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ORIGINAL ARTICLE

Alveolar bone level is not associated with vitamin D receptor gene polymorphism and bone density in mandible

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Abstract The objective of this study was to determine, using digital panoramic radiographs, whether the bone level at the alveolar crest is related to the mandibular bone density and/or to vitamin D receptor (VDR) gene polymorphisms. We analyzed 319 digital panoramic radiographs from the same number of patients. Alveolar bone level was expressed as percentage of root length. The mandibular cortical width index was calculated as a measure of mandibular bone density, and, in 72 randomly selected cases, the haplotype of the VDR gene (BsmL) was determined by polymerase chain reaction. Alveolar bone level was not related to the mandibular cortical width index (p=0.568) or VDR gene expression (p=0.575). Bone loss was greater in smokers than in non-smokers (p=0.036), and the mandibular cortical width index was higher in males (p=0.04), the older age group (p=0.032), and in those with more teeth (p=0.01). Multivariate analysis confirmed the association between these variables and alveolar bone loss. Alveolar bone loss showed no significant relationship with the mandibular bone density evaluated on digital panoramic radiographs or with VDR genotype (BsmL) in Caucasian females and males aged under 47 years.

Keywords Bone density · Alveolar bone loss · Dental digital radiography · VDR · Polymorphism

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Introduction

Jaw bone quality and quantity in the jaw can be evaluated on oral radiographs, which are important diagnostic tool in dental practice [1, 2] and are routinely used to assess bone quantity when screening for or diagnosing periodontitis. However, the overall quality of bone is less often assessed, despite its usefulness to diagnose bone diseases such as osteoporosis [3, 4] and to identify individuals at higher risk of alveolar (periodontal) bone loss [5]. The mandible is highly sensitive to alterations in body bone mass density (BMD), and numerous studies have demonstrated a correlation between mandibular and skeletal (vertebral) bone densities [6–8]. Bone quality differs among individuals [9] and can be assessed on different types of radiographs. Various indexes

are available for the assessment of mandibular bone quality assessment on panoramic X-rays, based on the manual measurement of anatomical structures [10–13].

The mandibular cortical width (MCW) was measured at the mandibular angle level by Bras et al. [10] and in the area between premolars and molars by Yang et al. [11]. Benson et al. [12] proposed a "panoramic mandibular index" based on the ratio between the MCW and the shortest perpendicular distance between the lower edge of the foramen and the lower edge of the mandible. Taguchi et al. [13] measured the MCW on a vertical line to the center of the foramen, passing through both cortical bones (Fig. 1). Index values were correlated with BMD values obtained by quantitative computerized tomography, considered the gold standard test [14].

Vitamin D plays an important role in skeletal metabolism, including calcium absorption and bone loss, and has also been shown to play an important role in other metabolic pathways, such as those involved in immune response and cancer [15]. Vitamin D receptor (VDR) gene can have profound effects on mineral metabolism and bone mineral density [16]. VDR gene polymorphisms may therefore play a role in the pathogenesis of periodontal and systemic diseases that affect the bone tissue.

The objective of this study was to determine on digital panoramic radiographs whether the bone level at alveolar crest (bone quantity) is related to the MCW, as a measure of the BMD (bone quality) and/or to VDR gene polymorphisms.

Materials and methods

Radiological assessment

This radiological study initially included all 1,609 panoramic radiographs of male and female patients aged 21–50 years taken at our school of dentistry clinic during 2008. The lower age limit was selected to avoid the effects of bone development and the upper limit to avoid the effect of menopause on bone mass in females. Study exclusion criteria were: poor visibility of mental foramen, mandibular cortical bones, or cement–enamel junction (due to caries or fillings); presence of an artifact or development defect in the radiograph; history of bone metabolism disease in the patient; active osteoporosis treatment (estrogen hormone, calcium, calcitonin, vitamin D, fluorides, or bisphosphonates), history of radiotherapy, and the presence of <6 teeth in mandible. After application of these criteria, the final study sample comprised of 319 panoramic radiographs.

