40 gm/cm^2 in group B. Horizontal alveolar bone resorption in group A was found in 97% of the patients where as only 3% of the patients had vertical alveolar bone resorption. About 88% of the patients showed horizontal bone resorption and 12% were vertical bone resorption in group B. Changes of mandibular cortical bone is shown in table-4. Mandibular cortical bone had C3 type about 60% and 72% of the patients in group A and group B respectively. 23% patients in group A and 12% patients in group B had C2 mandibular cortical changes. Only

17% and 16% of patients in group A and group B respectively had no change in mandibular cortical bone (Table-4). There were no any other changes in mandibule to compare the initiation of bisphosphonate related osteonecrosis of jaw (BRONJ).

Table 1. Age, Lumber spine and femoral neck BMD

Variables	Group A (osteoporotic patient) n=100	Group B (treated osteoporotic patient) n=50	p-value (p=0.05)
Age (in years)	60.1±9.58	63.1±11.44	p=0.158
Lumber BMD (gm/cm^2)	0.695±0.11	0.743±0.15	p=0.07
Femoral BMD (gm/cm^2)	0.714±0.13	0.694±0.11	p=0.4

Table 2. Pixel intensity of mandibular bone and presenting teeth

Variables	Group A (osteoporotic patient) n=100	Group B (treated osteoporotic patient) n=50	p-value (p=0.05)
Pixel intensity (min)	63.5±25.19	77.14±31.65	p=0.02
Pixel intensity (max)	106±25.19	118.16±34.45	p=0.04
Presenting teeth	26.4±6.98	23.88±6.98	p=0.13

Table 3. Resorption pattern of alveolar bone

Variables	Group A (osteoporotic patient) n=100	Group B (treated osteoporotic patient) n=50
Horizontal (%)	97%	88%
Vertical (%)	03%	12%

Table 4. Changes of mandibular cortical bone

Variables	C1 (%)n=100	C2 (%)	C3 (%)
Group A (osteoporotic patient) n=100	17	23	60
Group B (treated osteoporotic patient) n=50	16	12	72

DISCUSSION

In this study, we found that the mean lumbar and femoral BMD of non-treated postmenopausal osteoporotic patients and treated postmenopausal osteoporotic patients was not significantly different. Although the pixel intensity of the treated group was significantly higher. There is no other study about pixel intensity value of postmenopausal osteoporotic patients and treated postmenopausal osteoporotic patients. So we can't compare our results with other studies. But there are some studies found the strong correlation between BMD and pixel intensity value (Jeffcoat, 2005 and Law *et al*., 1996). In clinical trials, bisphosphonate like Alendronate has been found to reduce the risk of progressive loss of alveolar bone (Bone *et al*., 2004 and Haster *et al*., 2011). Zoledronic acid – the preferable Bisphosphonate was used in enrolled treated patients. Bisphosphonate maintain trabecular micro-architecture of bone in post-menopausal women. The degree of mineralization of bone matrix is a determinant of bone strength (Hedstrom *et al*., 2010). In other study found that bone mineral content was significantly increased in therapeutic treatment by Etidronate (Guizhen Jiang *et al*., 2004). The potency of Etidronate is less than Zoledronate. Among all the bisphosphonate , Zoledronic acid is superior till now (Dennis M Black *et al*., 2012; Ma Chao *et al*., 2013; Ieva Ruza *et al*., 2013 and Steven Boonen *et al*., 2012). Zoledronic acid, an annual intravenously administrated bisphosphonate showing an increase in activity of osteoblast rather than the mean degree of mineralization (Roux, 2009). Alveolar bone develops as a membranous bone (Fratzl *et al*., 2007). There are minor phenotypic difference between osteoblasts depending on their site of origin and anatomical location, which can be demonstrated biochemically (Meikle, 2002). Membranous bone osteoblasts also have an increased rate of cell division as compared to iliac crest osteoblast (Kasperk *et al*., 1995 and Hall, 1999). For this reason femoral and lumbar BMD of both groups were not significantly different but pixel intensity value was significantly higher in treated group.

Digital periapical radiograph by RVG was used due to their minimal radioactive emission and high image quality that are not lost upon digitalization. The rectangular tool, used when the pixel intensity value was assessed, included a larger area than the circle. It was placed halfway between the crest and the apical area, which is the area shifting from a denser cervical trabeculation to a sparse trabeculation (Jonasson *et al*., 2001). The ROIs were set on the apical radiograph of the individual on the 6mm step of the reference radiograph with "rectangular tool" avoiding the lamina dura and the most crestal locations. No apical bone was included. Osteoporotic cortical bone result in an increased number of lacunae and porosity and later on thinner cortical plates (Von Muhan *et al*., 1999 and Fratzl *et al*., 2007) it leads to larger inter trabecular spaces and thinning of the trabeculae in the cancellous bone (Jonasson *et al*., 2001). The mineral content is also decrease in a certain area (ROI) and therefore also the pixel value of radiographed area is decrease. On the other hand treated osteoporosis had been shown to increase the pixel value in certain area (ROI).

Cortical width and porosity on dental panoramic radiograph have been shown to be potentially useful assessment method. (Taguchi *et al.,* 1995) In present study 83% mandibular cortex (C2 & C3) had eroded in non treated postmenopausal osteoporotic patients. Almost same, 84% of mandibular cortex had eroded in treated postmenopausal osteoporotic patients. Some studies have found that low bone mineral density is related with high MCI value (C3) which can extrapolated to clinical practice (Bone *et al*., 2004; Jonasson *et al*., 2001 and Jeffcoat, 2005). Systemic bone loss has been proposed as a risk factor for periodontal disease. Osteoporosis the underlying loss of bone mass characteristic of this disease is associated with periodontal disease and tooth loss (Haster *et al*., 2011). In this study, the horizontal alveolar bone resorption in non-treated postmenopausal osteoporotic patients and treated postmenopausal osteoporotic patients were 97% and 88% respectively. Whereas vertical alveolar bone resorption in non-treated postmenopausal osteoporotic patients and treated postmenopausal osteoporotic patients were 3% and 12% respectively. In some studies there was no association between alveolar bone height, number of anterior teeth present and bone mineral density (Haster *et al*., 2011). But some studies had found the association of teeth loss with osteoporosis (Marcelo *et al*., 2003 and Bone *et al*., 2004).

Conclusion

In post menupousal osteoporotic patients, treatment with Zoledronic acid (Bisphosphonate) significantly improved

mandibular alveolar bone in parameter of pixel intensity determines by RVG and mandibular cortical index by OPG. Post menopausal osteoporosis patient had eroded mandibular cortex. Lumbar BMD is improved in Zoledronic acid treated postmenopausal osteoporotic patients. To establish an expectable conclusion, management protocol and diagnostic correlation of osteoporosis it requires a large scale prospective study.

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