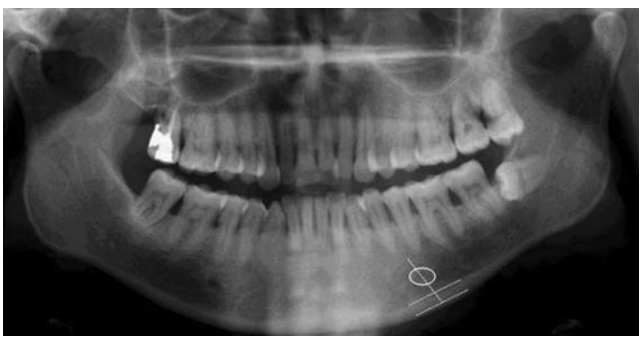

Fig. 1 Example of panoramic radiographs used to calculate Taguchi's MCW index. Distance calculated by drawing a perpendicular line from the mental foramen through both mandibular cortical bones

All panoramic radiographs were taken by the same operator using the same Xmind TOME® ceph analog orthopantomograph (Satelec, Orion Corporation Soredex, Helsinki, Finland) at ×3 magnification, exposure values: 70 Kv (male), 65 Kv (female), 10 mA, and 19 s. Radiographs were then digitalized in an HP scantjet G2710® with Photosmart Essential software (Hewlett Packard) and Dent-a-View® (ver. 1.0) specific software program (Digident CR, Wehmer Co., NJ, USA), for linear measures, was applied to calculate the alveolar bone level and Taguchi's MCW index for a single calibrated researcher (S.N.).

Alveolar bone level was expressed as an average percentage and calculated as $A/B \times 100$, where "A" is the distance from cement–enamel junction to alveolar crest (at the most coronal location of the bone margin adjacent to the ligament space) and "B" is the distance from the cement–enamel junction to the apex [17]. Mesial and distal measurements were made on teeth 36, 41, and 44 (Ramfjord's mandibular teeth) [18] or on the adjacent teeth when absent. Because of normal anatomical variance, bone loss was only considered when the distance from cement–enamel junction to alveolar crest was >1 mm, and a loss of ≤10% was not included as bone loss in the analyses.

Taguchi's MCW index was calculated by measuring a perpendicular line from the mental foramen through both mandibular cortical bones. A single determination on one side is adequate, as reported by Taguchi, due to the close correlation between the values on either side of the mandible [13].

Clinical assessment

Data on the age, sex, and tobacco consumption (cigs./day) of the patients were gathered from their clinical records. All included patients were white Caucasians, as are the vast majority of the Spanish population.

VDR polymorphism determination

Out of the 319 radiographs in the sample, 80 (with and without alveolar bone loss) were randomly selected to assess the VDR gene expression in the patient by means of polymerase chain reaction (PCR). The assessment was not possible in eight of these patients due to lack of genetic material.

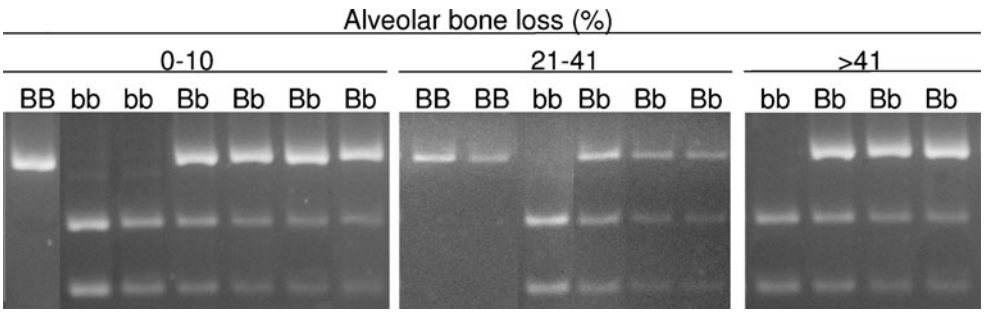

Fig. 2 Distribution of VDR polymorphism according to percentage of alveolar bone loss

Oral mucosa samples were collected with swabs, and DNA was isolated by resuspending the cell pellets with a lysis buffer containing detergents and proteinase K and incubating at 55°C for 24 h (DNA extraction kit ref.: MAD-003951M, Master Diagnóstica S. L. Spain). The VDR restriction fragment length polymorphism (VDR-RFLP) was studied by amplification of total genomic DNA by PCR and endonuclease digestion of the PCR product with BsmI restriction enzyme. VDR intron 7 was amplified with the following primers: forward 5′-AGT GTG CAG GCG ATT CGT AG-3′ and reverse 5′-ATA GGC AGA ACC ATC TCT CAG-3′, resulting in a 191-bp fragment encompassing the BsmI polymorphic site. PCR reaction was performed in 50 μl 1X reaction buffer containing 25 pmol of each primer, 1,5 mM of $MgCl_2$, 200 μM of each dNTP (MBI, Fermentas, Lithuania), 2 U Taq DNA polymerase (DyNAzyme™ II DNA Polymerase, Finnzymes Oy, Finland), and 5 μl of the patient's DNA. Amplification conditions were 95°C 5 min, followed by 30 cycles of denaturation at 94°C for 1 min, annealing at 62°C for 1 min, extension at 72°C for 1 min, and a final extension at 72°C for 5 min. PCR products were analyzed by agarose gel electrophoresis to confirm amplification of the 191-bp fragment; digesting 10 μl of PCR products with 10 U BsmI enzyme (MBI, Fermentas, Lithuania) at 37°C for 2 h; digested products were resolved on a 4% agarose gel, stained with ethidium bromide, and then photographed and analyzed for VDR genotype.

The expected patterns were: allele B, 191-bp fragment; allele b: 115+76 bp fragments (contains target for BmsI restriction endonuclease). Patients homozygous for bb genotype should show two fragments (115 and 76 bp), patients homozygous for BB genotype one fragment (191 bp), and patients with Bb heterozygous genotype three fragments (191, 115, and 76bp) (Fig. 2).

Ethical considerations

The study was performed in accordance with the principles of the Declaration of Helsinki and agreed by the ethical committee of the School of Dentistry, University of Granada. Before oral mucosa samples were collected, the

Table 1 Patient description (n=319)

Variable	n (%)
Sex	
Male	137
Female	182
Age (years)	
21–30	52 (16.3)
31–46	267 (83.7)
Mean±SD	36.5±5.3
Tobacco	
Non-smoker	245 (77.3)
<10 cig./day	44 (13.9)
10–20 cig./day	19 (6.0)
>20 cig./day	9 (2.8)
Not known	2
VDR polymorphism	
bb	20 (27.8)
BB	9 (12.5)
Bb	43 (59.7)
Not analyzed[a]	247
Number of teeth present	
6–12	119 (37.3)
13–16	200 (62.7)
Mean±SD	13.0±2.0
Mandibular cortical width (mm)	
2.2–4.2	142 (44.5)
4.3–8.7	177 (55.5)
Mean±SD	4.39±0.97
Aveolar bone loss (%)	
0–10	99 (31.0)
11–20	146 (45.8)
21–40	62 (19.4)
41–60	11 (3.4)
61–80	1 (0.3)
Mean±SD[b]	13.0±13.3

SD standard deviation, *cig.* cigarettes

[a] Because of the high analytical costs, this variable was measured in 72 randomly selected patients

[b] The mean was calculated by assigning the average value for each category (0 for 0, 11 for 1–20, 31 for 21–40, etc.)

patients were informed carefully and patient consent was obtained.

Statistical analysis

SPSS-Windows v.17.0 (SPSS Inc., Chicago, IL) was used for the statistical analysis; the tests used are reported in table footnotes. Multiple regression analysis was performed with alveolar bone loss as dependent variable and sex, age, tobacco use (converted into dummy variables), VDR genotype (converted into dummy variable), number of teeth, and MCW as potential predictors, using a forward stepwise method ($p<0.10$ to include and $p>0.15$ to exclude a variable).

Results

Some characteristics of the 319 patients in the sample are listed in Table 1. The mean age was 36.5 years (range, 21–46 years) and mean alveolar bone loss was 13.0%. Higher age, tobacco use, and smaller number of teeth were

Table 2 Association of different variables with alveolar bone loss ($n=319$)

Variable	*n*	Alveolar bone loss (%)					Association[c]
		0–10 ($n=99$)	11–20 ($n=146$)	21–40 ($n=62$)	≥41 ($n=12$)	Mean[b]±SD	
Sex							
Male	137	50.5	39.0	35.5	66.7	12.7±14.7	$p=0.683$[d]
Female	182	49.5	61.0	64.5	33.3	13.3±12.3	
Age (years)							
21–30	52	19.2	18.5	8.1	8.3	9.7±10.7	$r=0.17$, $p<0.01$[e]
31–46	267	80.8	81.5	91.9	91.7	13.7±13.7	
Mean±SD[a]		35.6±5.3	36.3±5.4	38.3±4.7	38.0±5.7		
Tobacco							
Non-smoker	245	81.8	79.2	67.7	66.7	12.2±13.0	$r_s=0.12$, $p=0.036$[f]
Smoker	72	18.2	20.8	32.3	33.3	16.0±14.4	
(Not known)	(2)		(2)				
VDR polymorphism							
bb	20	30.0	30.3	20.0	25.0	12.7±13.5	$p=0.575$[g,h]
BB	9	5.0	12.1	26.7	0.0	18.7±12.2	
Bb	43	65.0	57.6	53.3	75.0	14.2±14.7	
(Not analyzed *n*)	(247)	(79)	(113)	(47)	(8)		
Number of teeth							
6–12	119	23.2	31.5	67.7	66.7	18.8±15.2	$r=-0.27$, $p<0.001$[e]
13–16	200	76.8	68.5	32.3	33.3	9.6±10.8	
Mean±SD[a]		13.5±1.9	13.2±1.9	11.8±2.0	12.3±1.6		
Mandibular cortical width (mm)							
2.2–4.2	142	33.3	50.0	51.6	33.3	14.1±12.4	$r=-0.03$, $p=0.568$[e]
4.3–8.7	177	66.7	50.0	48.4	66.7	12.2±14.0	
Mean±SD[a]		4.51±0.89	4.32±1.12	4.31±0.71	4.59±0.84		

The table shows the percentage distribution of different variables for each category of bone loss together with quantitative descriptions when applicable

VDR vitamin D receptor

[a] Mean±standard deviation with the original data (i.e., with no collapsing of categories)

[b] For mean calculation, i.e., to consider this variable as quantitative, the average value of each category was assigned (0 for 0, 11 for 1–20, 31, for 21–40, etc.), without collapsing categories

[c] Calculated without collapsing categories in any variable and considering the bone loss as quantitative variable

[d] Student *t* test for independent groups

[e] Pearson's linear correlation

[f] Spearman's rank correlation

[g] One-way ANOVA

[h] If stratified by age, not significant until 30 years ($p=0.528$) or older ($p=0.508$)

significantly associated with greater alveolar bone loss (Table 2). Sex (male), higher age, and larger number of teeth were associated with higher MCW (Table 3). Multiple regression analysis confirmed that alveolar bone loss was significantly related to age, tobacco use, and number of teeth, but not to sex, MCW, or VDR genotype, as shown in Table 2, the polymorphism distribution was similar in cases without alveolar bone loss and in the cases with alveolar bone loss was more severe.

Discussion

Alveolar bone loss is a critical periodontal disease variable, representing an accumulative measure of the disease suffered over a lifetime [19]. This study examined whether alveolar bone loss, as digitally evaluated on digital radiographs, is associated with mandibular BMD and/or with a specific VDR gene anomaly that could magnify alveolar bone destruction. The use of absolute linear measures is not the method of choice in panoramic radiographs, and the loss of alveolar bone level was expressed relative to the root length, thereby overcoming the difficulty of localizing other reference points [20].

Table 3 Association of different variables with mandibular cortical width (n=319)

Variable	Mean[a]±SD	Association[b]
Sex		
Male	4.52±1.03	p=0.040[c]
Female	4.29±0.92	
Age (years)		
21–30	4.34±0.88	r=0.12, p=0.032[d]
31–46	4.39±0.99	
Tobacco		
Non-smoker	4.40±0.99	r_s=0.003, p=0.955[e]
Smoker	4.34±0.91	
VDR polymorphism		
bb	4.49±1.03	p=0.695[f,g]
BB	4.46±0.38	
Bb	4.27±1.10	
Number of teeth		
6–12	4.22±0.85	r=0.15, p<0.01[d]
13–16	4.49±1.03	

VDR vitamin D receptor

[a] Mean±standard deviation

[b] Calculated without collapsing categories in any variable

[c] Student's t test for independent groups

[d] Pearson's linear correlation

[e] Spearman's rank correlation

[f] One-way ANOVA

[g] If stratified by age, not significant until 30 years (p=0.657) or older (p=0.851)

The MCW, selected as radiomorphometric index, has been significantly associated with the BMD of the skeleton in general (e.g., spine and femur) and biochemical markers of bone turnover [14, 21–24]. Measurements in this anterior area of the mandible have been proven to be more accurate to predict bone mass alterations in comparison to those at the angle or ramus [21, 25], and they are more easily performed due to the lack of superposition by anatomical structures. In the present study, a single researcher (S.N.) carried out the same measurement in all cases, avoiding inter-observer variability, and he used a digital software program and excluded radiographs with unclear cortical margins, minimizing intra-observer variability.

Our findings revealed no significant difference in the mean MCW value between the patients with and without alveolar bone loss according to the radiographic findings. Although the group with greatest bone loss showed the highest mean MCW value, only 12 patients were in this group.

Periodontitis is the main cause of alveolar bone height loss. All of our patients with bone loss had been diagnosed with periodontitis of different severity, but the clinical assessment of these patients was beyond the scope of this study.

Over the past 9 years, only three clinical studies and one radiological study of periodontitis have examined the relationship between clinical attachment/alveolar bone level and the BMD, as measured at various sites by different methods. Von Wowern et al. determined BMD at the mandible and forearm in 24 young adults with severe periodontitis and reported that periodontitis is a local disorder and not associated with systemic bone mineral alterations, although no control group was included and there was no consideration of the influence of smoking or gender, among other potential confounders [26]. Inagaki et al. studied the metacarpal bone density in 190 Japanese women and found a relationship between periodontitis and reduced bone mass in both pre- and post-menopausal subjects [27]. Hattatoglu-Sönmez et al., who used dual energy X-ray absorptiometry to study lumbar vertebrae and left hip joint, found no association between periodontal clinical variables and BMD in 85 pre-menopausal women, although they did not verify the alveolar bone levels from X-rays [28]. Nackaerts et al. applied two approaches to bone density measurement in 91 females from digital panoramic X-rays, one using imaging software and expressed in gray values and the other calculating a quality index based on the amount and proportion of cortical and trabecular bone. Results were correlated with alveolar bone level expressed as a percentage and calculated as in the present study, finding a weak association with the first

method and no association with the second; however, the authors did not stratify results by the age or menopausal status of their exclusively female population [1]. Since most published studies were based on women pre/post menopause, comparison with our results (in male and female subjects free of systemic disease) should be made with caution. Furthermore, our study is a radiographic evaluation, and the other studies are clinical evaluations.

It is not clear whether VDR genotypes are associated with alveolar bone loss in periodontitis patients or whether the VDR gene is related to susceptibility to periodontitis. Aggressive and early-onset forms of periodontitis have been associated with this gene but chronic adult forms have not [16]. In the VDR gene, four common restriction fragment length polymorphisms (BsmI, TaqI, ApaI, and FokI) have been associated with BMD. In this sense, VDR gene polymorphisms have been strongly associated with BMD in some studies [29, 30]; however, recent meta-analysis study have shown conflicting results of the relationship between VDR polymorphisms and BMD and founded only a modest but statistically significant association between lower frequency of BsmI bb genotypes and BMD in cases of bone fracture [31].

In our 72 Spanish patients (20 without bone loss; 6 with bone loss, and <30 years of age; and 46 with bone loss and >30 years), the genotype study of Bsml VDR gene by PCR and Bsml restriction endonuclease digestion revealed no significant association between the distribution of allele b, B (haplotypes bb, bB, BB), and alveolar bone loss in either bivariate or multivariate analyses.

In a recent longitudinal study, Nibali et al. [32] found a moderate association between VDR Taq-I polymorphism and periodontitis presence/progression in smokers but no association in non-smokers, concluding that VDR genetic factors may interact with smoking in the pathogenesis of periodontitis [32]. In our study, the association of different BsmL haplotypes was not significant when the analysis controlled for tobacco consumption, age, and number of teeth present.

In conclusion, alveolar bone loss showed no significant relationship with mandibular bone density on digital panoramic radiographs or with VDR genotypes (BsmL) in this Caucasian population of females and males under 47 years old. Further studies are required to establish whether local bone density and VDR gene are predictive factors for alveolar bone loss or whether the bone destruction is a local inflammatory process independent of bone density status.

Conflicts of interest The authors declare that they have no conflicts of interests.

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